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EDITORIAL

Screening dementia and predicting high dementia risk groups using machine learning

Haewon Byeon

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Abstract

New technologies such as artificial intelligence, the internet of things, big data, and cloud computing have changed the overall society and economy, and the medical field particularly has tried to combine traditional examination methods and new technologies. The most remarkable field in medical research is the technology of predicting high dementia risk group using big data and artificial intelligence. This review introduces: (1) the definition, main concepts, and classification of machine learning and overall distinction of it from traditional statistical analysis models; and (2) the latest studies in mental science to detect dementia and predict high-risk groups in order to help competent researchers who are challenging medical artificial intelligence in the field of psychiatry. As a result of reviewing 4 studies that used machine learning to discriminate high-risk groups of dementia, various machine learning algorithms such as boosting model, artificial neural network, and random forest were used for predicting dementia. The development of machine learning algorithms will change primary care by applying advanced machine learning algorithms to detect high dementia risk groups in the future.

Key Words: Dementia; Artificial intelligence; Clinical decision support system; Machine learning; Mild cognitive impairment

Core Tip: The predictive performance of machine learning techniques varies among studies because of the difference in machine data (especially, Y variables) imbalance, characteristics of features included in the model, and measurement methods of outcome variables. Therefore, further studies are continuously needed to check the predictive performance of each algorithm because, although some studies have proven that the performance of a specific machine learning algorithm is excellent, the results cannot be generalized for all types of data.

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INTRODUCTION

New technologies such as artificial intelligence, the internet of things, big data, and cloud computing have appeared with the advent of the Fourth Industrial Revolution. These new technologies have changed the overall society and economy, and the medical field particularly has tried to combine traditional examination methods and new technologies. The most remarkable field in medical research is the technology of predicting high-risk groups using big data and artificial intelligence. The picture archiving and communication system and electrical medical records have been implemented in hospitals over the past 20 years, and it has accumulated an enormous amount of medical data. However, there is a limit to analyzing patterns or characteristics of the data using only traditional statistical methods due to the size (volume) and complexity of such medical big data.

However, studies have persistently predicted dementia based on machine learning[1-5] over the past 10 years by using cognitive abilities such as neuropsychological tests, in addition to brain imaging and image analysis, which has shown new possibilities for screening dementia and predicting groups with high dementia risk based on medical artificial intelligence. It is expected that the clinical decision support system (CDSS) using artificial intelligence including machine learning will be widely introduced in medical research and it will affect disease prediction and early detection. It is critical to collect high-quality data and analyze the data with an appropriate machine learning technique suitable for the properties of the data to create safe and meaningful medical artificial intelligence. It is necessary to understand the characteristics of machine learning algorithms, different from traditional statistical methods, in order to develop a CDSS that is scientifically meaningful and shows good performance with the participation of medical experts in this process.

Machine learning has been widely used over the past 20 years mainly because of the emergence of big data[6]. It is because the performance of machine learning mostly depends on the quantity and quality of data, and the required level of data has become available only recently. The amount of digital data produced worldwide has been skyrocketing, and it is forecasted that it will be 163 zettabytes per year in 2025[7]. Big data that can be used for medical research include electronic medical record and picture archiving and communication system data individually constructed by a medical institution, insurance claim data of the Health Insurance Corporation, and epidemiological data such as the National Health and Nutrition Examination Survey data. More mental science studies[8,9] have tried to identify risk factors for mental disorders such as depression and cognitive disorders such as dementia using these epidemiological data.

Machine learning algorithms have been successfully applied in medical image processing fields such as neurology and neurosurgery. However, mental science, which mainly deals with clinical data (structured data) such as cognition and emotion, has relatively fewer studies on disease prediction using machine learning. Furthermore, researchers in mental science do not have a deep understanding on machine learning, either. This review introduces: (1) The definition, main concepts, and classification of machine learning and overall distinction of it from traditional statistical analysis models; and (2) The latest studies in mental science to detect dementia and predict high-risk groups in order to help competent researchers who are challenging medical artificial intelligence in the field of psychiatry.

DEFINITION OF MACHINE LEARNING

The machine learning technique is a representative method for exploring the risk factors or high-risk groups of a disease by analyzing medical big data (Figure 1). Many studies mix the concepts of artificial intelligence, machine learning, and deep learning. Machine learning means the algorithm for data classification and prediction, while deep learning is the algorithm that is composed of an input layer, multiple hidden layers, and an output layer, imitating human neurons, among many machine learning

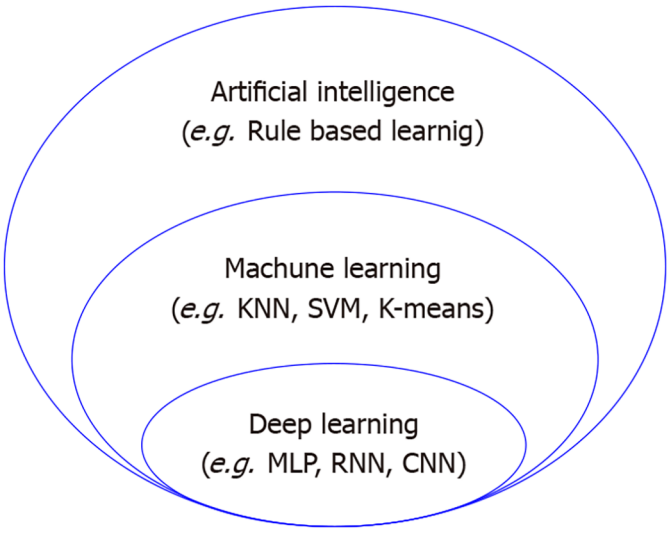

Figure 1 Diagram for concepts of artificial intelligence, deep learning and machine learning. KNN: K-nearest neighbors; SVM: Support vector machine; RNN: Recurrent neural network; MLP: Multilayer perceptron; CNN: Convolutional neural network.

algorithms. Moreover, artificial intelligence can be defined as the highest concept encompassing both deep learning and machine learning. Traditional statistical techniques such as analysis of variance and regression analysis can also be used for analyzing big data. However, traditional statistical techniques cannot identify the complex linear relationships among variables well because big data contain multiple independent variables, and they are limited in analyzing data with many missing values.

Machine learning refers to a method of improving the performance of an algorithm by itself through learning from data. Mitchell[10], a world-renowned machine learning scientist, defined machine learning using task, experience, and performance measure. If there is a computer program, which gradually performs a task better as it accumulates experience through performance measures, it is considered that learning has been accomplished in that computer program. In other words, machine learning is a method that allows a computer to learn using data and finds an optimal solution as a result of it.

In general, machine learning algorithms develop various machine learning models to predict disease risk factors and select the model showing the best performance as the final model. While traditional statistical techniques such as regression analysis use the significance probability to evaluate the predictive performance of models, machine learning algorithms use a loss function. Mean squared errors and mean absolute errors are used as loss functions to evaluate the performance of machine learning for continuous variables, while cross entropy is used for categorical variables[11]. If there are many model parameters or there is a possibility to misrepresent the result due to biased parameters, regularization, a method of adding a penalty to a loss function, is used. L1 (lasso) regularization and L2 (ridge) regularization are representative regularizations used in machine learning, and the Akaike information criterion and Bayesian information criterion are also used[12].

EVALUATING THE PREDICTIVE PERFORMANCE OF MACHINE LEARNING MODELS

Generally, hold-out validation and k-fold validation are mainly used to evaluate the predictive performance of machine learning models. Hold-out validation validates the accuracy by separating the dataset into a training dataset and a test dataset (Figure 2A). For example, 80% of the dataset is used as a training dataset to train a learning model, and the remaining 20% is used as a test dataset to evaluate predictive performance (accuracy). However, if the size of data is not large enough, the hold-out validation may suffer from overfitting. The k-fold validation can be used as an alternative to overcoming the limitation of the hold-out validation. The k-fold validation divides the data into k groups, uses each group as a verification group, and selects the model with the smallest mean error (Figure 2B).

THE STRENGTH OF MACHINE LEARNING IN PREDICTING HIGH DEMENTIA RISK GROUPS

Many previous studies[4,5] did not define the high dementia risk group as a dementia group because

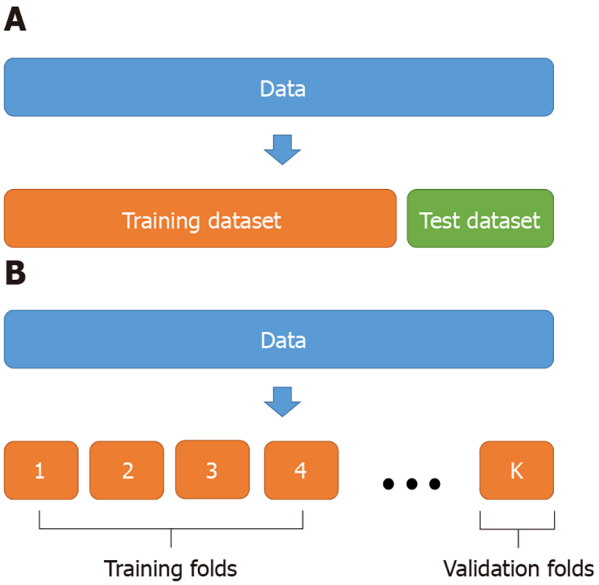

Figure 2 The concept of two validations. A: The concept of hold-out validation; B: The concept of k-fold validation.

although their memory or cognitive functions were lower than the group with the same age and education level in a standardized cognitive test, the ability to perform daily life (*e.g.* activities of daily living) was preserved. In other words, since it is the preclinical stage of dementia, it has been receiving attention in terms of early detection and prevention of dementia.

In general, the main goals of data analysis for predicting high dementia risk groups are inference and prediction. The inference is based on theories and previous studies, and it assumes that data is generated by a specific statistical-based model and tests hypotheses established by the researcher. Even though traditional statistical analyses emphasize inference, prediction using machine learning, unlike inference, often does not establish hypotheses or does not conduct hypothesis testing. Therefore, statistical learning can be considered more advantageous than machine learning in analyzing social science data (or mental science data) emphasizing the relationship between variables. However, as convergence studies on disease prediction have been active recently, this comparison is gradually becoming meaningless. In other words, it has become more common not to strictly distinguish terminologies such as machine learning, statistical analysis, and predictive analysis. Nevertheless, the followings are the strengths of machine learning over traditional statistical analyses. First, it is important to build a predictive model and identify the relationship between key variables associated with the issue in traditional statistical analyses. On the other hand, machine learning focuses on identifying patterns and exploring predictive factors of dementia rather than testing a specific hypothesis. Therefore, machine learning techniques can be applied more flexibly to more diverse data than traditional statistical analysis techniques.

Second, while traditional statistical analysis techniques focus on linear models, machine learning has the advantage of handling nonlinear models and complex interactions between variables[13].

Third, machine learning can analyze a large amount of data that are difficult to handle with traditional statistical methods. Data generally used in statistics are called “long data” and they refer to data in which the number of cases exceeds the number of variables, while “wide data” indicate data in which the number of variables is larger than the number of cases[14]. Even though it is hard to analyze wide data with traditional statistical techniques, machine learning has the advantage that it can analyze long data as well as wide data easily. In other words, while traditional statistical techniques are optimized to analyze data collected through researchers' research design, machine learning can analyze large volumes of data collected without a specific intention.

LIMITATIONS OF MACHINE LEARNING IN PREDICTING HIGH DEMENTIA RISK GROUP

The limitations of machine learning in detecting dementia or predicting high dementia risk groups are as follows. First, it is difficult to interpret the relationship between explanatory variables and response variables with black-box techniques (*e.g.*, boosting models, artificial neural networks, and random forests) among machine learning techniques. While traditional statistical analysis techniques aim to explain (interpret) the relationship between independent and dependent variables, the goal of machine learning techniques is to predict. For example, studies that aim to infer high dementia risk groups develop a study model based on theories and previous studies and test hypotheses. It is possible to

Table 1 Summary of studies

Ref.	Data	Features	Models/algoritms	Results
Bansal *et al*[2]	Total of 416 subjects in cross-sectional data and 373 records in longitudinal data	Age, sex, education, socioeconomic status, mini-mental state examination, clinical dementia rating, atlas scaling factor, estimated total intracranial volume, and normalized whole-brain volume	J48, naive Bayes, random forest, multilayer perceptron	Classification accuracy; J48: 99.52%; Naive Bayes: 99.28%; Random forest: 92.55%; Multilayer perceptron: 96.88%
Bhagyashree *et al*[3]	Total of 466 men and women, health and ageing, in South India	Consortium to establish a registry for Alzheimer's disease, community screening instrument fordementia	Jrip, naive Bayes, random forest and J48, synthetic minority oversampling technique	Sensitivity; Word list recall (WLR) score lower than the population mean: 92.5%; cog-score/verbal fluency/WLR score lower than 0.5 SD lower than population mean: 85.1%
Zhu *et al*[4]	Total of 5272 patients were analyzed. Normal cognition, mild cognitive impairment, very mild dementia	History of cognitive status, objective assessments including the clinical dementia rating, cognitive abilities screening instrument, and montreal cognitive assessment	Random forest, AdaBoost, LogitBoost, neural network, naive Bayes, and support vector machine (SVM)	Overall performance of the diagnostic models; Overall accuracy; Random forest: 0.86; AdaBoost: 0.83; LogitBoost: 0.81; Multilayer perceptron: 0.87; Naive Bayes: 0.87; SVM: 0.87
Jammeh *et al*[5]	Total of 26483 patients aged > 65 yr (National Health Service data)	Total of 15469 read codes, of which 4301 were diagnosis codes, 5028 process of care codes, and 6101 medication codes	SVM, naive Bayes, random forest, logistic regression	Naive Bayes classifier gave the best performance with a sensitivity and specificity of 84.47% and 86.67%; The area under the curve naive Bayes: 0.869

WLR: Word list recall; SVM: Support vector machine.

explain the characteristics of these high dementia risk groups through the model. On the other hand, studies that aim to predict usually don't have a clear study model and often don't test a hypothesis. However, it is possible to confirm which variables are critical to predicting dementia. In particular, when there are new learning data, even if dementia does not develop, it has the advantage of providing the necessary help to the high dementia risk group by categorizing the elderly in the community into a high-risk group and a low-risk group. In summary, traditional statistical analyses emphasize inference, and machine learning focuses on prediction. Machine learning models such as random forests and neural networks partially overcome the issues of the black box by visually presenting the relative importance of variables using "variable importance" and "partial dependence plot". However, it still has limitations in interpreting the relationship or causality between variables.

Second, it may be difficult for mental science researchers to understand machine learning techniques that emphasize the accuracy of prediction rather than explaining the relationship between variables and do not focus on inference of hypotheses. Among the machine learning techniques, the penalized regression model, which is relatively close to the traditional statistical model, presents which explanatory variable is related to the response variable in which direction and how much, but it generally does not show the statistical significance of the explanatory variable like the linear regression model.

Third, unlike the traditional statistical model that models a small number of variables for a theoretical test, the machine learning technique is data-driven. Therefore, unless the data are unbiased good quality data, it is highly likely that biased results will be derived.

TYPES OF MACHINE LEARNING

Regression algorithm

Regression models based on stepwise selection have very poor performance in high-dimensional models. Therefore, it is compensated by using the regulation method, which gives a penalty every time the number of variables is increased. Lasso regression is a representative method[15]. In order to reduce the effect of outliers or singularity in the data, a robust regression technique that selects and trains a part of the data and reiterates this process can also be used[16].

Clustering algorithms

The clustering algorithm classifies data into a specified number of clusters according to the similarity of the attributes. Since the data have only attribute values and labels do not exist, it is called unsupervised learning. The k-means algorithm is a representative clustering algorithm.

Classification algorithms

Classification algorithms include decision tree (DT), support vector machine (SVM), k-nearest neighbor, and multilayer perceptron (MLP) ensemble learning. It is important to treat the imbalance of y-class when applying the classification algorithm. If there is an imbalance of classes, the group with a larger number of data is treated as more important, and the predictive performance decreases. Undersampling, oversampling, and synthetic minority over-sampling technique (SMOTE) methods are mainly used to deal with data imbalance[17], and it has been reported that the performance of SMOTE is generally better than that of undersampling and oversampling[18].

DT

DT is a classifier that repeats binary classification based on the threshold value of a specific variable to the desired depth. Classification criteria variables and values are automatically learned from the data. The classification and regression tree algorithm is used for the learning of DT, instead of gradient descent. This method adds nodes step by step to minimize Shannon entropy or Gini index. The advantage of DT is that the learned classification results can be easily understood by people.

SVM

SVM is a machine learning algorithm that finds the optimal decision boundary through linear separation that separates the hyperplane optimally. If data have a non-linear relationship, the same method is applied after transforming the input variable using a kernel function. SVM solves nonlinear problems related to input space (*e.g.*, two-dimension) by transforming it into a high-dimensional feature space. For example, when A = (a, d) and B = (b, c) are non-linearly separable in 2D, it has linearly separable characteristics if they are mapped in 3D. Thus, when adequate nonlinear mapping is used in a sufficiently large dimension, data with two classes can always be separated in the maximum-margin hyperplane. The advantage of SVM is that it can model complex nonlinear decision-making domains.

MLP

Until the late 20th century, studies using artificial neural networks used shallow networks with two or less hidden layers[19]. However, as the effectiveness of deep neural networks was confirmed in the 21st century[19], the dropout technique and a rectified linear unit function were developed after 2010[20]. Through them, the era of deep learning has begun. The advantage of MLP is its excellent accuracy. Since the accuracy of deep neural networks is generally higher than that of shallow networks[21], it is recommended to apply deep neural networks to obtain more accurate classification or prediction in disease data. Although deep neural networks generally have slightly higher accuracy than other machine learning models, the learning time of it is longer[22]. Therefore, researchers need to select an algorithm suitable for the purpose when developing a machine learning model.

Ensemble learning methods

Ensemble learning refers to a method to learn many models using only some samples or some variables of the data and use these models at the same time, which usually provides better predictive performance than when using a single model. Bootstrap aggregating (bagging) and boosting are representative ensemble learning techniques. Bagging is a method of determining the final output by fitting the result variables several times using some samples or only some variables of the training dataset[23]. Bagging shows good performance because as the number of classifiers increases, the variance of the prediction means of the classifiers decreases. Boosting refers to a method of sequentially generating multiple classifiers. The bagging of DT and random forest are typical examples of the ensemble learning technique. Fernandez-Delgado *et al*[24] compared the performance of classifiers for 121 datasets and reported that random forest impressively outperformed the rest 179 classifiers.

STUDIES OF PREDICTING DEMENTIA BASED ON MACHINE LEARNING

Most of the previous studies[25,26] on the detection of dementia and the prediction of high-risk groups used traditional statistical methods such as regression analysis or structural equation models, but some studies[2-5] applied machine learning (Table 1). Previous studies using machine learning techniques for the elderly with dementia predicted dementia, mild cognitive impairment, and very mild dementia using various features including demographic information[2], medical records[2-5], dementia test scores [3,4], and normalized whole-brain volume[2]. Previous studies have shown that machine learning models had different predictive performance. Bansal *et al*[2] reported that the accuracy (99.52) of the DT model (J48) had the highest accuracy compared to other machine learning models (*e.g.*, naïve Bayes, random forest, and MLP). On the other hand, Zhu *et al*[4] revealed that the accuracy (predictive performance) of MLP (87%), naive Bayes (87%), and SVM (87%) was excellent. Jammeh *et al*[5] confirmed that the area under the curve (AUC) (predictive performance) of naive Bayes (AUC = 0.869) was the best compared to other machine learning models. The predictive performance of machine

learning techniques varies among studies because of the difference in machine data (especially, Y variables) imbalance, characteristics of features included in the model, and measurement methods of outcome variables. Therefore, further studies are continuously needed to check the predictive performance of each algorithm because, although some studies have proven that the performance of a specific machine learning algorithm is excellent, the results cannot be generalized for all types of data.

CONCLUSION

This study introduced the definition and classification of machine learning techniques and case studies of predicting dementia based on machine learning. Various machine learning algorithms such as boosting model, artificial neural network, and random forest were used for predicting dementia. After the concept of deep learning was introduced, multilayer perceptron has been mainly used for recognizing the patterns of diseases. The development of machine learning algorithms will change primary care by applying advanced machine learning algorithms to detect high dementia risk groups in the future. If researchers pay attention to machine learning and make an effort to learn it while coping with these changes, artificial intelligence technology can be used as a powerful tool (method) for conducting mental science studies.

FOOTNOTES

Author contributions: Byeon H designed the study, involved in data interpretation, preformed the statistical analysis, and assisted with writing the article.

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REVIEW

Prenatal nicotine alters development of the laterodorsal tegmentum: Possible role for attention-deficit/hyperactivity disorder and drug dependence

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Abstract

As we cycle between the states of wakefulness and sleep, a bilateral cholinergic nucleus in the pontine brain stem, the laterodorsal tegmentum (LDT), plays a critical role in controlling salience processing, attention, behavioral arousal, and electrophysiological signatures of the sub- and microstates of sleep. Disorders involving abnormal alterations in behavioral and motivated states, such as drug dependence, likely involve dysfunctions in LDT signaling. In addition, as the LDT exhibits connectivity with the thalamus and mesocortical circuits, as well as receives direct, excitatory input from the prefrontal cortex, a role for the LDT in cognitive symptoms characterizing attention-deficit/hyperactivity disorder (ADHD) including impulsivity, inflexibility, and dysfunctions of attention is suggested. Prenatal nicotine exposure (PNE) is associated with a higher risk for later life development of drug dependence and ADHD, suggesting alteration in development of brain regions involved in these behaviors. PNE has been shown to alter glutamate and cholinergic signaling within the LDT. As glutamate and acetylcholine are major excitatory mediators, these alterations would likely alter excitatory output to target regions in limbic motivational circuits and to thalamic and cortical networks mediating executive control. Further, PNE alters neuronal development and transmission within prefrontal cortex and limbic areas that send input to the LDT, which would compound effects of differential processing within the PNE LDT. When taken together, alterations in signaling in the LDT are likely to play a role in negative behavioral outcomes seen in PNE individuals, including a heightened risk of drug dependence and ADHD behaviors.

Key Words: Prenatal nicotine exposure; Pregnancy outcome; Addiction risk; Laterodorsal tegmentum; Arousal; Attention

Core Tip: Offspring of women who used nicotine-containing products while pregnant exhibit risk factors for later-life development of cognitive deficits, including attention deficit/hyperactivity disorder and drug dependence. This suggests that circuits that play a role in cognition are being altered by nicotine. The laterodorsal tegmental nucleus of the pons plays a role in attention, motivation, and other cognitive-related processes, and nicotine during gestation has been shown in animal studies to alter functioning of this nucleus. In this review, we discuss the human and animal literature that indicate that alterations in functioning of the laterodorsal tegmental nucleus could arise following prenatal nicotine exposure, and that these alterations could play a role in the negative risks associated with early-life nicotine exposure.

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INTRODUCTION

Prenatal nicotine and the contribution of the laterodorsal tegmentum to executive control

Smoking during pregnancy exposes the fetus to a variety of chemicals known to have effects on development. Arguably, the most influential of these is nicotine, which crosses the placenta and sequesters within the fetal compartment, which is unfortunate as nicotine is a known teratogen likely involved in differences seen in the development of neural structures characterized in functional imaging studies (for review, see[1]). Many of the brain regions that have been found to be altered are known to play a role in cognitive processing and behavioral control, and differences in their development associated with prenatal nicotine exposure (PNE) could underlie negative cognitive and other behavioral outcomes. Clinically, among other maladaptive, neurally-based behavioral outcomes, PNE individuals exhibit a higher degree of drug dependence[2-6], impulsivity[7,8], and dysfunctions in attention[9-12]. Given the occurrence of these later two behaviors in PNE, an association between attention-deficit/hyperactivity disorder (ADHD) and PNE has been explicitly examined, with studies suggesting that there is a higher incidence of ADHD in offspring of women who smoked while pregnant[10,12-14]. Although few studies have addressed the topic, some reports detail sex-based differences in behavioral outcomes following PNE, which could be due to hormonally-based differential sensitivities to nicotine's ability to alter structural development[15]. In studies examining the damaging neural effects of nicotine that could underlie negative behavioral outcomes, the focus has been directed to changes within neural structures well known to play a role in cognition- and motivation control, such as the prefrontal cortex (PFC), amygdala, hippocampus, and mesoaccumbal circuits comprising the nucleus accumbens (NAc) and the ventral tegmental area (VTA). Unsurprisingly, the role of changes imposed by PNE in the brain stem in PNE-associated behavioral risks has been much less well studied.

While the literature supporting a role of the brain stem in cognitive functioning is scant, since the 1930s, it has been known that damage to the brain stem causes dysfunctions in executive control, suggesting that the brain stem transmits signals that are incorporated into high-order, cognitive processing[16,17]. While sparse, anatomical lesion, pharmacological, and stimulation data began to emerge supporting the interpretation that the brain stem plays a role that extends beyond simply receiving information, and its role may include participation as an inherent functional player in shaping cognitive function. Thanks in large part to the advent of optogenetics, which allows selective dissection of cellular contributions to behavior, the amount of data showing a role of the laterodorsal tegmentum (LDT) in cognitive-based behaviors has exploded, and when taken together, suggest that the brain stem is an integral functional component of the circuits that are involved with executive functions[18-20]. Specifically, determination of the role played by neurons within the LDT of the pons in motivation, attention, and other facets of goal-directed behaviors[21-25] suggests that a re-evaluation is warranted of the perception that the brain stem receives input from top-down circuits and passively transmits it onwards. At this time, it appears clear that the LDT is not a region that passively complies with and executes commands from higher order centers, but rather that the LDT plays a significant role in the coding of information in associative circuits in a bottom-up direction. Further, data suggest that the LDT could be involved in behavioral and mental behaviors known to be altered in PNE individuals. In this review, we discuss data from recent studies that should lead to redefinitions of the extent of control of behavior played by what is considered the most ancestral region of the brain, the brain stem. In addition, results from these studies should raise alarm that early life exposures to nicotine could alter the way by which the LDT responds to input, which would subsequently impact LDT output. This alteration could participate in the generation of PNE-associated behavioral abnormalities in motivation and executive control.

COGNITION RELIES ON ACETYLCHOLINE, AND ONE OF THE MAJOR SOURCES OF ACETYLCHOLINE IS THE LDT

Cognitive functioning, including that involved in attention, relies on acetylcholine (ACh) acting at neuronal nicotinic ACh receptors (nAChRs) and muscarinic ACh receptors. Cholinergic dysfunction has been correlated with impairment of long-term memory[26-28], and manipulations of cholinergic systems have been shown to play a role in attentional states[29]. In humans, augmentation of cholinergic signaling at nAChRs in individuals not sensitized by nicotine has been shown to improve cognitive functions, such as memory and attention[30,31]. Transdermal nicotine delivery in non-smoking subjects increases attention by reducing omission errors and response time variability in the human continuous performance task[32]. Further, nicotine has been shown to improve attentional performance in a variety of cognitive disorders in non-sensitized adults, including ADHD[33], Alzheimer's disease[34], and schizophrenia[35]. These and other studies have focused on the development of cognitive enhancing drugs based upon agonism or potentiation of nAChRs.

While nicotine is an excellent agonist for the nAChR, endogenous signaling at nAChRs is mediated by ACh. The majority of neuronal ACh is sourced from two main clusters in the brain, one within the forebrain and another within the pontine brain stem, with both clusters sending diffuse projections to a variety of targets. The LDT and the pedunculopontine tegmental nucleus (PPT) comprise the cholinergic cluster in the pontine brain stem and send ACh projections widely to both caudal and rostral targets. Both the PPT and the LDT participate in the reticular activating system and, as part of it, exert cholinergic control over the thalamus, which has been implicated in behavioral state control and electro-encephalographic states of arousal and attention. Both cholinergic brain stem nuclei also play a role in sensorimotor integration, reinforcement, and learning; however, their contribution to the control of these processes differs, which is supported by the distinct segregation in the projection patterns of the two nuclei and by divergent functional outcomes upon stimulation[18,36]. The PPT appears particularly involved in control of gait and posture, which is supported by a heavy innervation of structures involved in motor functions, and findings that, when stimulated, the PPT modulates activity in the basal ganglia as well as in the formation and updating of action-outcome associations and rapid decision making[37,38]. The LDT does send projections to the substantia nigra, suggesting it could participate in control of movement; however, optogenetic stimulation of this projection did not result in locomotion, which provides functional evidence in line with the interpretation that the projection from the LDT to the portion of the striatum involved in motor control is not as involved as the PPT projections are in movement control[18,25]. The LDT appears to be more involved than the PPT in the control of cognition and behavior, as suggested from a plethora of anatomical, behavioral, and stimulation studies. This control appears to be exerted directly *via* connectivity of the LDT to limbic structures as well as indirectly *via* synapses within specific thalamic nuclei (Figure 1).

Role of LDT cholinergic transmission in thalamic control

Projections from the LDT synapsing within the principle relay nuclei of the thalamus suggest control of the LDT over thalamic cellular activity that would impact output to cortical regions *via* thalamo-cortical tracts. Thalamo-cortical radiations are involved in relaying information critical in mediation of consciousness, arousal, and alertness. While thought to be a passive relay station, recent evidence suggests the possibility that the thalamus may govern amplification of cortical signaling and therefore be involved more centrally in cognitive behaviors, including behavioral flexibility, than previously appreciated. The more active role emerging of the thalamus in cognitive processes highlights that afferent input to the thalamus, such as that sourcing from the LDT, likely plays a modulatory role in cognitive control[39]. Retrograde studies revealed that the major cholinergic input into the thalamus, particularly in the cognitive-relevant anterior, reticular, ventroposterior, mediodorsal, and central medial nuclei, sources from LDT neurons through both ipsi- and counter-lateral projections[40-43]. Double retrograde labeling approaches showed that many of the LDT neurons that send projections to the thalamus also send collaterals to extra thalamic targets. One of these extra thalamic targets is the VTA, which is also involved in cognitive and limbic functioning through dopamine (DA)-mediated transmission in the mesoaccumbal and mesocortical pathways[18]. Since both the thalamus and VTA project to the NAc, a central nucleus in limbic processing that sends input both to the thalamus and to cortical targets *via* the mesocortical pathway, this collateralized projection pattern provides the LDT with direct and indirect control of striatal regions that project to and release DA within the cortex. Therefore, regulation of cognitive functions *via* variations in DA levels in the PFC, which exerts executive functioning, could occur *via* LDT actions within the thalamus or, more indirectly, *via* LDT collaterals in the VTA, suggesting a complex potential for LDT control over DA transmission. However, this dual projection pattern is not consistently seen in all LDT thalamic targets.

The anterior thalamus, which is known to be involved in alertness, learning, and memory, receives cholinergic projections from the LDT that arise from a different population of cholinergic LDT cells than those sending input to the VTA, suggesting presence of distinct sub-populations of LDT cells[44].

Functional activation of the LDT-thalamic pathway has been shown. LDT cholinergic neurons fire action potentials most vigorously during rapid eye movement sleep and aroused wakefulness[45,46],

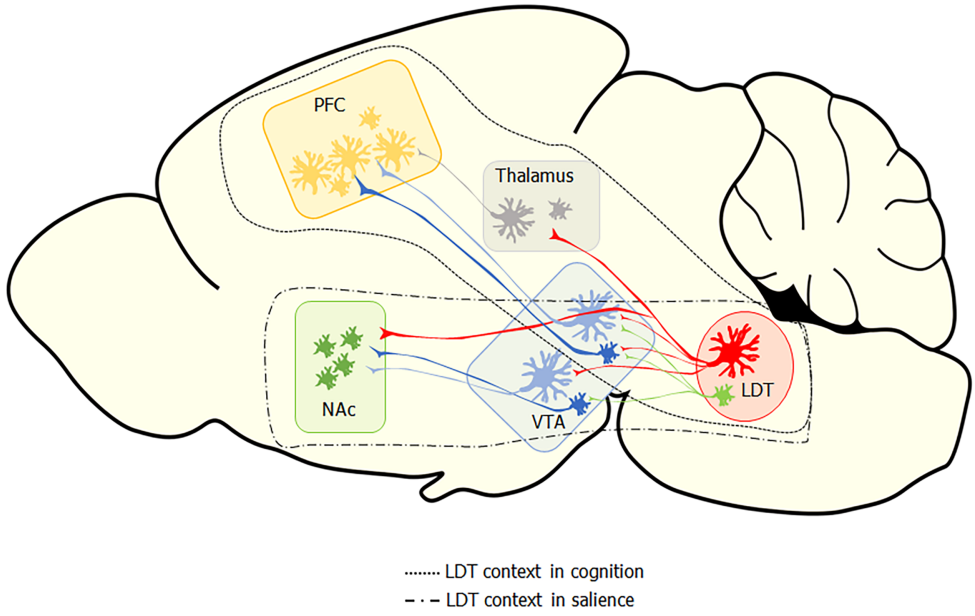

Figure 1 Overview of laterodorsal tegmental nucleus efferent to reward-related brain areas and to thalamic centers involved in modulating cortical function. PFC: Prefrontal cortex; Thal: Thalamus; NAc: Nucleus accumbens; VTA: Ventral tegmental area; LDT: Laterodorsal tegmental nucleus.

which has been shown with *in vivo* micro dialysis to result in increases in the levels of ACh within the thalamus during these states[47]. Functional connections between the LDT and different thalamic centers have also been shown by *in vivo* electrophysiology, combined with pharmacological approaches. Electrical stimulation of the LDT, as well as pharmacological stimulation of the thalamus *via* application of the muscarinic ACh receptor agonist carbachol, enhanced firing rates of ventroposterior medial thalamic cells, indirectly modulating sensory-related cortical areas involved in selective attention[19,48]. Actions of cholinergic agonists in the ventroposterior medial thalamus were associated with modulation of tonic firing patterns and activation of thalamic-cortical projecting centers, such as the somatosensory cortex responsible for processing sensory perception[49,50]. Lesions of the mediodorsal thalamic nucleus, one of the thalamic regions that receives the heaviest cholinergic inputs from the LDT and exhibits reciprocal innervation with the PFC, resulted in working memory deficits in rats, as assayed by impaired radial maze performance[51]. Injection of cholinergic agents enhanced mediodorsal thalamus-PFC synaptic plasticity and inhibited mechanisms underlying depotentiation, which is a mechanism behind the weakening of strength of synapses[52]. Weak *in vivo* stimulation of the LDT nucleus was shown to eliminate spontaneous and evoked burst-firing in the reticular nucleus of the thalamus in anesthetized rats, whereas strong LDT activation induced discharge within this region[53]. In addition, pulse trains injected within the LDT enhanced the responsiveness of anterior thalamic neurons to cortical stimuli[54]. Further, lesions of the anterior or central thalamic nuclei reduced performance in memory testing and diminished attention, which were effects also seen upon local infusion of cholinergic antagonists at these sites, thereby linking the deficits in ACh in the thalamus to working memory and attentional impairments[55-57]. Functional imaging studies in humans have shown that the improvement of attention induced by nicotine is associated with increased activation of the thalamus[58,59], and, furthermore, functional magnetic resonance imaging has provided evidence that more general cognitive improvements observed upon nicotine exposure could be due to activation of nAChRs in the thalamus[60]. When taken together, it is clear that cholinergic actions in the thalamus are involved in attention and cognition, and cholinergic input is provided by a functional connection between the LDT and the thalamus. Therefore, LDT-thalamic cholinergic projections confer upon the LDT an indirect control of cortical excitability through thalamic relay centers and could be involved in amplification of cognitive processing controlled by the thalamus.

Role of cholinergic and GABAergic transmission from the LDT to limbic control pathways

Besides participating in cholinergic modulation of cortico-thalamic circuits, ultrastructural, immunolabeling, and optogenetic studies indicate that the LDT exerts a cholinergic modulatory role within structures and circuits associated with the limbic system that underlie motivation and salience, including the VTA and the NAc[61,62]. The LDT has been shown to be the main source of cholinergic inputs into the NAc core and the VTA, and studies have suggested that LDT cholinergic inputs onto VTA cells modulate activity of DA-containing VTA neurons that participate in both the mesocortical and mesoaccumbal pathways[61-65]. The LDT has been shown to form mainly asymmetric, putatively excitatory, synapses within the striatal complex, particularly onto DA-containing VTA cells and within

the NAc core[64]. While the majority of VTA neurons are DA-containing, 35% of the cells in the VTA are non-dopaminergic, with 25 % of these being inhibitory gamma-aminobutyric acid (GABA)ergic neurons [66]. GABAergic VTA neurons in both mesoaccumbal and mesocortical pathways were found to receive symmetric synapses, putatively inhibitory inputs, from LDT projections, which led to the suggestion that the LDT could participate in disinhibitory mechanisms by inhibiting striatal GABAergic interneurons[22,63]. This point was reinforced by findings that following optogenetic activation of LDT cholinergic cells projecting to DA VTA neurons, a late activation could be observed, consistent with a rebound excitation after the stimulation of GABAergic interneurons[18]. Inhibitory input from the LDT directed to GABAergic cells of the mesocortical pathways could also participate in disinhibitory processes occurring indirectly between the LDT and PFC[63], which could occur in combination with thalamic inhibitory input. Interestingly, symmetric synapses from the LDT were selectively found on DA neurons in the mesocortical pathway, as there was no evidence for their presence in mesoaccumbal DA neurons, indicating that directly mediated, inhibitory influences of the LDT on limbic DA output are mainly targeted to mesocortical DA pathways[63].

ROLE OF DA, THE VTA, AND THE LDT IN DRUG DEPENDENCE

Activation of the mesoaccumbal DA system resulting in DA output to the NAc is involved in reward reinforcement to natural stimuli including sex[67], social interaction[68], and food[69]. Large rises in DA encode a positive valence to these triggering stimuli, which is reinforcing and leads to incentive for repeat of behaviors leading to acquisition of the triggering stimulus. However, in addition to activation of this system by stimuli promotive of health and continuation of our species, drugs of abuse also activate this system and do so to a greater extent than natural stimuli, leading to rises in DA of several fold greater than those evoked by non-drug stimuli[70]. All drugs of abuse share the common ability to activate the mesoaccumbal system, whereas this property is not shared by the majority of drugs that do not exhibit dependence-inducing effects[70]. While drugs of abuse lead to rises in DA, diverse pharmacologic properties across drug classes confer differences in the way by which rises in DA are elicited. The pharmacologic actions leading to rises in DA can be directly-mediated excitatory cellular effects on DA cells, or actions can be indirectly-mediated *via* afferent input to DA cells, which can include cells within the VTA that are not DA-containing neurons, including GABAergic cells and glutamate cells[71] or non VTA sourced projections. Following a large body of studies showing the critical role of VTA DA in incentive salience, the central paradigm regarding the neural processes underlying development of dependence to drugs of abuse involves a high degree of drug-induced DA activation of the mesoaccumbal pathway *via* actions on the heterogenous VTA cell population but also activation of extra-VTA input terminating in the VTA or NAc.

Excitatory LDT cells

Extensive evidence shows that the connectivity of the LDT to the VTA and NAc plays a role in drug addiction behaviors suggestive of drug actions on the LDT-VTA-NAc circuit. Early microdialysis studies showed that electrical stimulation of the LDT resulted in large rises in DA in the NAc, which was reduced by intra-VTA application of nAChR, muscarinic ACh receptor, and ionotropic glutamate receptor antagonists, suggesting ACh and glutamate output from the LDT play a role in DA rises[21]. Further, rises in DA induced by morphine were reduced in LDT lesioned rats[72]. Behaviorally relevant, large rises in DA were found to result from high frequency, burst firing of VTA DA neurons, which was a firing pattern impossible to elicit in VTA brain slices[73-76]. This finding suggested that afferent input severed in the slice preparation was crucial for firing activity of VTA DA-neurons. Consistent with this, *in vivo* studies revealed that DA VTA burst firing was reliant on an intact LDT, since pharmacologic inactivation of the LDT eliminated this firing pattern[77]. The influence of the LDT was thought to be mediated *via* cholinergic inputs[77], and further work showed that cholinergic output from the LDT shapes the firing of VTA neurons and biases VTA activity towards a burst pattern from a more disorganized discharge that likely results in higher release of DA to levels sufficient to underlie the encoding of value of stimulus value, as the rises were associated with evidence of changes in motivated behaviors[18].

Initial optogenetic studies of the role of the LDT in motivated behaviors showed that stimulation of the LDT engendered conditioned place preference (CPP), a model of both associative learning and drug-dependent behavior, which was an effect attributed to the demonstrated presence of glutamatergic output in the LDT-VTA circuit, albeit direct *in vivo* evidence of the role of this circuit in behavioral outcome was not provided[22]. Further optogenetic work confirmed the ability of stimulation of the LDT to induce CPP, and a role of the cholinergic LDT population was shown[64,78]. The role of the cholinergic LDT cells in motivated behaviors mediated by the VTA was additionally supported by loss of CPP conditioning to cocaine when associated with pharmacologic inactivation of the cholinergic LDT cells as well as failure to induce CPP when muscarinic and nicotinic receptors were blocked in the VTA [79]. In addition, photo excitation of LDT cholinergic terminals in the VTA was shown to cause positive reinforcement as subjects spent more time in the compartment in which they received photo

stimulation, which was an effect similar to that induced when cholinergic LDT-NAc input was activated [25]. In a study designed to tease apart the relative contribution of excitatory LDT neurons to motivated behavior, the role in CPP of both glutamate and cholinergic LDT cell populations was examined under identical laboratory conditions[80]. Selective activation of either the glutamate or cholinergic LDT projections to the VTA by light pulses resulted in induction of CPP in mice, leading to the conclusion that both glutamate and cholinergic LDT inputs to the VTA play a role in the net rewarding effects of drugs of abuse[80]. However, the role played by the two excitatory transmitters was found to differ, suggesting that glutamatergic LDT projections may be important for initial reinforcement of place preference, whereas cholinergic mechanisms underlie continued reinforcement, as longer stays in the light drug-paired chamber were seen upon stimulation of cholinergic LDT projections[80]. Glutamatergic neurons, which exhibit very different connectivity to limbic structures and different firing patterns due to differences in intrinsic membrane properties to that exhibited by cholinergic neurons, likely do play a role in the control of VTA neurons, but that role is probably complementary to that served by ACh-containing cells[18,80]. Whether or not the ACh or the glutamatergic LDT afferents to the VTA play a more relevant role in drug dependence behaviors remains an open and very interesting question to address, especially vis a vis treatment targets; however, what is clear from the data is that the LDT can control DA efflux from the VTA in a behaviorally relevant fashion *via* both major excitatory transmitter systems that project to the mesoaccumbal pathway.

Inhibitory LDT cells

The role of the GABAergic LDT neurons, which can be local or projecting, and their impact on eventual VTA DA efflux have been less well examined. A role of LDT-mediated disinhibition of VTA GABAergic cells, especially those within mesocortical circuits, has been proposed[63]. Stimulation of GABAergic VTA cells was found to inhibit firing of DA cells, whereas their optogenetic activation led to conditioned place aversion, a behavioral model of aversive stimulation, suggesting that their inhibition would be promotive of DA release and the encoding of stimuli with a positive valence[81,82]. However, excitation of GABAergic LDT neurons was found to mediate innate fear responses following exposure to predator odorant in rodents[81]. This action was found to be mediated by the lateral habenula, which sends input to the VTA and the GABAergic rostromedial tegmental nucleus, also identified as the tail of the VTA, known to mediate aversive responses. While direct evidence is needed, this raises the interpretation that GABAergic LDT neurons projecting to the VTA do not play a functionally relevant role in inhibiting GABAergic VTA cells, leading to rises in DA sufficient for reinforcement. It is also possible that they inhibit a subset of the remaining 75% of the non-GABAergic VTA population, and/or LDT input directed to the lateral habenula and rostromedial tegmental nucleus supersedes any effect of local VTA disinhibition. A non-mutually exclusive possibility is that different populations of LDT GABAergic projection neurons exist. The role of the local GABAergic interneurons in the LDT, which abut the cholinergic neurons, and their impact on excitatory output are unexplored. When taken together, while it remains to be determined how the three main neuronal phenotypes of the LDT work in concert as a whole, output from the LDT results in significant changes in DA-VTA neuronal activity. As rises in DA efflux from the VTA are involved in reward prediction of salient stimuli and the LDT has been shown to control DA VTA output, the LDT is believed to be critically involved in DA-mediated striatal-control of behavior[83].

Role of DA and the LDT in PFC-controlled behaviors: A role of the LDT in ADHD?

In addition to the heavy projections in the mesoaccumbal pathway, the LDT also provides the major cholinergic input to VTA neurons participating in the mesocortical pathway, which suggests the LDT has control over DA output to cortical regions as the direct projection from the striatum to the PFC of the mesocortical pathway provides the major DA innervation of the PFC. Connections from PFC back to limbic regions are present, creating a striatum cortical loop that is importantly involved in controlling behavioral flexibility and decision making[22,63,65]. Two such loops, comprised of dorsolateral PFC-striatum and anterior cingulate cortex-striatum connections, are suggested to control sustained and selective attention, respectively[84-86]. Dysfunctions within the mesocortical loop have been associated in humans with the expression of ADHD cardinal phenotypes. ADHD is a predominantly childhood mental disorder characterized by a combination of persistent maladaptive behaviors, including hyperactivity as well as cognitive impairments leading to failure to sustain directed attention and impulsivity, which involves decision making before full cognitive processing has occurred[87,88]. The classic triad of symptoms can manifest in several different negative ways, however, effects on emotionality and cognition tend to become exacerbated with age, likely due to increased stresses, whereas motor overactivity tends to abate in adulthood, which are clinical features relevant to note in animal experimentation of ADHD mechanisms[88].

Given the role of striatal cortical loops in control of behavior and the role of DA within behavioral controlling networks, DA dysfunctions within the PFC have been hypothesized to be involved in ADHD[87,89,90]. One of the most compelling findings supporting the hypothesis of a role of DA in ADHD is that stimulants of catecholaminergic systems have been among the most successful treatment of ADHD patients[90]. In addition, reductions in striatal DA transmission have been reported in ADHD patients[91]. Several animal studies have implicated DA function in mesocortical circuits encompassing

the PFC as involved in control of executive functions shown to be altered in ADHD as well as in the control of one of the hallmarks of ADHD, hyperactivity. Lesions of DA-containing mesocortical inputs to the PFC were associated with a hyperactive phenotype in rats[92]. Extracellular DA levels were increased in the PFC during the training phase of a radial maze task in rats, which assays working memory performance[93]. In addition, DA depletion in the PFC was associated with working memory deficits in a T-maze paradigm[94], and similar cognitive deficits were seen after intra-PFC administration of type I DR receptor (DR1) antagonists[95,96]. Depletion of DA release into the PFC was shown to induce cognitive deficits in rhesus monkeys[97], and subsequent studies found that application of D1R antagonists into the PFC promoted deficits in oculomotor delay responses and working memory tasks[98,99]. Behavioral flexibility and decision making were reduced following antagonism of D1R and type 2 DA receptors in the PFC[65]. Interestingly, while D1R agonists injected at low doses within the PFC increased visual attentional performance in rats[100], increased activation by higher concentrations of the D1R agonists impaired performance in both rodents and primates, suggesting optimal D1R activation in the PFC is necessary for proper working memory performance[101-104]. These data support the hypothesis that DA levels within the PFC exert cognitive effects; however, this control is likely exerted in an "inverted U shape" manner, as originally suggested more than 100 years ago[105]. According to this suggestion, optimal dopamine levels within the PFC are believed to be associated with maximum behavioral performance, and either hyper- or hypo-DA function in this brain region compromises executive behaviors[106].

Since PFC-projecting DA VTA neurons contribute to the DA tone of cortical circuits brain regions, which modulate mesocortical VTA activity, the LDT could indirectly contribute to cortical DA functioning. Therefore, activity in the LDT could be indirectly involved in ADHD behaviors *via* the control exerted on mesocortical pathways *via* excitatory synapses on DA mesocortical VTA cells directed to the PFC. A role of the LDT in control of PFC DA levels is indirectly supported by findings that local infusions of nAChR antagonists in the rat VTA resulted in deficits in PFC-controlled behaviors that are DA dependent[107]. Further, control of PFC DA levels could be exerted by the LDT *via* disinhibitory mechanisms mediated by inhibitory LDT inputs directed to GABAergic mesocortical neurons controlling PFC function[63]. In addition, non-DA control of the LDT in ADHD behaviors could be mediated by LDT-thalamic connections, since thalamic-cortical circuits associated with ADHD-related hyperactivity receive input from the LDT[84-86,88]. In addition, the LDT could be involved in other ADHD features, including impulsive behavior. This conclusion is supported by findings that reductions in activation in thalamic relay nuclei are seen in gamblers exhibiting poor impulse control[108]. When taken together, altered neurotransmitter signaling from the LDT could be involved in increasing susceptibility for dysfunctions of attention and cognition. Thus, although no direct evidence has linked LDT function or dysfunction with ADHD-related phenotypes, studies investigating dysfunction of DA mesocortical, mesostriatal, and thalamo-cortical pathways in working memory and other cognitive-related behaviors support the assumption that alterations in the LDT-VTA and LDT-thalamic circuitry could contribute to ADHD-related behavioral deficits. In support of this hypothesis, the brain stem reticular activating system has been suggested to contribute to attention and filtration of interfering stimuli and, accordingly, was thought to play a potential role in disorders involving disorganization in cognitive processes[109]. However, detection of structural abnormities in the brain stem of human patients suffering from ADHD-associated cognitive dysfunctions awaits as these structures have proven to be more challenging than forebrain structures to image[87].

AFFERENT INPUT TO THE LDT IS LIKELY TO INFLUENCE LDT OUTPUT

When taken together, anatomical and functional studies suggest a complex and regulatory role of LDT neurons on VTA functioning and provide further support of the influence of the LDT on mesoaccumbal DA transmission as a relevant step in encoding the valence of environmental stimuli[21]. In addition, these data suggest that the LDT plays a regulatory role in other cognitive functions *via* actions in PFC through direct striatal influence on DA transmission or through indirect actions mediated by thalamic relay centers. However, the circuits in which the LDT participates are not one way, and the LDT receives dense afferent input from many extra-LDT regions throughout the brain (Figure 2). A high number of LDT inputs were shown to source from pontine and midbrain nuclei, including the PPT, central gray, and deep mesencephalic nucleus[61]. In addition, afferents sourcing from cerebellum, spinal cord, basal ganglia, medulla, the bed nucleus of the stria terminalis, and the hypothalamus, particularly from the lateral hypothalamus that houses neurons importantly involved in state-control, were noted[61,110]. Relevant to circuits involved in motivated behaviors and cognition, substantial projections sourced from the VTA as well as the cerebral cortex, including the medial and orbitofrontal PFC[61,111]. These studies demonstrate that LDT afferents source from cortical, limbic, and somatosensory systems, which do, in some cases, themselves receive projections from the LDT. If the LDT passively transmitted information from higher order brain regions, alterations in LDT functioning would not be expected to have a significant impact on downstream signals. However, as the LDT processes signals before they are transmitted, alterations in LDT functioning would be expected to have

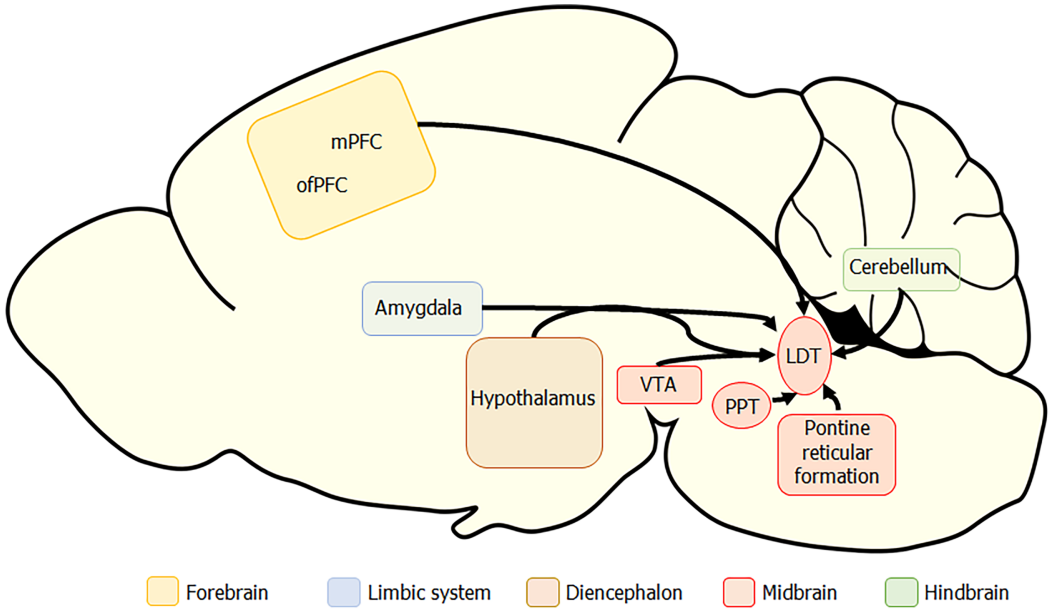

Figure 2 Overview of input sourcing from cognitive and limbic regions synapsing within the laterodorsal tegmental nucleus. PFC: Prefrontal cortex; Hippoc: Hippocampus; NAc: Nucleus accumbens; VTA: Ventral tegmental area; LDT: Laterodorsal tegmental nucleus.

an exponential effect on signal transmission if processing occurs on signals that themselves are altered. Therefore, in dysfunctional conditions, the effect of alterations in LDT functioning would be expected to have a high degree of impact *via* alteration of input and output transmission within networks important in behavioral outputs.

PNE EFFECTS ON COGNITIVE-BASED BEHAVIORS THAT COULD INVOLVE THE LDT

PNE animal models

PNE has been associated with a higher risk of several adverse behaviors that are controlled by signaling in the striatum, thalamus, and PFC. Functional and anatomical studies have shown that molecular, cellular, and structural changes present in these regions are found following PNE. Control over these regions is exerted by the LDT either *via* direct or indirect pathways. When taken together with the fact that there is currently no human data available regarding structural development within the LDT associated with PNE, experimentally examining the issue of PNE-associated changes in the LDT is warranted if we wish to understand fully the mechanisms underlying the higher risk of these maladaptive, cognitive-based behaviors in PNE individuals. While three-dimensional human-derived brain organoid models have recently been used to examine effects on neural development of environmental factors, including nicotine, they do not allow for examination of behavioral associations[112] (for review, see[113]). Accordingly, for studies examining synaptic changes that could underlie behavioral outcomes, we require animal models of PNE in which both cellular and behavioral studies can be conducted. However, PNE animal models vary in several very important factors, making it difficult to choose the model best suited for translational significance.

One major difference in PNE models to date in the choice and breed of animal that have been used, which is a not insignificant confound as different species, and strains within the same species can respond with diverse behavioral outcomes suggestive of different cellular changes[114]. PNE studies also have varied in the experimental design regarding the method by which nicotine was applied, which has included subcutaneous application either *via* injection or implantation of osmotic mini pumps, intravenous application, intraperitoneal injection, or inhalation of cigarette smoke. In a less invasive approach, nicotine can be applied *via* the drinking water of the pregnant dams. Each of these methods would be expected to result in blood nicotine levels that are different and perhaps not similar in kinetics to those seen in humans, as nicotine concentrations in the blood of regular smokers are usually constant during periods of wakefulness in order to abate symptoms of withdrawal.

Other variations in the model utilized have sourced from differences in the nicotine dose utilized, the age at which the animal behaviors were assessed, the behavioral tests which were employed, and the time during pregnancy at which nicotine exposure occurred. This later point is relevant to physiological, peripheral effects engendered by first time exposures to nicotine, and concern of induction of stress, which is known to induce neural changes in offspring and maternal behaviors, as nicotine can be aversive in drug naïve individuals. If the first-time exposure occurs to the pregnant dam during the

gestational period, which has been necessary in experimental designs when pumps with limited lifetimes have been utilized, the confound of stress' role in physiological responses complicate attribution of effects to nicotine. As it is known that sex plays a role in PNE behavioral outcomes, interpretation of data where sexes have been pooled, or extrapolation to the opposite sex when single sex selective studies have been conducted, limits applicability of the data. These and other variables inherent to any laboratory study with rodents make it difficult to compare results across studies and further complicate determination as to which is the superior model in order to make conclusions relevant to the human situation [see[115] for a full discussion of the issue].

Despite these complications, examination of results from many PNE studies has led to the conclusion that the most robust rodent model of PNE is the oral nicotine intake method during pregnancy[115]. Arguments for this model include that it reflects pharmacodynamics/kinetics observed in human smokers, ADHD- and addiction-related behaviors have been seen in the rodent offspring with features similar to those seen in humans exposed to nicotine *in utero*, the nicotine exposure pattern is very similar to that seen in humans as it occurs during wakefulness, and stress levels are minimized, as no manipulations or surgical procedures are required. Finally, it avoids the issue of first-time exposure to nicotine to the dam occurring during gestational periods, which could introduce confounding factors. Accordingly, this model has been utilized by many laboratories to examine alterations in excitatory signaling within several brain regions associated with PNE. Further, in work conducted in the LDT, an outbred strain of mouse, the Naval Medical Research Institute (NMRI) mouse, was used in our investigations in order to attempt to reflect better the genetic diversity of the human population.

Behavioral alterations in PNE rodent models and in humans exposed gestationally to nicotine

Validation of the PNE NMRI model *via* maternal drinking water model was provided by evaluation and detection of high cotinine levels in newborn PNE pups, confirming the gestational nicotine exposure of the fetus following maternal ingestion of nicotine *via* the drinking water[116]. Behavioral tasks were also employed in order to characterize the behavioral phenotype associated with early-life exposure to nicotine *via* the drinking water[116]. Although an extensive review of the behavioral deficits associated with PNE treatment in rodents is beyond the scope of this article, it is of interest when comparing dysfunctions of behaviors in which the LDT plays a role to compare sex-based findings of PNE-associated effects on affective state, cognition, and locomotion in the NMRI mouse exposed to nicotine *via* maternal drinking water with data from other laboratories using different PNE models, and with human clinical data, in order to evaluate the face validity of the oral NMRI PNE model.

Anxiety and PNE: Within young adulthood [postnatal day (PND)42-48], PNE treatment in NMRI mice was associated with anxiety-like behaviors that were effects only seen in male offspring[116]. In inbred C57BL/6J mice exposed to nicotine *via* maternal drinking water, anxiety levels of males have been reported to be increased[114,117]. However, it appears that the nicotine concentration is relevant for the anxiolytic action, since in another study using lower concentrations PNE did not alter anxiety levels in the offspring[118]. The method of nicotine administration is also likely important, as failure to detect anxiolytic-like behavior is common in studies in which nicotine was administered subcutaneously[119-121]. Early life exposures to nicotine have been suggested to heighten the risk of anxiety disorders in humans[122]. However, very few studies have been conducted examining the influence of smoking during pregnancy on anxiety in offspring, and in those conducted, mixed results have been reported with no gender segregation[123-125]. In perhaps the largest and well-characterized cohort examined, the Norwegian Mother and Child Cohort (1999-2009), maternal smoking was associated with an increase in externalizing behaviors, including anxiety; however, unfortunately, sex-based effects were not taken into account[122]. Interestingly, a larger impact was noted when the amount of cigarettes was considered as well as the time during gestation when smoking was present, with a more negative effect on anxiety the earlier nicotine was present in the pregnancy. This later finding was supported by a study of a much smaller population of Australian mother and child pairs[124-126]. In conclusion, while an enhanced risk of anxiety-like behavior remains a point to be examined in both human and animal studies, available data suggest that the PNE mouse model, in which nicotine is provided in the drinking water, represents a reasonable, translational model that can be used to study the mechanistic neural link between anxiety and PNE.

Hyperactivity and PNE: The oral administration method of PNE in NMRI mice was associated with hyperactivity in the offspring of both sexes in the open arena test (PND42-48)[116]. When nicotine was delivered *via* drinking water to pregnant rodent dams in other studies, PNE treatment was associated with hyperactivity in males, albeit some data showed that this effect could be present in both sexes or it could be linked to the genetic background of the mouse employed[114,127-130]. Differences can also be due to strain, as in a study using outbred mice, hyperactivity was seen in male PNE Swiss mice during late adolescence[119]. Further, it is relevant to consider the nicotine concentrations employed to draw associations between PNE and locomotor behavior, as no locomotor effects were seen in both sexes in a study employing a lower nicotine level before and during pregnancy[118], contrasting with previous findings showing PNE hyperactivity in similar models and ages investigated when higher doses of nicotine were utilized[116,127,130,131]. Although one study reported greater hyperactivity in 3-year-old

boys following exposure to tobacco during gestation[132], another study suggested that prenatal tobacco exposure could have a causal relationship with hyperactivity seen in both adolescent and adult women[8]. Thus, the sex-dependency of hyperactive effects on offspring following PNE in experimental studies and prenatal tobacco exposure in clinical investigations is still unclear. Further, sex-dependent effects on motor activity of nicotine exposure *via* e-cigarette usage during pregnancy need to be examined as neurobehavioral evaluation of a small population of neonates exposed to e-cigarettes reported abnormal motor reflexes linked to later life motor development that were similar to those seen in prenatally cigarette exposed infants[133]. The small sample size precluded sex-based comparisons.

Cognitive deficits, ADHD, and PNE: In the oral PNE NMRI model, poorer outcomes have been detected in the spontaneous alternate behavior test, which is a Y-maze based test quantifying performance of a cognitive-dependent behavior. Scores indicative of cognitive impairments and working memory deficits were found in both sexes in young adult NMRI PNE offspring. In the outbred NMRI PNE model, both male and female offspring displayed deficits in the percentage of correct alternate behavior in the Y-maze, suggesting deficits in hippocampal-dependent working memory[116]. Moreover, this same model was associated with performance impairments in the rodent continuous performance task, particularly in scores related with learning, impulsivity, and attention, but only male offspring were investigated[134]. In inbred mice in which nicotine was delivered *via* drinking water of pregnant dams, deficits in the spontaneous alternate behavior performance assessed in adult offspring were seen only in males[118,135]. However, another study using twice the concentration of nicotine in the same inbred strain found that PNE cognitive deficits in this test were present in both PNE males and females[131], suggesting that the concentration of nicotine given could play a role in the sex-dependent outcomes. Further, young adult rats exposed prenatally to nicotine through the drinking water displayed impaired performance in another test of working spatial memory, the radial maze test. This effect was seen in both sexes[136], but little or no effect was found in PNE models using minipumps or subcutaneous injections[137-139]. A higher risk of cognitive deficits has been found in children born from pregnant smokers[9,12,140]. This association was also found in a study with a cohort of 574 children born from mothers who used NRTs during pregnancy[141]. Additionally, children prenatally exposed to smoke exhibited alterations in cognitive control circuitry and exhibited attention dysfunctions[142]. When taken together, the data strongly support the conclusion that nicotine during the prenatal period is associated with cognitive deficits. PNE individuals show up to a three-fold higher risk of ADHD, and a strong association has been made between nicotine levels in the mother during the first and second trimesters and diagnosis of ADHD[9]. Interestingly, ADHD has shown a sex bias, with reports of the male/female ratio being 4:1. However, carefully controlled, large population studies indicate the ratio is more likely 2:1 in adolescence, which was a proportion maintained into adulthood, leading the authors to suggest the possibility that males exhibit a greater level of hyperactivity/impulsive symptoms that are disruptive than manifestations of these behaviors in females, and that female ADHD behaviors tend to be more cognitive-based and require more probing to detect[143]. Although clinical studies have employed both sexes to draw associations between prenatal tobacco exposure and ADHD, sex-dependent effects in the offspring were not taken into consideration to date in these studies, as genders were pooled together[144]. Our findings and others suggest that perhaps more clinical investigative attempts to identify and better recognize ADHD symptoms, especially in females, are warranted.

Conclusions on the animal models of PNE: In conclusion, we found a greater level of anxiety, locomotion, and cognitive deficiencies, with sex-specificity regarding emotional behaviors, in young adult NMRI mice prenatally exposed to nicotine *via* the drinking water[116,134]. The behavioral associations seen reproduced some of the relevant features observed in ADHD patients, which are associated with exposures prenatally to nicotine. When taken together, behavioral outcomes associated with PNE models in which gestational nicotine exposure occurs *via* maternal drinking water suggest that this model provides reasonable face validity relative to others by recapitulation of risk outcomes of individuals exposed to prenatal tobacco which have been seen in epidemiological investigations. This conclusion leads us to suggest that this model displays high translational potential for research focused on the connection of developmental exposure to nicotine to later-life appearance of ADHD-associated symptoms,= as well as in the search of relevant brain circuit alterations that could contribute to this phenotype. Studies using other rodent models of PNE have provided data that these models do exhibit characteristics of drug dependence and in some cases, recapitulate sex-differences seen in humans[3,145-147]. However, whether the NMRI PNE drinking water model exhibits features seen related to drug dependence and whether sex-based differences exist remains an open question which must be experimentally addressed.

SYNAPTIC AND CELLULAR ALTERATIONS IN PNE LDT NEURONS

The oral administration PNE NMRI model has demonstrated many of the behavioral risks associated

with gestational nicotine exposure in humans that could involve the LDT, and other models of PNE have shown the heightened risk of drug dependency, suggesting a role of nicotine in this outcome. This model has been utilized to explore the molecular changes occurring in the LDT during development when nicotine is present in order to gain insight into alterations that could contribute to the behavioral risks found in PNE individuals in which this brain stem nucleus is implicated.

Cholinergic signaling is altered in PNE LDT neurons

We have reported that gestational exposure to nicotine induces cellular changes in cholinergic signaling within the LDT that are findings in line with other studies, which have shown alterations in players in cholinergic transmission in diverse regions of the brain using alternative PNE models[145,148]. Indeed, reductions in the expression of nAChRs in different regions of the PNE brain, including the brain stem= as well as lower striatal and cortical DA levels[149-151], led to the suggestion that alterations in nAChRs induced by PNE are involved in dysfunctions in DA functioning in these regions underlying the higher drug dependence and ADHD risks in PNE individuals[152], which could involve changes in function of nAChRs in the LDT. Consistent with this, we have provided evidence that PNE is associated with alterations in functioning of nAChRs in the LDT. Nicotine application *ex vivo* in LDT-containing brain slices resulted in significantly smaller rises in calcium in LDT cells from PNE individuals when compared to rises elicited in control LDT cells. Further, in the PNE LDT, a reduced proportion of cells responded with rises in calcium upon nicotine application[153]. Although the mechanism of altered nAChR-stimulated calcium was not examined, changes in calcium responses seen could be due to reductions in numbers of nAChRs and/or could be due to alterations in nAChR subunit composition, as the subunit composition determines calcium permeability.

Glutamate signaling is altered in LDT neurons of PNE mice

Glutamate transmission was also altered in the LDT of PNE mice, which has been seen in other regions of the rodent brain examined across several different PNE models. Glutamate mediates fast excitatory transmission *via* actions at three ionotropic receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartate (NMDA), and kainate. AMPA receptors (AMPARs) are tetramers composed of different assemblies of subunits (GluA1-4)[154], exhibit widespread expression in the brain, and are the major mediators of fast glutamate synaptic transmission[155]. Further, expression of AMPAR subunits follows a distinct ontogenetic pattern, which suggests specific functional roles at different periods during development. In the rat hippocampus, GluA1 expression remains constant until young adulthood, whereas GluA3 increases, and both GluA2 and GluA4 expressions are reduced over time[156], with GluA2 expression mostly limited to interneurons[157]. Within the VTA, electrophysiological evidence has suggested that GluA2-lacking AMPARs are abundant during the first postnatal days with a reduction in functional presence across age, with similar findings in cortical pyramidal cells and other brain areas[158-160]. NMDA receptors (NMDARs) are composed of heteromeric assemblies of GluN1-3 subunits, with obligatory presence of GluN1 with four GluN2 (GluN2A, GluN2B, GluN2C and GluN2D) and two GluN3 (GluN3A and GluN3B) possible isoforms. NMDAR subunit expression levels also shift during ontogeny, particularly among GluN2 and GluN3 subunits. GluN2A expression starts after birth, with a steady rise during development so that levels are at their highest in the adult brain. GluN2B/D subunits are expressed during the intra-uterine period, with GluN2B expression maintained at high levels up to the first postnatal week, and progressively decreasing in expression across age, culminating gradually in a limited restriction of presence within the forebrain, whereas GluN2D is markedly reduced in expression immediately after birth. GluN2C subunits appear late during development, at PND10, and exhibit a restricted expression and are primarily found within cerebellum and olfactory bulb. Finally, GluN3A subunits increase expression following birth, but thereafter, decline progressively to low levels; whereas, conversely, GluN3B expression shows a slow and steady increase throughout development[161-164].

Investigations from other laboratories have reported alterations in glutamate receptor subunit expression from expected patterns in the PNE brain. Differences in levels of expression of the GluA2, GluN1, and GluN2C subunits were seen in the PNE hippocampus at PND63 following osmotic pump-mediated PNE for 14 gestational days, whereas changes in glutamate signaling-related molecules were observed at younger ages[165]. Using a similar PNE model in which nicotine exposure was also provided by osmotic minipumps, a reduced expression of GluA1 subunits, smaller amplitudes in glutamate-mediated, miniature postsynaptic excitatory currents, reduced long-term potentiation, and increased long-term depression in hippocampal CA1 neurons associated with PNE treatment were reported[166-168]. As changes in synaptic strength are mediated by alterations in AMPA and NMDA receptor functioning, PNE-associated differences in long-term potentiation and long-term depression suggest changes in the functionality of glutamate receptors. Further, PNE from gestational day 5 was associated with a reduced frequency of excitatory postsynaptic currents and altered AMPA-mediated synaptic transmission in hypoglossal motoneurons in brain slices from rat neonates[169,170]. In addition, reduced glutamatergic input was found in the PNE auditory brainstem[171]. Finally, gestational nicotine exposure was associated with suppression of progenitor cell differentiation in the glutamatergic-projecting granule cells within the hippocampal dentate gyrus at PND21 in rats[172] as well as with the impairment of progenitor cell proliferation during gestation, resulting in reductions in

the availability of pyramidal glutamate neurons within the postnatal medial PFC in mice[173]. Overall, these studies indicate that the teratogenic effects of nicotine can affect glutamate signaling in different brain regions, which could affect both pre- and postsynaptic mechanisms in neuronal circuits.

Our studies in the LDT extend the observations of PNE effects on glutamate functionality. When the effects of PNE treatment in the NMRI model in male offspring were examined, early life exposure to nicotine was associated with larger, AMPA receptor-mediated intracellular calcium rises and inward currents in LDT cells (Figure 3)[174]. Pharmacological examination suggested a delayed switching of GluA2-lacking AMPA receptors in PNE LDT neurons, suggesting a time lag in appropriate development of AMPA receptors associated with early exposure to nicotine. Presynaptic release of glutamate was lower in PNE LDT cells, which would contribute to reductions in postsynaptic excitability of these neurons[174]. Notably, an unpublished observation in our group was that, despite the finding that PNE LDT neurons exhibited significantly higher AMPAR-stimulated current amplitudes, enhanced membrane responsiveness was not sufficient to activate these neurons to fire action potentials to the same extent as observed in control cells, further suggesting reduced excitability. NMDA receptors in the LDT were also shown to be associated with alterations in functionality following PNE. Our data indicated that PNE was associated with changes in both synaptic and extrasynaptic NMDAR function, which was cell-type specific. In putatively GABAergic inhibitory LDT cells, PNE treatment was associated with higher functional presence of GluN2B-containing synaptic NMDARs and higher levels of silent synapses, without major functional effects detected in extrasynaptic NMDARs. Further, putatively cholinergic cells displayed reduced functional presence of GluN2B subunits in synaptic NMDARs, and changes in extrasynaptic NMDARs[175]. Our electrophysiological findings were in line with a previous calcium imaging study conducted in our group that did not include electrophysiology, suggesting lower intracellular calcium increases upon a second bath application of NMDA, which was interpreted to reflect a shift in properties of NMDARs in LDT cells following PNE treatment[176].

Membrane property differences leading to alterations in excitability

Passive and active properties of cholinergic neurons of the LDT were also examined in the PNE as membrane properties underlie cellular excitability. Lower neuronal excitability among LDT cells in PNE mice was exhibited in several different paradigms. PNE LDT neurons exhibited a higher rheobase, which is defined as the minimum amount of current necessary to elicit an action potential[177], and smaller activity-induced rises in calcium putatively due to PNE-associated alterations in voltage-operated calcium channels, although this point was not directly examined[174]. Examination of the action potential revealed a broader spike in the PNE, due to a slower decay slope that was likely reflective of differences in ionic conductance underlying the kinetics of the rise and decay times. Further studies revealed data consistent with a reduction in function of K^+-channels activated by Ca^{+2}[174]. In addition, the amplitude of the afterhyperpolarization was significantly larger in the PNE, which also suggested alterations in ionic conductance[153]. When taken together, the effects on the kinetics of the action potential and the amplitude of the afterhyperpolarization would likely result in a limitation in the firing frequency.

Summary of the impact of cellular changes associated with PNE in the LDT

In summary, our studies of PNE LDT neurons found reductions in membrane excitability, effects on the action potential kinetics and the amplitude of the afterhyperpolarization that likely resulted in limitations in firing frequency, reductions in nAChR-induced calcium rises suggestive of a reduction in excitability mediated by nAChRs, and changes in glutamate signaling that would lead to decreases in excitability in cholinergic neurons, with concurrent increases in activity of GABAergic cells, which could be local or projection neurons. Interestingly, some of these changes were present in young animals but did not persist into adulthood, suggesting that nicotine-associated alterations in development of LDT transmission would result in changes in output that would participate differentially across ontogeny and thereby, affect neuronal excitability differentially across age. When taken together, our studies have led us to the working hypothesis that PNE is associated with a hypofunctioning LDT, which would lead to reductions in output of excitatory neurotransmitters onto projection targets, including those within the VTA, NAc, and thalamus.

LDT TARGETS INVOLVED IN DA-MEDIATED BEHAVIORS: RELEVANCE TO THE HIGHER RISK OF DRUG DEPENDENCE AND ADHD AFTER PNE

Reductions in cholinergic transmission from the LDT to target areas would be expected to have a significant effect on behaviors controlled by those target regions. Data from the oral NMRI PNE model have led to our development of the 'hypocholinergic hypothesis', and predictions from this hypothesis could mechanistically play a role in adverse behavioral outcomes associated with PNE.

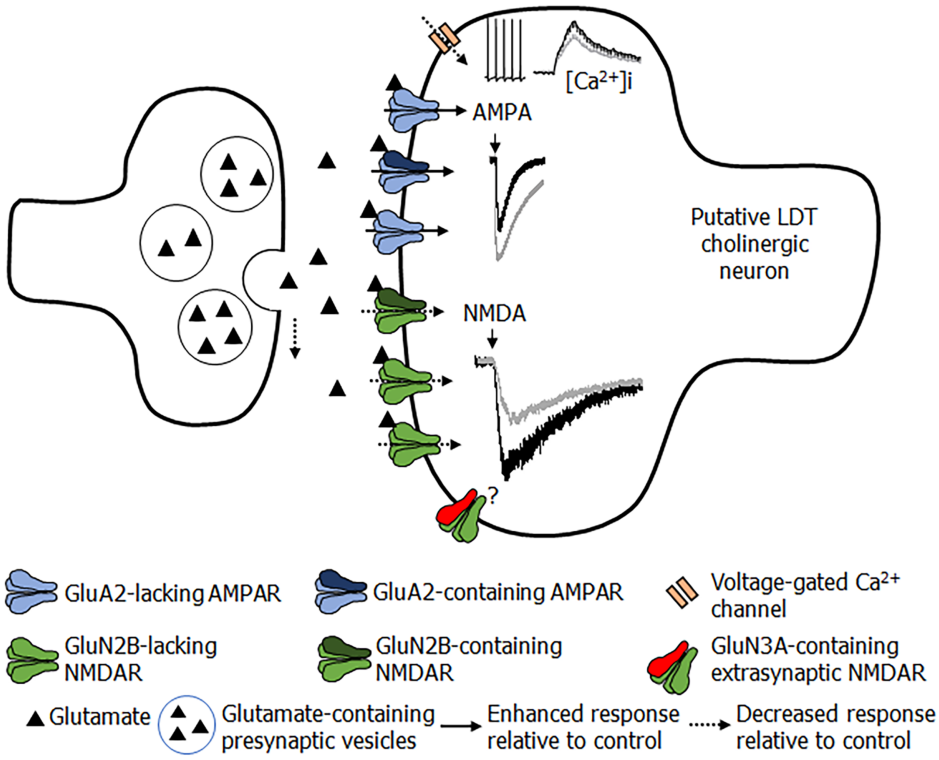

Figure 3 Overview of input sourcing from cognitive and limbic regions synapsing within the Laterodorsal tegmental nucleus. PFC: Prefrontal cortex; Hippoc: Hippocampus; NAc: Nucleus accumbens; VTA: Ventral tegmental area; LDT: Laterodorsal tegmental nucleus.

Drug dependence and the hypocholinergic hypothesis

PNE has been associated with a higher risk of later life development of drug dependence, especially to nicotine as well as a higher risk of drug experimentation and abuse, which is an association seen in studies correcting for confounds such as maternal cigarette consumption after birth[2-5]. Importantly, an increased risk for nicotine dependence was also seen in investigations including sibling-pairs discordant for prenatal tobacco exposure that were controlled for such confounds as postnatal maternal smoking, which linked prenatal cigarette exposure with increased liability for nicotine addiction[178-180]. Gestational exposure to nicotine has been associated with a higher likelihood for abusing drugs, particularly during the adolescent time, including marijuana and cocaine, which is only explained in part by increased experimentation during the adolescent period and incomplete development of cortical regions of the brain[6,181]. An association has also been found during adulthood, in which gestationally-exposed young adults displayed significantly higher rates of cigarette smoking and nicotine dependence, which has been shown in independent studies[3,182].

As burst firing in mesoaccumbal circuits leads to behaviorally relevant levels and temporal patterns of DA in the NAc, which signal salience and engender continued usage of drugs, if PNE was associated with alterations in DA VTA burst firing engendered by exposure to drugs of abuse, or endogenous rewarding stimuli, this could alter coding of salience to the triggering stimuli. Interestingly, PNE was associated with alterations in the burst firing pattern of DA-VTA neurons of adolescent rats who were exposed to nicotine prenatally *via* mini-pump implantation[183], and several different models have identified an association between PNE treatment with lower DA release within the striatum[149,151,184]. When findings from these and other PNE cellular studies conducted in the VTA are taken together with our PNE LDT data, it is tempting to speculate that since the LDT is a critical modulator of burst firing in the VTA[77], PNE-associated alterations in LDT excitability are likely involved in differences seen in VTA neuronal firing in PNE. As a working hypothesis, our LDT cellular data have led us to propose that the alterations seen in the PNE LDT would result in a reduced cholinergic tone into target brain areas upon activation of the LDT following exposure to drugs of abuse. As ACh is excitatory to DA VTA neurons, among other consequences, a hypocholinergic tone from the LDT in PNE individuals would be expected to reduce, or at least drastically alter, behaviorally relevant, excitatory drive mediated, phasic DA VTA firing in response to stimuli. This hypothesis is also in line with very recent findings that inhibition of cholinergic transmission from the LDT influences neuronal firing of striatal neurons, associated with blockade of goal-directed behaviors, resulting in a more habitually-directed brain reflective of reduced flexibility in development of action strategies[18]. This hypothesis is somewhat in line with the 'hypoexcitability hypothesis' of drug dependence, which postulates that individuals with a higher liability for drug dependence possess a hypodopaminergic function within the mesolimbic circuit, a condition that could be due to genetic and epigenetic factors as well as *in utero*

insults, including drug exposure[178,185-188]. Arguably, hypodopaminergic functioning within the mesoaccumbal circuit could lead to a bias towards coding a relatively higher reward value upon drug intake when compared to natural rewards, or when compared to coding conferred by normal functioning of the mesolimbic circuit[189], and this higher reinforcement could underlie continuous usage and engender escalation in drug consumption[190,191]. Further, a progressive development towards a switch to habitual and non-flexible responses to stimuli, rather than development of novel adaptive strategies integrated within experienced behaviors, has been noted as a feature of drug dependence, although drug dependency can be seen perhaps more correctly as an imbalance between habit and goal-directed behaviors[192]. Neuroimaging studies are in line with our hypothesis, since a weaker response in striatum to reward anticipation was noted in adolescents born to smoking mothers, which was suggested to contribute to an increased risk factor for substance dependence[193]. Although our hypothesis requires experimental validation, it places the PNE-associated changes in the LDT as critically involved in the negative behavioral outcomes related to a higher risk of drug dependence in this population.

ADHD and the hypocholinergic hypothesis

PNE has also been associated with a higher risk of later life development of ADHD-like behaviors. Modulation of catecholamine levels within the PFC has provided compelling experimental evidence of the role of DA pathways in impulsivity and attention deficits in behavioral performances[87,89,90]. Studies employing the PNE model in which nicotine was delivered *via* drinking water reported a reduced DA content in the PFC of adolescent male PNE mice[151], which corroborates findings of lower levels of DA in the cortex associated with PNE induced by minipump nicotine delivery model, an effect more pronounced at juvenile and adolescent stages[184], but which does not support findings in a later study with the minipump method in which DA levels were greater in the PFC of males and female offspring; however, the turnover ratio from DA to the DA metabolite homovanillic acid (HVA) was reduced only in the PNE males, suggestive of a sex-based PFC DA alteration[194]. Gestational tobacco smoke exposure was associated with a reduction in the DA and tyrosine hydroxylase levels within the striatum of PTE adult mice[149]. In adult PNE mice born to mothers exposed to nicotine *via* the drinking water, microdialysis of medial PFC showed reduced basal extracellular levels of DA[151]. Reductions in tyrosine hydroxylase, which catalyzes the conversion of L-tyrosine to L-DOPA, a precursor of DA, were detected using immunohistochemistry in DA-positive cells in the medial PFC and in the NAc core and shell in PNE animals[151].

As further evidence that alterations in DA signaling might be a common outcome following PNE, diminished levels of HVA were noted in the PFC in the mouse and rat PNE[151,195], which interestingly, while seen in the males of another study, was not noted in the female mice in that same work[194]. As lower HVA levels in spinal fluid and urine has been seen in clinical studies with both children and adult ADHD patients[196,197], alterations in DA turnover in the PFC could represent a common signaling dysfunction in both PNE and ADHD individuals. Accordingly, alterations in DA levels within the PFC seen in PNE rodents could underlie the higher risk of ADHD-type behaviors following early life exposure to nicotine. While it remains to be explored, alterations in LDT output to the DA cells of the mesocortical pathway could be involved in alterations of DA release in the PFC and NAc, which could represent a circuit-based alteration with great relevance for the heightened risks seen in PNE individuals to the development of ADHD. In line with this possibility, imaging studies on ADHD individuals have reported reduced activation of the ventral striatum in response to rewards, which is a similar response detected following PTE[193,198].

The thalamus and the hypocholinergic hypothesis

The ascending cholinergic projections which encompass LDT output to thalamic regions suggest that the LDT could play a role in cognitive functions by modulating cortico-projecting thalamic neurons. Therefore, changes induced by gestational nicotine associated with synaptic alterations in the LDT could lead to alterations in cholinergic output terminating in the thalamus, which could also play a role in ADHD-like phenotypes associated with PNE. Interestingly, it has been hypothesized that alterations in cholinergic signaling in corticothalamic circuits induced by PNE could underlie deficits in sensory processing, contributing to the behavioral alterations seen in these individuals in response to environmental stimuli, including ADHD related behaviors[199]. The majority of studies of effects of PNE on cholinergic transmission in cognition-associated regions have focused on alterations in nAChRs; however, deficits suggestive of reduced cholinergic transmission were noted in cerebral regions[145,199]. When taken together, PNE-induced alterations in neuronal excitability and cholinergic and glutamate signaling within the LDT nucleus presumably affect LDT cholinergic input to thalamic relay nuclei. Our working hypothesis is that cholinergic output from the LDT to targets including those within the thalamo-cortical circuit is reduced in PNE, altering cortical activation in this network, leading to higher risks in this population of negative, cognitive behaviors controlled by the cortex. This conclusion is paralleled by findings of a reduced activation of the thalamus seen in conditions exhibiting poor impulse control characteristic of both ADHD and drug dependence[108]. Interestingly, PNE-associated alterations in cortical transmission were found to be sex-dependent, with a striking effect in males[145]. Although females were not as affected, PNE appeared to sensitize females to a greater

extent as they exhibited poorer cognitive outcomes upon later life exposure to nicotine when compared to those in males[145]. In summary, PNE-induced alterations in excitability, cholinergic, and glutamate signaling within the LDT nucleus would presumably affect LDT cholinergic tone present in thalamic centers leading to a dysfunction in thalamo-cortical brain circuits. This dysfunction in input could lead to altered processing of sensory stimuli and to cognitive deficits seen in ADHD present in those gestationally exposed to nicotine. Further, while this effect might be more prominent in males, early life exposure appears to leave behind a liability in females, in that later life exposure to nicotine could result in reductions in cholinergic transmission, which could have deleterious behavioral consequences on processes controlled by cortico-thalamic loops.

CONCLUSION

While the brain stem might not be the obvious neural target in studies interested in cognitive processing, or in studies focused on cognitively-based disorders, over time, irrefutable evidence of the role the LDT plays in cognitive processes has been provided, and accordingly, alterations in LDT neuronal output could play a significant role in dysfunctions of cognitively-based behaviors. As regions of the brain known to modulate psychomotor, reward, memory, and attentional behaviors[93,200-202] are altered in PNE, and since the LDT exerts direct or indirect control over these regions, it would be expected that changes in glutamate and cholinergic receptor signaling, as well as in excitatory membrane processes in this nucleus seen in experimental models of gestational exposure to nicotine, would lead to reductions in excitatory cholinergic and glutamatergic output from the LDT to target regions. This scenario would lead in the PNE to a hypodopaminergic midbrain function, lower cholinergic tone in the NAc, and reduced cholinergic strength within ascending reticular activating system participating pathways to thalamic relay centers. Many of the regions targeted by LDT afferent input are DA releasing, which strongly suggests that DA release would be altered, as has been seen in the PNE brain. In addition, ACh stimulatory input to thalamic nuclei that control the cortex, including the PFC, would be altered, implying that changes in DA are also likely to be accompanied by non-DA changes due to PNE-associated differences in cholinergic tone within cortico-thalamic circuits. Finally, resulting postsynaptic processing of afferent input to the LDT would be altered, as cellular changes impacting on synaptic integration would likely be affected in this nucleus. Given the neural regions under control by activity of the LDT, PNE-associated alterations in LDT function would likely contribute to the enhanced risk of drug dependence and ADHD-like behaviors seen in PNE individuals, placing the brain stem as notably involved in these cognitively-based risks following PNE.

Increases in magnetic strength is allowing functional magnetic resonance imaging to reveal unprecedented details of the human brain, and as improvements are made in spatial resolution, it may become possible to conduct studies in humans to evaluate potential structural changes in LDT in PNE. Moreover, powerful *in vivo* electrophysiological techniques such as utilization of Neuropixels probes have emerged, allowing unprecedented recordings of deep brain structures in rodent models. Future studies employing *in vivo* electrophysiology, pharmacology, and optogenetic approaches in animal models should be used to determine the extent of LDT involvement in demonstrated PNE-induced alterations of midbrain DA functioning. Such studies could also dissect the effects of the LDT-thalamo-cortical pathway in cognitive and behavioral control. If our working hypothesis of PNE-associated reductions in ACh transmission sourcing from the LDT is confirmed, data obtained from future studies could identify a target brain substrate for therapeutic interventions involving cholinergic function within the LDT to VTA, NAc, and thalamic circuits in order to ameliorate drug dependence and ADHD-like associated behaviors, such as those seen in PNE individuals.

FOOTNOTES

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REVIEW

Drug-induced stuttering: A comprehensive literature review

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Abstract

Drug-induced stuttering (DIS) is a type of neurogenic stuttering (NS). Although DIS has not been reported as frequently as other cases of NS in the literature, it is not a negligible adverse drug reaction (ADR) which can significantly affect the quality of life if not treated. This literature review aims to evaluate the epidemiological and clinical characteristics of DIS and suggests some pathophysiological mechanisms for this ADR. Relevant English-language reports in Google Scholar, PubMed, Web of Science, and Scopus were identified and assessed without time restriction. Finally, a total of 62 reports were included. Twenty-seven drugs caused 86 episodes of stuttering in 82 cases. The most episodes of DIS were related to antipsychotic drugs (57%), mostly including clozapine, followed by central nervous system agents (11.6%) and anticonvulsant drugs (9.3%). The majority of the cases were male and between the ages of 31 and 40 years. Repetitions were the most frequent core manifestations of DIS. In 55.8% of the episodes of DIS, the offending drug was withdrawn to manage stuttering, which resulted in significant improvement or complete relief of stuttering in all cases. Based on the suggested pathophysiological mechanisms for developmental stuttering and neurotransmitters dysfunctions involved in speech dysfluency, it seems that the abnormalities of several neurotransmitters, especially dopamine and glutamate, in different circuits and areas of the brain, including cortico-basal ganglia-thalamocortical loop and white matter fiber tracts, may be engaged in the pathogenesis of DIS.

Key Words: Drug; Dysfluency; Dysphemia; Psychotropics; Speech; Stammering

Core Tip: Stuttering has two main types, developmental and acquired stuttering. Acquired stuttering is a manifestation of psychogenic or neurogenic disorders. Neurogenic stuttering is caused by brain injury, stroke, drugs, *etc.* Because most drugs inducing stuttering are used in the management of psychiatric and/or neurologic disorders, clinicians may merely attribute a new-onset stuttering to the worsening of the underlying disorder and neglect drugs as the causes of stuttering. Therefore, in this review, reports of drug-induced stuttering (DIS) are collected to provide information about epidemiological and clinical characteristics of DIS. Moreover, some pathophysiological changes are proposed as the underlying mechanisms of DIS.

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INTRODUCTION

Speech production is a complex process involving various areas of the brain. Stuttering is a fluency disorder classified as developmental or acquired stuttering. Developmental stuttering, which is mentioned as childhood-onset fluency disorder in the diagnostic and statistical manual of mental disorders, fifth edition[1], often manifests between the ages of 2 and 6 years and spontaneously remits in most cases[2,3]. Acquired stuttering which has a secondary cause can occur in both children and adults. There are two types of acquired stuttering, psychogenic and neurogenic stuttering (NS). NS is caused by the traumatic brain injury, stroke, neurodegenerative disorders like Parkinson's disease (PD) and multiple sclerosis, seizure disorders, drugs, *etc.*[4]. In contrast to the other cases of NS, in which injuries to the brain areas involved in the speech production result in neuroanatomical and neurochemical abnormalities leading to stuttering, in the cases of drug-induced stuttering (DIS), short intervals between the initiation of culprit drug and the occurrence of stuttering and also between the dose reduction or discontinuation of the drug and the relief of stuttering suggest that DIS may be caused merely by neurochemical changes in the brain[5].

Although DIS has not been reported as frequently as other cases of NS in the literature, it is not a rare and negligible adverse drug reaction as Trenque *et al*[6] have reported that 724 individual case safety reports (ICSRs) containing the lowest level terms "stuttering" or "stutter" have been registered in Vigibase, the world health organization international pharmacovigilance database, up to May 31, 2020. The aim of this review is to describe the reported cases of DIS, including their demographic characteristics, medical history, predominant manifestations of stuttering, and the interventions done to manage stuttering and propose some probable pathophysiological mechanisms of this type of NS.

SEARCH STRATEGY

The electronic databases Google Scholar, PubMed, Web of Science, and Scopus were searched by two reviewers without time limitation to find the relevant data. The keywords "stutter", "stuttering", "speech dysfluency", "drug-induced stuttering", "medication-induced stuttering", "psychotropics" "antipsychotics", "antiepileptics", "antiseizure drug", "anticonvulsants", "antidepressants", "clozapine", and "mood stabilizers" were used as search terms. The references of published articles were also examined to find any additional relevant reports. Case reports and case series were included. The reports whose full texts were not available and those being written in non-English language were excluded. According to the above-mentioned inclusion and exclusion criteria, 63 articles reporting DIS in 82 cases were considered in this review.

Twenty-seven drugs caused 86 episodes of stuttering in 82 cases. In four cases, two drugs caused stuttering[8-11]. Of 86 episodes of DIS, 49 (57%) were caused by antipsychotic drugs, followed by 10 (11.6%) by central nervous system (CNS) agents and 8 (9.3%) by anticonvulsant drugs (Table 1). As mentioned above, Trenque *et al*[6] have done a disproportionality analysis using reports registered in Vigibase to estimate the association between exposure to a drug and occurrence of stuttering. Of 22632669 reports registered in this database, 724 ICSRs contained the lowest level term "stuttering" or "stutter". Consistent with our findings, the most reports of stuttering were related to clozapine (n = 40), pregabalin (n = 33) methylphenidate (n = 27), adalimumab (n = 26), and olanzapine (n = 25)[6]. The results of the disproportionality analysis done by Trenque *et al*[6] showed that the following drugs had the highest reported odds ratio: Methylphenidate (19.57; 95%CI: 13.3-28.7); topiramate (12.48; 95%CI: 7.1-22.1); olanzapine (11.98; 95%CI: 8-17.9); golimumab (10.25; 95%CI: 5.5-19.1); clozapine (8.44; 95%CI: 6.1-11.6); and pregabalin (8.36; 95%CI: 5.9-11.9).

Table 1 Number of episodes of drug-induced stuttering reported in the online literature and included in the present review

Therapeutic category	Number of episodes of stuttering, *n* = 86 (%)
Antipsychotics	
Clozapine	30 (34.9)
Olanzapine	8 (9.3)
Risperidone	4 (4.6)
Aripiprazole	3 (3.5)
Trifluoperazine	1 (1.2)
Chlorpromazine	1 (1.2)
Fluphenazine	1 (1.2)
Levomepromazine	1 (1.2)
Anticonvulsants	
Phenytoin	2 (2.3)
Divalproex	2 (2.3)
Pregabalin	2 (2.3)
Gabapentin	1 (1.2)
Lamotrigine	1 (1.2)
Central nervous system agents	
Methylphenidate	3 (3.5)
Memantine	2 (2.3)
Levodopa	4 (4.6)
Dextroamphetamine and amphetamine salts (Adderall®)	1 (1.2)
Atomoxetine	1 (1.2)
Pemoline	1 (1.2)
Antidepressants	
Sertraline	3 (3.5)
Bupropion	3 (3.5)
Desipramine	1 (1.2)
Bipolar agents	
Lithium	3 (3.5)
Respiratory tract agents	
Theophylline	4 (4.6)
Anxiolytics	
Alprazolam	1 (1.2)
Antineoplastics	
Methotrexate	1 (1.2)
Pyrethrin	1 (1.2)
Total	86 (100)

DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS

Twenty-eight (34.6%) cases were female. Most patients were in the age range of 31 to 40 years. Fifteen cases were less than 12 years old. Gender and age of a patient were not reported in one case report[12] (Table 2).

Table 2 Demographic characteristics and clinical history of patients

Characteristic/history[1]	*n* (%)
Gender	
Female	28 (34.6)
Male	53 (65.4)
Age (yr)	
< 12	15 (18.5)
12-20	3 (3.7)
21-30	15 (18.5)
31-40	16 (19.7)
41-50	13 (16)
51-60	10 (12.3)
> 60	9 (11.1)
History of speech dysfluency	11 (13.4)

[1]The total number of the patients is 82, but the age and gender of one patient was not reported.

MANIFESTATIONS OF STUTTERING

The primary or core behaviors of stuttering include sound, syllables, and monosyllabic whole-word repetitions, sound prolongations, and speech blocks[4]. The core behaviors were described only in 40 cases. Repetitions (n = 42) were the most frequent primary behavior, followed by blockages (n = 21) and sound prolongations (n = 16). Twenty-one cases had more than one type of primary behavior (Table 3).

Individuals with developmental stuttering and persistent developmental stuttering (PDS) have anxiety related to stuttering[4]. However, patients with acquired stuttering may be annoyed by stuttering but do not experience anxiety. None of the reports included in this review described the psychological presentations of patients when producing a dysfluent speech.

Individuals with developmental stuttering[4,13] as well as patients with NS[13-15] often develop secondary behaviors including eye blinking, facial grimacing, interjections, word or phrase substitution, *etc*. The secondary behaviors are acts that are learnt in long term to cope with stuttering[13]. In the cases included in the present review, the secondary behaviors related to the stuttering were not reported. It may not be unusual because in comparison to the developmental stuttering, secondary behaviors are less prominent in the acquired stuttering[13]. Furthermore, we believe that since the development of the secondary behaviors requires a sufficient period, it is unlikely that patients with DIS have enough time to present these behaviors because interventions such as dose reduction or discontinuation of the culprit drug are carried out as soon as possible, which result in the complete relief or significant improvement of stuttering.

MANAGEMENT

Therapeutic measures that resulted in significant improvement or complete relief of stuttering were drug withdrawal in 48 (55.8%) episodes, dose reduction in 18 (21%), addition of a new drug in three (3.6%), addition of a new drug besides dose reduction of the culprit drug in three (3.5%), and slow dose titration in two (2.3%). Moreover, in three (3.5%) episodes, the stuttering spontaneously remitted despite continuation of the offending drug with no dose reduction[16-18]. However, three (3.5%) episodes did not respond to the dose reduction[19-21]. For four (4.6%) episodes, the authors did not describe the actions taken to manage stuttering[22-25]. In two (2.3%) cases with PDS and PD, stuttering was exacerbated during levodopa-on periods, and levodopa was not discontinued[26,27] (Table 3).

PATHOPHYSIOLOGY

In this section, the abnormalities suggested in the pathogenesis of developmental stuttering and PDS are described. Then, we propose some mechanisms for DIS based on the underlying impairments involved in the pathogenesis of PDS and developmental stuttering.

Table 3 Summary of the case reports of drug-induced stuttering

Offending drug (dosage)	Patients' gender/age (yr)	Main indication of drug administration	Concomitant medications (dosage)	Onset/aggravation of stuttering	Primary behaviors	Concomitant symptoms	Management, response	Recurrence of stuttering after medication resumption	Concomitant disorders	Ref.
Adderall XR® (20 mg/d)	Male/10	ADHA	No other drugs	Within two weeks after the initiation of Adderall XR®	Single word and syllable repetitions and audible/silent sound prolongations	Increased tic behaviors, increased levels of social anxiety and communication related frustration	DC of Adderall XR® and start of atomoxetine (10 mg/d), significant reduction of stuttering	NR	Developmental stuttering, Tourette Syndrome, allergies, chronic ear infections, frequent phonic and motor tics	Donaher *et al* [82]
Alprazolam (1 mg)	Female/22	Anxiety and depression	No other drugs	Shortly after increasing the dose	Not restricted to initial syllables, occurred on small grammatical words and substantive words, persisted during singing, not associated with secondary symptomatology such as facial grimacing or fist clenching	A right carotid bruit and a grade II/IV systolic murmur without a click, Minimal late systolic mitral valve prolapse and mild stenosis of both internal carotid arteries	DC of alprazolam, complete relief after two days	Within one hour after a single morning dose of 0.5 mg alprazolam, stuttering started, then 10 to 12 h later it was stopped. Stuttering did not happen with placebo	No history of speech dysfluency	Elliott *et al* [83]
Aripiprazole (2 mg/d)	Male/8	ADHD combined-type	Atomoxetine (25 mg/d)	After 10 d of starting aripiprazole	NR	NR	DC of Aripiprazole, complete relief	NR	Developmental stuttering	Ünay *et al*[84]
Aripiprazole (10 mg/d)	Male/11	Mild intellectual disability	No other drugs	4 wk after increasing the dose to 10 mg/d	NR	Addition of clonazepam 0.75 mg/d, no improvement. Reduction of aripiprazole dose to 5 mg, complete relief over 10 d	NR	Increasing the dose to 10 mg resulted in re-emergence of stuttering which responded to DC of aripirazole	No history of speech dysfluency	Naguy *et al* [85]
Atomoxetine (started at 25 mg/d and gradually increased to 40 mg/d)	Male/14	ADHD	No other drugs	Three weeks after the initiation of atomoxetine	NR	NR	Dose reduction to 25 mg/d, no improvement. DC of atomoxetine and initiation of methylphenidate, complete relief of atomoxetine-induced stuttering and	NR	Developmental stuttering since the age of 7 yr. ADHD predominantly inattentive	Cicek *et al*[86]

							considerable reduction of developmental stuttering			
Bupropion (SR) 150 mg BID	Female/59	Major depressive disorder	No other drugs	Four days after starting the drug	Sound prolongations, silent blocking, word production with excess physical tension, and monosyllabic whole-word repetitions. The stuttering was anxiogenic and restricted to initial syllables	Slight finger dysdiadochokinesia	DC of bupropion, complete relief of stuttering after 2 d	NR	No history of speech dysfluency	Fetterolf *et al* [78]
Bupropion SR (300 mg/d)	Male/38	Major depressive disorder	No other drugs	Two days after increasing the dosage from 150 to 300 mg/d	Involuntary silent pauses or blocks, repetitions, prolongations of sounds, syllables, and words, affected rhythm of speech	NR	DC of bupropion, complete relief of stuttering	Re-administration of bupropion 150 mg after 1 wk caused stammering, and the drug was stopped immediately	A history of occasional smoking, no history of speech dysfluency	Bhatia *et al* [79]
Bupropion XL (300 mg/d)	Male/53	Depression	No other drugs	After increasing the dosage of Bupropion	Difficulty starting words and repetition of syllables	NR	Administration of 5 mg oral haloperidol, stuttering was improved after 3 h and completely relieved after 7 h	Medication was continued	No history of speech dysfluency	McAllister *et al*[80]
Clozapine (up to 400 mg/d)	Female/32	Paranoid schizophrenia	No other drugs	4 wk after the initiation of clozapine	NR	Pharyngeal dystonia and buccolingual and facial dyskinesia associated with laryngeal dystonia	DC of clozapine, complete relief after 5 d	Clozapine was reintroduced at 100 mg/d. All symptoms reoccurred and relieved by clozapine cessation	History of neuroleptic-induced parkinsonism but not concomitant with dysarthria, no history of speech dysfluency	Thomas *et al* [63]
Clozapine (was initiated at 400 mg/d and gradually increased to 900 mg/d)	Female/28	schizoaffective disorder	No other drugs	Shortly after the initiation of clozapine at 400 mg/d and not relieved during the gradual increase in the dosage to 900 mg/d	NR	NR	Dosage reduction to ≤ 700 mg/d, complete relief	The dose was not increased again	No history of speech dysfluency	Ebeling *et al* [87]
Clozapine (450-750 mg/d)	Female/49	Psychosis	No other drugs	Stuttering was initiated when the clozapine dosage was	NR	Generalized seizure followed by myoclonic jerks of	The addition of phenytoin and then sodium valproate and	Clozapine was continued at 600 mg/d in addition to sodium	History of neuroleptic-induced acute	Supprian *et al* [59]

				increased to 700 mg/d		her arms at the clozapine dosage of 750 mg/d	the reduction of clozapine dosage to 600 mg/d, complete relief	valproate 900 mg/d with no recurrence of stuttering	dystonia, no history of speech dysfluency	
Clozapine (300 mg/d)	Male/28	Paranoid schizophrenia	No other drugs	Stuttering was initiated when the dosage of clozapine was increased from 150 mg to 300 mg/d and worsened with further increases in the clozapine dosage	NR	Generalized tonic colonic seizure at 425 mg/d along with the increased severity of stuttering	The reduction in the dosage of clozapine to 200 mg/d and addition of sodium valproate, significant improvement	The clozapine dosage was increased to 300 mg/d, but stuttering was not reoccurred albeit in the presence of sodium valproate 800 mg/d	No history of speech dysfluency	Duggal *et al* [64]
Clozapine (300 mg/d)	Male/57	Schizoaffective disorder	Lithium (900 mg/d), sodium valproate (600 mg/d)	Four days after the initiation of clozapine	NR	NR	Dose reduction and DC of clozapine, complete relief after 7 d	NR	History of alcohol dependency, diabetes mellitus, no history of speech dysfluency	Bar *et al*[15]
Clozapine (up to 500 mg/d)	Not mentioned	Schizophrenia	No other drugs	A few days after the initiation of clozapine at 300 mg/d	NR	Myoclonic jerks at night and facial tics	Addition of sodium valproate, significant improvement, reducing the dosage of clozapine from 500 to 300 mg/d, complete relief	Clozapine was not discontinued	No history of speech dysfluency	Begum *et al* [11]
Clozapine (700 mg/d)	Female/33	Schizophrenia	No other drugs	After reaching the daily dose to 700 mg (interval was not reported)	NR	Facial tics, seizure (seizure was initiated after the occurrence of stuttering)	Reduction in the dosage of clozapine to 600 mg/d, remarkable improvement, addition of sodium valproate to control seizure, no effect on stuttering	Clozapine was not discontinued	No history of speech dysfluency	Hallahan *et al* [58]
Clozapine (300 mg/d)	Female/34	Schizophrenia	No other drugs	2 wk after the initiation of clozapine	NR	Orofacial dyskinesia	Clozapine dosage reduction to 50 mg/d, complete relief	Clozapine was not discontinued	No history of speech dysfluency	Hallahan *et al* [58]
Clozapine (50-125 mg)	Male/62	Delusional disorder	No other drugs	NR	Unsustained phonation, hesitation, irregular articulatory break down, sound repetition (not related to any specific sound, occurred at irregular word positions)	Orofacial dyskinesia, laryngeal and pharyngeal tardive dystonia, harsh and strangulated voice	Addition of tetrabenazine, patient could not tolerate the clozapine dosages more than 100 mg/d, DC of clozapine, complete relief	Clozapine was not restarted	No history of speech dysfluency	Lyall *et al*[9]

Risperidone and then clozapine (450 mg/d and 75 mg/d)	Male/55	Schizophrenia	No other drugs	NR	Occasional blocking, prolongation on word-initial sounds and repetitions of speech elements including one-syllable words at the beginning of his speech utterances	Stammering and unusual limb and trunk movements related to risperidone, belching, persistent hiccupping, worsening of the facial tic, and the orofacial dyskinesia involving the lips and tongue related to clozapine	Risperidone-induced stuttering: NR, the first episode of clozapine-induced stuttering, dose reduction to 125 mg/d and cessation of clozapine; significant improvement and complete relief of stuttering; the second time of clozapine-induced stuttering: addition of sodium valproate, considerable improvement	Clozapine was restarted at 75 mg/d, recurrence of stuttering, the addition of sodium valproate, 600 mg/d, significant improvement in the stuttering	History of head injury resulting in problems with executive functioning and a significant discrepancy, between the patient's verbal and performance IQ, making various clicking noises and blowing sounds when speaking before the initiation of antipsychotic drugs	Lyall *et al*[9]
Clozapine (up to 600 mg/d)	Male/35	Schizotypal personality disorder	No other drugs	At clozapine dosage of 250 mg/d and progressive worsening with dose escalation	NR	NR	Reducing the dosage of clozapine to 200 mg/d, complete relief	Clozapine was continued at 200 mg/d without causing stuttering	History of trifluoperazine-induced truncal dystonia, no history of speech dysfluency	Krishnakanth *et al*[88]
Clozapine (200 mg/d)	Male/24	Paranoid schizophrenia	No other drugs	After increase in the dosage of clozapine to 200 mg/d	NR	NR	DC of clozapine, complete relief	Clozapine was not restarted, amisulpiride was started and did not cause stuttering	No history of speech dysfluency	Krishnakanth *et al*[88]
Clozapine (250 mg/d)	Male/23	Paranoid schizophrenia	No other drugs	At clozapine dosage of 250 mg/d (interval was not reported)	NR	NR	Clozapine dosage reduction to 150 mg/d, complete relief	Clozapine was not discontinued	History of neuroleptic-induced tardive dyskinesia, no history of speech dysfluency	Krishnakanth *et al*[88]
Clozapine (350 mg/d)	Male/15	Undifferentiated schizophrenia	Clomipramine (225 mg/d)	Three years after the initiation of clozapine and clomipramine	Repetitions of syllables and transient accelerations of speech rate	Involuntary paroxysmal perioral movements, facial tic-like movements, myoclonic jerks of the upper limbs, GTC seizure	Addition of valproic acid at 500 mg/d, complete relief of stuttering within days	Clozapine was continued with valproic acid without reoccurrence of seizure and speech dysfluency during 2 yrs of follow-up	Symptoms of obsessive-compulsive disorder, no history of epilepsy or speech dysfluency	Horga *et al* [66]
Clozapine (up to 250 mg/d)	Male/29	Undifferentiated schizophrenia	No other drugs	After the clozapine dosage titration from 137.5 mg/d to 150 mg/d	Frequent repetition and prolongation of syllables or words with frequent hesitations, blocking and	No focal dystonia or any evidence of seizure-like activity	Reducing and splitting the dose of clozapine to 50 mg in morning and 75 mg at night, improvement of stuttering	Reoccurrence of stuttering at clozapine dosage of 250 mg/d, improvement of stuttering after dose reduction to 225 mg/d, a later increase in the	History of antipsychotic-induced extrapyramidal symptoms, no history of speech dysfluency	Grover *et al* [61]

					pauses			dosage to 300 mg/d did not cause recurrence of stuttering		
Clozapine (400 mg/d)	Female/33	Severe MDD with psychotic features	No other drugs	Stuttering was started after increasing the dosage of clozapine to 400 mg/d and worsened when the dosage was increase to 450 mg/d	Excessive prolongation of syllables or words	Sialorrhea	Addition of benztropine, no improvement. Reduction of the dosage of clozapine to 350 mg/d, complete relief	Stuttering recurred 16 d after increasing the clozapine dosage to 400 mg/d, but completely relieved after dosage reduction to 300 mg/d	None	Kumar *et al* [89]
Clozapine (up to 650 mg/d)	Male/32	Paranoid schizophrenia	Sertraline (300 mg/d), lamotrigine (500 mg/d), haloperidol (4 mg/d), clonazepam (1 mg/d)	Noticeable stuttering at clozapine dosages of ≥ 600 mg/d	Expressive speech dysfluency with hesitancy and frequent pauses	Involuntary twitching of muscles of jaw	Clozapine dose reduction by 25 mg, improvement of stuttering	Clozapine was not discontinued	No history of speech dysfluency	Murphy *et al* [20]
Clozapine (400 mg/d)	Male/43	Schizoaffective disorder	Paroxetine (20 mg/d)	Stuttering became noticeable when the clozapine daily dose was increased to more than 350 mg	Expressive speech dysfluency	NR	Clozapine dose reduction by 50 mg, improvement of stuttering	Clozapine was not discontinued	No history of speech dysfluency	Murphy *et al* [20]
Clozapine (450 mg/d)	Male/33	Paranoid schizophrenia	No other drugs	Stuttering was developed during the initiation and dose titration of clozapine	Intermittent stuttering of speech	NR	Reducing the rate of dose titration, improvement of stuttering	Clozapine was not discontinued	No history of speech dysfluency	Murphy *et al* [20]
Clozapine (up to 300 mg/d)	Female/46	Delusional disorder	No other drugs	Stuttering was developed during the initiation and dose titration of clozapine	Hesitancy with specific syllables	Orofacial dyskinesia	Clozapine dose reduction to 50 mg, improvement of stuttering	Clozapine was not discontinued	No history of speech dysfluency	Murphy *et al* [20]
Clozapine (325 mg/d)	Male/67	Schizoaffective disorder	Duloxetine (60 mg/d), hyoscine (30 mg/d), aripiprazole (10 mg/d)	Stuttering was developed during the initiation and dose titration of clozapine	Expressive speech dysfluency	Orofacial twitching, upper limb jerking, hypersalivation	Reducing the rate of clozapine dose titration, improvement of stuttering	The clozapine dose was increased again to control psychotic symptoms, but nothing about the recurrence of stuttering was reported	Hearing impairment, hypertension	Murphy *et al* [20]
Clozapine (650 mg)	Female/63	Paranoid schizophrenia	Amisulpride 200 mg/d, amitriptyline 25 mg/d, paroxetine 20 mg/d, zopiclone 3.75 mg/d	Stuttering was developed on a stable dose of clozapine	Expressive speech dysfluency with hesitancy	NR	Reducing the dose of clozapine by 50 mg, no improvement	Clozapine at 650 mg/d was recommenced, but authors did not report its effects on the recurrence of stuttering	No history of speech dysfluency	Murphy *et al* [20]
Clozapine (100 mg), aripiprazole (7.5	Female/21	Schizophrenia	No other drugs	At clozapine dosage of 100 mg/d and	NR	NR	Reduction of the dose of clozapine and	The drugs were not discontinued	Turner syndrome, no history of	Ertekin *et al* [8]

mg/d)				aripiprazole dosage of 7.5 mg/d			addition of aripiprazole (5 mg/d), complete relief. Reduction of the dose of aripiprazole from 5 to 7.5 mg/d, complete relief		speech dysfluency	
Clozapine (gradually increased to 450 mg/d)	Male/16	Schizoaffective disorder	Citalopram (NR), clonazepam (NR), atenolol (NR), lithium (NR)	Approximately 22 d after increasing the clozapine dosage to 400 mg/d	Persistent stuttering (difficulties with the pronunciation of letters "I," "D," and "T")	Orofacial dyskinesia with perioral twitching (started at clozapine dosage of 350 mg/d), microseizure according to EEG (at clozapine dosage of 400 mg/d)	Substituting lithium with divalproex sodium, improvement in stuttering 4 wk after receiving divalproex sodium at 500 mg BID	Clozapine was not discontinued because of its considerable therapeutic effects	History of type 1 DM, DKA with episodic hallucinations, GERD, cerebral contusion, occasional cocaine use, anxiety-induced intermittent stuttering, family history of stuttering	Rachamallu *et al*[62]
Clozapine (up to 600 mg/d)	Female/22	Schizophrenia	Fluoxetine (60 mg/d)	Stuttering was developed after the clozapine dose escalation to 300 mg/d	NR	NR	Reduction in the clozapine dose and initiation of ECT, minimal improvement	Clozapine was not discontinued	NR	Das *et al*[19]
Clozapine (450 mg/d)	Man/in early 40s	NR	No other drugs	After increasing the clozapine daily dose from 400 mg to 450 mg	NR	Marked increase in seizure activity	DC of clozapine, nothing was clearly reported by the authors	NR	NR	Kranidiotis *et al*[24]
Clozapine (200 mg/d)	Male/38	Schizophrenia	No other drugs	Stuttering was evident at 200 mg/d and became so disabling at 350 mg/d	NR	NR	Dose reduction of clozapine and addition of amisulpiride and BDZ, reduction of stuttering, DC of clozapine, complete relief	Clozapine was not restarted	NR	Kranidiotis *et al*[24]
Clozapine (300 mg BID)	Male/57	Paranoid schizophrenia	Risperidone, IM injection (37.5 mg every 2 wk), Risperidone, oral (1.5 mg/d which increased to 2 mg BID on admission)	Two days after admission (the dosage of clozapine, 300 mg BID, was not changed on admission)	NR	Orofacial and extremities myoclonic jerks, drop attacks	Clozapine dosage reduction to 100 mg BID, resolution of stuttering within two days	The patient was discharged on clozapine 150 mg BID, but author reported nothing about stuttering at follow-up	History of COPD, hypertension, DM, and chronic back pain, cigarette smoking	Chochol *et al*[60]
Clozapine (125 mg/d)	Male/29	Schizophrenia	No other drugs	A few days after titrating the clozapine dosage to 125 mg/d	Frequent repetitions of words that included broken words	NR	Reducing the clozapine dosage to 100 mg/d, significant improvement	Clozapine dosage was not re-escalated	No history of speech dysfluency	Nagendrappa *et al*[90]

Clozapine (up to 200 mg/d)	female/25	Schizophrenia	No other drugs	At clozapine dosage dose of 150 mg/d (interval was not mentioned)	NR	Tonic-clonic epileptic seizure	DC of clozapine and start of amisulpiride and biperiden, complete relief of stuttering and seizure	Clozapine was not rechallenged	No history of speech dysfluency	Gica *et al*[65]
Divalproex sodium (600 mg/d)	Male/45	Affective instability and irritability	Citalopram (30 mg/d), promazine (100 mg/d)	Four days after initiation of divalproex sodium	Sound repetitions and prolongations (not restricted to the initial syllable and caused pronounced difficulty in starting and completing his sentences)	NR	DC of divalproex, complete relief after 3 d	Divalproex sodium was not restarted	A 10-yr history of post-traumatic stress disorder and alcoholism, no history of speech dysfluency	Aukst-Margetić *et al* [91]
Divalproex sodium (1500 mg/d in divided dose)	Male/56	Bipolar affective disorder	Olanzapine (10 mg/d), lorazepam (4 mg/d, gradually stopped along with increase in the dose of divalproex)	Two weeks after increasing the dosage of divalproex from 1000 to 1500 mg/d	A moderately pressured speech, articulation of speech, alterations in intensity and timings of utterance segments, Involuntary repetitions and prolongations of sounds, syllables, words or phrases, involuntary silent pauses or blocks	NR	DC of divalproex, instant amelioration of the stuttering	Re-initiation of the drug after one week caused resurgence of symptoms, so the drug was stopped	No history of speech dysfluency	Mukherj *et al* [92]
Desipramin (300 mg/d)	Male/28	Dystimia, primary type, major depression	Doxepin (50 mg at bed time)	Two months after increasing the dosage of desipramine	Stuttering with difficulty in articulation	Minimal dryness of mouth before stuttering, myoclonic jerking (twitching movements around his jaw) concomitant with stuttering	DC of both drugs, complete relief after 48 h	Twenty-four hours after restarting both drugs stuttering happened again, the desipramin dosage was decreased to 250 mg/d, but stuttering was persisted occasionally, on 4 different occasions, desipramin was discontinued and stuttering was solved within 24-48 h; an increase in the doxepin dosage to 200 mg at bed time had not resulted in stuttering	Opiate and alcohol dependence in remission, retinal detachment and ruptured disc and chronic back pain in the past, no history of speech dysfluency	Masand *et al* [93]
Fluphenazine (up to 50 mg/d)	Male/35	Schizophrenia	Benztropine mesylate (4 mg/d)	12 d after increasing fluphenazine dosage to 50 mg/d	NR	EPS	Dosage reduction to 30 mg/d, complete relief	Increasing the dosage of fluphenazine to 40 mg/d caused stuttering	No history of speech dysfluency	Nurnberg *et al*[10]

								recurrence		
Gabapentin (NR)	Female/58	Intractable seizure	Phenytoin (NR)	NR	NR	NR	DC of gabapentin, relief after 4 d	NR	No history of speech dysfluency	Nissani *et al* [94]
Lamotrigine (up to 5 mg/kg/d)	Female/5	BECTS	Valproic acid (30 mg/kg/d)	Stuttering was initiated after increasing the dosage of lamotrigine to 5 mg/kg/d	NR	Frequent diurnal absence seizures, poor concentration and forgetfulness, clumsiness and poor coordination, emotional lability, dysarthria, and slurred speech	DC of lamotrigine, speech improvement in a couple of days	Lamotrigine was not rechallenged	NR	Catania *et al* [95]
Levodopa/carbidopa (100/25 mg TID)	Male/44	PD	NR	Patient had a history of PDS, and stuttering was exacerbated during on periods, 1 h after levodopa/carbidopa intake	NR	Dyskinesia during drug-on phases and akinesia, bradykinesia, resting tremors, and rigidity in drug-off phases	The severity of stuttering return to baseline during levodopa-off periods	Levodopa was not discontinued	PDS	Anderson *et al*[25]
Levodopa (200 mg/d)	Male/72	PD	None	Nearly one month after increasing the dosage to 200 mg/d	NR	Palilalia, speech freezing	DC of levodopa and initiation of pramipexole, return to the baseline level of dysfluency	Reinitiating levodopa caused stuttering	Speech dysfluency due to PD	Louis *et al*[22]
Levodopa (up to 1000 mg/d)	Male/42	PD	Pergolide (1.5 mg/d), quetiapine (50 mg at bed time)	After increasing the levodopa dosage to 300 mg/d	Pressured speech and sound repetition	Palilalia, speech freezing	NR	NR	None	Louis *et al*[22]
Levodopa 600 mg/d	Male/57	PD	Cabergoline (4 mg/d), selegeline (10 mg/d), amantadine (300 mg/d)	Patient had a history of PDS, and stuttering was exacerbated during on phases after levodopa consumption	Speech repetitions and speech blocks	Speech problems associated with PD including hypokinetic dysarthria and hypophonia occurred during levodopa-off phases	Severity of stuttering return to baseline during levodopa-off periods	Levodopa was not discontinued	PDS	Burghause *et al*[26]
Levomepromazine (50 mg at bed time)	Male/65	Bipolar disorder	Quetiapine (NR), valproate semisodium (NR), zolpidem, moxonidin (NR), propafenone (NR), insulin (NR)	Five days after the initiation of levomepromazin	NR	NR	DC of Levomepromazin, complete relief three days later	Levomepromazin was not recommenced	History of drug induced EPS, supraventricular tachycardia, type 2 DM, HTN, and mild cognitive impairment	Margeticet al [96,97]
Lithium (1200 mg at bed time)	Male/48	Bipolar affective disorder	Fluoxetine (20 mg/d)	One month after the initiation of lithium	Worsening his developmental stuttering, a repetitive word	Lightheadedness, hand tremor	Tapering off lithium, stuttering returned to baseline within a few weeks	Valproic acid (2750 mg/d) was started instead of lithium	PDS, depression	Netski *et al* [98]

					stutter that severely limited his verbal communication ability					
Lithium (900 mg twice daily)	Male/10	Bipolar disorder	Risperidone (4 mg bed time), clonidine (0.1 mg 3 times daily), melatonin (3 mg at bed time), famotidine (20 mg BID)	Two days after increasing the dose of lithium, stuttering was worsened	Syllable repetitions, occurred only at the beginning of sentences	NR	Dose adjustment of lithium to 600 mg in the morning and 900 mg at night, stuttering returned to baseline after 2 d	Lithium was not discontinued	History of developmental stuttering, bipolar disorder not otherwise specified, ADHD, and conduct disorder	Gulack *et al* [99]
Lithium (the dose was not mentioned, but lithium was used for a long time)	Female/86	Bipolar disorder	Donepezil (NR), primidone (NR), risperidone (NR)	After a chronic use of lithium, stuttering was started and stayed for 3 more mo. The lithium level was elevated (2.0 mmol/L)	Starting a few words fluently, then repeating syllables and words and terminating the sentence abruptly	NR	DC of lithium, complete relief of stuttering after two weeks	Lithium was not restarted	Past medical history of dementia and epilepsy, no history of speech dysfluency	Sabillo *et al* [100]
Memantine (10 mg/d)	Male/9	Autistic disorder	No other drugs	After increasing the dose	Deterioration of primary behaviors of developmental stuttering includingsound repetition, and sound prolongation on first and middle vowels, and difficulty for starting to speak. His parents explained that the child could only start to speak after a deep and audible breath	NR	Reduction of memantine dosage to 7.5 mg/d, improvement of acquired stuttering after several days. DC of memantine, stuttering was reduced to baseline after 3 wk	Risperidone was used instead	Developmental stuttering	Alaghband-Rad *et al*[17]
Memantine (5 mg/d)	Male/4	Autism	No other drugs	After increasing the dose	The difficulty was with the start of the speech and the child could only start to speak after a deep and audible breath	NR	The drug was continued at the same dose as the difficulty was tolerable, and gradually was increased to 7.5 mg/d, relief of speech difficulty	Medication was continued, and its dose was gradually increased	No history of speech dysfluency	Alaghband-Rad *et al*[17]
Methotrexate (cumulative dose of 62.5 mg, IT)	Female/22	Pre-B acute lymphoblastic leukemia	NR	After achieving cumulative dose of 62.5 mg (26 d after	NR	Dysphasia progressed to aphasia, mild	Three months after initiation of symptoms (no intervention was	NR	No history of speech dysfluency	Shuster *et al* [21]

				initiating IT MTX)		headache, low-grade fever, behavioral problems	described)			
Methylphenidate (10 mg/d)	Male/7	ADHD	No other drugs	10 d after the initiation of the drug	Sound prolongations, silent blocking, word production with excess physical tension, monosyllabic whole-word repetitions	NR	DC of methylphenidate, speech returned to normal after 1 wk	Atomoxetine was used instead	No history of speech dysfluency	Alpaslan *et al* [101]
Methylphenidate (5 mg in the morning and 5 mgat noon)	Male/7	ADHD	No other drugs	One day after drug initiation	Troubles during the pronouncing the first syllables and repetitions of some syllables	NR	DC of Methylphenidate, improvement after 10 d	Methylphenidate was restarted at 10 mg in the morning and5 mg at noon. After 10 d, stuttering was returned	NR	Copur *et al* [102]
Methylphenidate (2.5 mg BID) and pemoline (9.375 mg/d) after DC of methylphenidate	Girl/3	Pervasive hyperactivity	None	Three days after starting methylphenidate, four days after starting pemoline	Repetition of the first syllable of word which gradually worsened	NR	DC of methylphenidate, relief of stuttering, DC of pemoline, relief of stuttering	Methylphenidate and pemoline were not restarted	NR	Burd *et al*[7]
Olanzapine (15 mg/d)	Male/56	Depression	Intrathecal morphine (7.5 mg/d), clomipramine (225 mg/d)	Four days after the initiation of clozapine	Constant word repetition (acquired)	NR	DC of olanzapine, complete relief after two days	NR	Chronic pain syndrome, no history of speech dysfluency	Bar *et al*[15]
Olanzapine (7.5-10 mg/d)	Male/72	Psychotic depression	Clomipramine (50-150 mg/d)	3 wk after the initiation of olanzapine	Repetition and retention of first syllables and prolongation of phonemes	NR	DC of olanzapine, complete relief after 5 d	NR	Brain cortical atrophy, no history of speech dysfluency	Bar *et al*[15]
Olanzapine (5 mg/d)	Female/36	Manic episode	Sodium valproate (300 mg/d), prednisolone (75 mg/d)	7 d after the initiation of olanzapine	Repetition of syllables and words	NR	DC of olanzapine, complete relief after 4 d	NR	Ulcerative colitis and celiac disease, no history of speech dysfluency	Bar *et al*[15]
Olanzapine (10 mg/d)	Female/43	Schizophrenia	No other drugs	Approximately 21 d after the initiation of olanzapine	Repetition of first syllables and word prolongation	NR	DC of olanzapine, complete relief after 3-5 d	NR	Mild cluttering at the age of 19	Bar *et al*[15]
Olanzapine (2.5 mg/d)	Female/51	Depression	Sertraline (100 mg/d), promethazine (50 mg at night); both was started 14 wk before initiation of	14 d after the initiation of olanzapine	Blocking of speech and prolongation of phonemes	NR	Increase in olanzapine dose to 5 mg/d, relief of stuttering during the next weeks	Olanzapine was not discontinued	Symmetrical cerebellar hypoplasia and generalized cortical atrophy, no history of	Bar *et al*[15]

			olanzapine						speech dysfluency	
Olanzapine (10 mg/d)	Male/42	Schizophrenia	Zopiclone (7.5 mg/d)	Two days after the initiation of olanzapine	Difficulty in articulating words properly	NR	DC of olanzapine, complete relief after two days	NR (patient was not followed-up)	A fall without loss of consciousness 2 d before initiation of stuttering, no history of speech dysfluency	Bar *et al*[15]
Olanzapine (10 mg/d)	Male/42	Paranoid ideation	Venlafaxine (150 mg/d), promazine (200 mg/d)	Four days after the initiation of olanzapine	Repetition and retention of first syllables and prolongation of phonemes	NR	DC of olanzapine, complete relief after two days		PTSD, adjustment disorders, no history of speech dysfluency	Lasic *et al* [103]
Olanzapine (10 mg/d)	Male/21	Psychotic disorder	No other drugs	Three days after the initiation of olanzapine	disturbance in the fluency and time patterning of speech, repetition of sounds and syllables, blocking between words	NR	DC of olanzapine and start of quetiapine, complete relief after three days	Olanzapine was not restarted	No history of speech dysfluency	Asan *et al* [104]
Phenytoin (200 mg/d)	Male/42	Seizure due to head injury	No other drugs	Shortly after initiation of phenytoin	Predominantly part-word repetitions and prolongation	Abnormality of speech muscle fine motor control	Addition of CBZ and gradual DC of phenytoin, sustain decrease in the frequency of dysfluencies and improved motor performance	Phenytoin was not restarted	No history of speech dysfluency	Mcclean *et al* [105]
Phenytoin (20 mg/kg LD and 5 mg/kg/d MD)	Male/3	GTC seizure due to head trauma	No other drugs	10 d after the initiation of phenytoin	NR	NR	DC of phenytoin and initiation of sodium valproate, complete relief 10 d after DC of phenytoin	Phenytoin was not rechallenged	No history of speech dysfluency	Ekici *et al* [106]
Pregabalin (75 mg twice daily)	Female/31	Complex regional pain syndrome	No other drugs	After taking the second dose of pregabalin on the first day	A slurred speech	NR	DC of pregabalin, complete relief after one week	Pregabalin was not restarted	No history of speech dysfluency	Giray *et al* [107]
Pregabalin (75 mg twice daily)	Female/68	Herpes zoster	Acyclovir (800 mg five times daily)	Three days after the initiation of pregabalin	NR	Frequent blepharospasm	DC of pregabalin;alleviated of symptoms after four days and complete relief after one week	A 75 mg pregabalin capsule consumption after 4 wk resulted in stuttering and frequent blepharospasm	No history of speech dysfluency	Ge *et al*[108]
Pyrethrin product containing 0.33% pyrethrum extract and 4% piperonyl butoxide (3 times	Female/2 (the child's mother, who was breastfeeding	Repeated episodes of head lice	No other drugs	Two days after the last period of mother's treatment	An acute onset of stuttering especially at the initiation of the speech	An increase in clumsiness, slight erythematous rash ofapproximately 3 cm × 2 cm on the	Six weeks postexposure	Pyrethrin was not repeated	No history of speech dysfluency	Hammond *et al*[81]

overa period of 12 d left on the scalp for 10 min)	her atleast one time per day, were receiving this topical product)					occiput of the scalp				
Risperidone (4 mg/d, then 8 mg/d)	Male/32	Aggravated psychotic disorder	Lorazepam (1 mg/d)	Stuttering was initiated after the dose increase to 4 mg/d, and worsened 16 d after the dose increase to 8 mg/d	Severe sound repetitions and interjections in a way that it was difficult to understand his words	Slight akathisia-like symptoms such as anxiety and restlessness (not prominent)	No action, stuttering diminished 23 d later	He continued taking risperidone at 8 mg/d with only a slight stuttering	A 10-yr history of Schizophrenia. His friend during junior high school was a stutter, and the patient used to mimic his stuttering. He began stuttering at that time for 1 yr	Lee *et al*[16]
Risperidone (4 mg)	Female/48	Psychosis	Lorazepam (1 mg PRN), procyclidine (5 mg BID for treatment of EPS)	11 d after taking risperidone	Repetitions in the speech, pausing within a word and her speech, an excess of physical tension in the speech	NR	A little decrease in risperidone dose, a bit reduction in stuttering	Risperidone was not discontinued	No history of speech dysfluency	Yadav *et al* [18]
Risperidone (at a dose of 1 mg/d for 2 yr)	Male/21	Behavioral disorder	No other drugs	After chronic treatment with low-dose of risperidone	Prolongation of sounds, hearable blocks, repetitions of single-syllable words	NR	No action, stuttering was decreased to a minimal level after 17 d	Risperidone was not discontinued	Moderate mental retardation because of perinatal asphyxia, no history of speech dysfluency	İnci *et al*[23]
Sertraline (100 mg daily)	Male/36	Major depression	Alprazolam (0.25 mg 3 TID)	Two weeks after increasing the dosage from 50 to 100 mg/d	Normal vocabulary, decreased rate of speech, normal tone, interrupted words	NR	DC of serteraline, speech problem resolved after one day	Medication was not restarted. Later, administering phenelzine, imipramine, and fluoxetine caused milder speech hesitancy	No history of speech dysfluency	Makela *et al* [109]
Sertraline (50 mg daily)	Female/32	Recurrent depression	No other drugs	During the third week of starting the drug, stuttering occurred and worsened over a 3-d period	Difficulty in starting and completing the sentences	Feeling nervous, increased restlessness, and insomnia two days before the onset of stuttering	DC of sertraline, complete relief of stuttering after 3 d	Previously, patient has received sertraline and experienced stuttering, so discontinued the medication. Medication was not restarted. Desipramine was started and did not cause stuttering	No history of speech dysfluency	Christensen *et al*[76]

Sertraline (150 mg daily)	Female/22	Bulimia nervosa, anorexia nervosa, posttraumatic stress disorder, recurrent depression, panic disorder	Clonazepam (0.5 mg QID), trimethoprim-sulfamethoxazole (BID)	One week after increasing the dosage of sertraline	NR	Hyperreflexia and mild tremulousness, generalized muscle twitching (myoclonus), restlessness, and mild confusion	DC of sertraline and Antibiotic, gradual normalization of speech over two to three days	Seven days after restarting sertraline at 50 mg/d, stuttering and other symptoms returned, then the drug was discontinued	No history of speech dysfluency	Brewerton *et al*[77]
Theophylline (200 mg BID to 100 mg QID)	Male/the age of the onset of theophylline-induced stuttering was not reported, but it surely occurred when he was between 1.5 and 4 yr old	Asthma	Nothing was clearly mentioned	The patient only experienced stuttering during the autumn when he was receiving theophylline for the management of asthma attacks	Repeating whole words, six or seven times usually at the beginnings of the sentences, no dysfluency while singing	Being tense, havinginsomnia, and be frustrated by his speech problem	DC of theophylline at the end of autumn before age 4 yr, complete relief of stuttering. Changing the dosage from 100 mg QID to 200 mg BID at age 4 yr, complete relief after 7 d with no recurrence of stuttering	The patients had stuttered each time that he was on Theophyllineregimen 200 mg BID	No history of speech dysfluency	Rosenfield *et al*[110]
Theophylline (130 mg TID and sometimes QID)	Female/6.5	Asthma	Metaproterenol sulphate (PRN)	Within a few days after increasing the theophylline dosage to 130 mg TID	Multiple repetitions of the word "I", especially at the beginning of sentences, she could speak better when speak more slowly. Stuttering was worse when she was excited	NR	DC of theophylline, complete relief within two days	Resumption of theophylline resulted in the recurrence of stuttering which responded to drug withdrawal. Several months after the discontinuation of theophylline, the drug was resumed without causing any dysfluency	No history of speech dysfluency	Rosenfield *et al*[110]
Theophylline 200 mg BID to 200 mg TID	Male/4 yr and 3 mo	Asthma	Beclomethasone dipropionate and Theo-Dur sprinkle (200 mg BID) (at age 4 yr and 4 mo). Addition of metaproterenol sulphate, isoetharine HCL andatropine (at age 4 yr and 10 mo, DC of all drugs and initiation of cromolyn capsules (20 mg TID) (at age 5 yr)	Nine months after the initiation of theophylline	Repeating "ah, ah, ah" in the middle of sentences, stuttering was worse when he was excited	Anxiety, sleep problems	Withdrawal of theophylline at age 5 yr, complete relief within two weeks	After complete relief of stuttering, the patient only received theophylline during asthma attacks and experienced no stuttering	No history of speech dysfluency	Rosenfield *et al*[110]
Theophylline (400 mg BID)	Male/73	A long-standing chronic obstructive lung	Steroids and ranitidine as well as being on oxygen	One month after the introduction of theophylline	An intense tonic-clonic stuttering without any	NR	DC of theophylline, stuttering was diminished within 48	Theophylline was readministered 2 wk later at the same	No history of speech dysfluency	Gerard *et al* [111]

		disease secondary to pneumoconiosis			extrapyramidal components		h	dosage, and the same speech disorder recurred within a few daysand persisted until treatment was stopped		
1. Trifluoperazine (30 mg/d) 2. Chlorpromazine (up to 800 mg/d)	Male/40	Schizophrenia	Trihexyphenidyl (5 mg/d)	1. Four days after increasing the trifluoperazine dosage to 30 mg/d 2. After increasing chlorpromazine dosage to 800 mg/d	NR	NR	1. Increasing dosage of trihexyphenidyl, no improvement. DC of trifluoperazine, complete relief 2. Addition of benztropine, no improvement. Reduction of chlorpromazine dose to 400 mg/d, complete relief	Increasing the dosage of chlorpromazine to 700 mg/d caused the return of stuttering; reducing the dosage of chlorpromazine to 400 mg/d caused cessation of stuttering	No history of speech dysfluency	Nurnberg *et al*[10]

ADHD: Attention-deficit hyperactivity disorder; BECTS: Benign focal epilepsy of childhood with centrotemporal spikes; BID: Two times per day; BDZ: Benzodiazepine; CBZ: Carbamazepine; COPD: Chronic obstructive pulmonary disease; DC: Discontinue, DM: Diabetes mellitus; EPS: Extrapyramidal side effect; GERD: Gastroesophageal reflux disease; GTC: Generalized tonic-colonic seizure; HTN: Hypertension; IM: Intramuscular; IT: Intrathecal; IV: Intravenous; LD: Loading dose; MD: Maintenance dose; MDD: Major Depressive Disorder; MTX: Methotrexate; NR: Not reported; PD: Parkinson disease; PDS: Persistent developmental stuttering; PRN: Pro re nata (as needed); QID: Four times a day; TID: Three times a day; VPA: Valproic acid.

For producing a fluent speech, orofacial as well as respiratory muscles must work properly. Different areas of the brain including several parts of the cerebral cortex and subcortical structures such as the basal ganglia (BG) and cerebellum are involved in speech production. Functional abnormalities of each part of these areas may cause speech dysfluency. It has been suggested that dysfunction in the different parts and networks of cerebral cortex engaged in speech production[28], the impairments in the neural connections between the cerebral cortex, the BG, and the thalamus, which are called cortico-BG-thalamocortical circuit (CBTC)[28,29], and/or the dysfunction of the BG are involved in the pathogenesis of developmental stuttering[28,29].

CBTC AND STUTTERING

Several neural circuits are engaged in the process of speech production. One of these circuits that has received much attention in the pathogenesis of stuttering is CBTC[28,29]. The BG consist of input, intrinsic, and output nuclei. The input nuclei receive information from different parts of the brain, especially the cerebral cortex, the thalamus, and the substantia nigra, and send signals to the intrinsic nuclei for further processing and then to the output nuclei. The output nuclei relay signals to the thalamus which sends signals back to the part of the cerebral cortex from which the primary signal was originated. The input nuclei consist of the putamen and the caudate nucleus, collectively named the striatum. The intrinsic nuclei consist of the external segment of the globus pallidus (GPe), the subthalamic nucleus (STN), and the substantia nigra pars compacta (SNpc). The internal segment of the

globus pallidus (GPi) and the substantia nigra pars reticulata (SNpr) make the output nuclei[30].

The striatum has two types of neurons including gamma-aminobutyric acid-ergic (GABAergic) medium-sized spiny neurons (MSNs) representing 90%-95% of the striatal neurons and GABA-ergic/cholinergic interneurons. The striatum receives inputs from different parts of the brain including excitatory glutamatergic inputs from different parts of the cerebral cortex, motor cortex, supplementary motor area (SMA), pre-SMA, auditory cortex, somatosensory cortex, and the thalamus and dopaminergic inputs from SNpc[30]. BG match motor, sensory, and cognitive context received from different parts of the cerebral cortex[31] and send signals to the thalamus to stimulate the cerebral cortex to initiate the desired movement, *e.g.*, terminating production of the previous phoneme and initiating the next phoneme in the case of speaking, and inhibit competing movements[32]. The cerebral cortex sends signals through corticobulbar tracts to the orofacial and respiratory muscles including the muscles of larynx, pharynx, lips, and tongue[33], activates the proper group of muscles, and inhibits competing muscles whose activation interferes with the production of the desired movement.

The signals that are received by the input nuclei of BG are transmitted *via* two pathways: Direct and indirect. The activation of the direct pathway stimulates the cerebral cortex and therefore activates the right motor program while the activation of the indirect pathway inhibits the cerebral cortex and therefore, all other competing motor programs[2,28].

In the direct pathway, MSNs, which have N-methyl-D-aspartate (NMDA) glutamate receptors, D1 dopamine receptors, A1 adenosine receptors, and M4 muscarinic receptors[34] and release gamma-aminobutyric acid (GABA), substance P, and dynorphin[35], project to the SNpr and GPi, the output nucleus of BG. MSNs are stimulated by glutamatergic projections from the cerebral cortex. The activated MSNs release GABA, which inhibits the output nucleus. GABAergic projections from the output nucleus inhibit the glutamatergic neurons of the thalamus. Therefore, the inhibition of the output nucleus by MSNs disinhibits thalamic neurons which ultimately activate the cerebral cortex and increase locomotor activity[35] (Figure 1).

MSNs in the indirect pathway, which have NMDA glutamate receptors, D2 dopamine receptors, A2A adenosine receptors, and M1 muscarinic receptors[34] and release GABA and enkephalin, project to the output nucleus through the GPe and STN. The GPe has GABAergic neurons that inhibit STN neurons which are glutamatergic cells. The release of glutamate because of the activation of the cerebral cortex stimulates MSNs in the indirect pathway to release GABA. GABA inhibits the GPe and therefore disinhibits the STN. Release of glutamate from the STN stimulates the inhibitory GABAergic neurons of the output nucleus, which inhibits thalamic neurons and therefore cerebral cortex, resulting in decreased locomotor activity (Figure 1). It has been proposed that the direct and indirect pathways have interactions with each other, and their integration and balanced activation during movement selection is required for the proper execution of motor programs[36,37].

ROLE OF DOPAMINE IN THE BG MOTOR CIRCUIT

As mentioned above, D1, A1, and M4 receptors are colocalized on MSNs in the direct pathway[34]. The stimulation of D1 receptors activates MSNs in the direct pathway and stimulates this pathway[28]. Blocking A1 and M4 receptors facilitates the dopamine neurotransmission. Therefore, A1 and M4 antagonists also stimulate the direct pathway[34]. Neurons of the indirect pathway have D2, A2A, and M1 receptors[34]. The activation of D2 receptors inhibits the indirect pathway[28]. A2A and M1 receptors antagonists also increase the dopamine signaling and therefore suppress the indirect pathway. Since these two pathways have a cross talk and coordinated activity, disturbing their coordination can cause movement disorders such as dystonia, dyskinesia, and stuttering. Therefore, both increased and decreased dopamine neurotransmission in the striatum may cause stuttering by impairing the balance between the direct and indirect pathways.

WHITE MATTER FIBER TRACTS AND STUTTERING

Other changes that can affect connectivity between different areas of the brain involved in the speech motor control are the white matter abnormalities. The white matter tracts, bundles of myelinated axons, relay signals between different areas of the brain and therefore coordinate their communication and function[38]. Several *in vitro* and animal studies and a small number of human studies have found multiple neurotransmitters, including glutamate, adenosine, GABA, glycine, dopamine, serotonin, acetyl choline, histamine, norepinephrine, and substance P, and their receptors in the white matter. It has been proposed that glutamate and purine signaling have the most prominent effects on the white matter functioning; however, it seems that the white matter requires a coordinated action of all of these neurotransmitters for conduction of action potentials and maintaining signal integrity through very long signal transmission axonal pathways[38]. Different studies in adults[33,39] and adolescents and young people[40] with developmental stuttering demonstrated the reduced integrity of the white matter fiber tracts. It may be proposed that an agent that impairs the normal activity of one or some of the

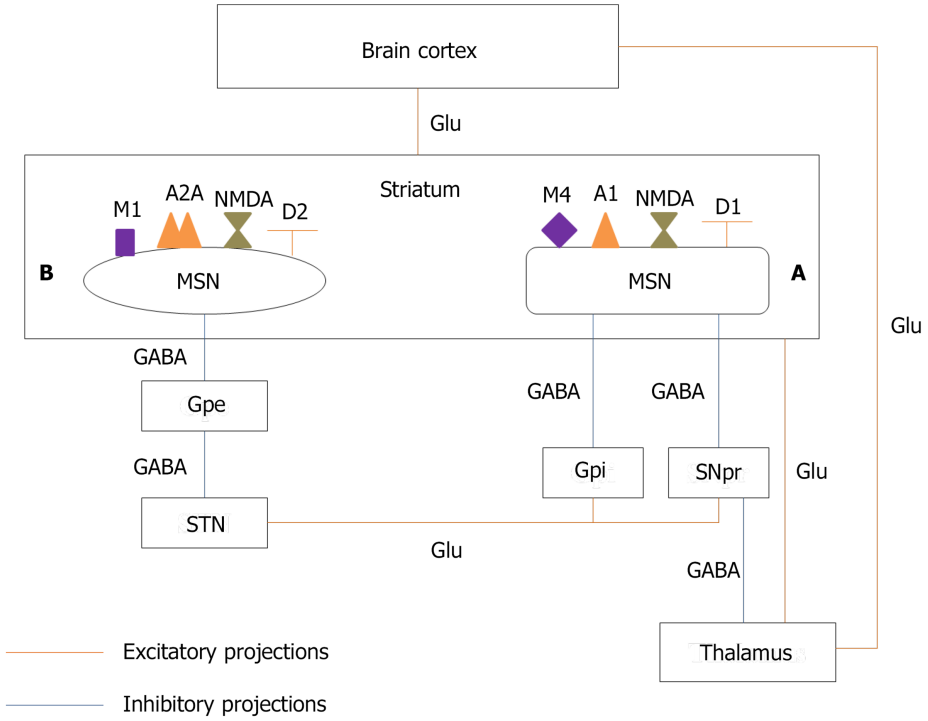

Figure 1 Schematic graph of direct and indirect pathways of basal ganglia. A: Direct pathway; B: Indirect pathway. A1: A1 adenosine receptor; A2A: A2A adenosine receptor; D1: D1 dopamine receptor; D2: D2 dopamine receptor; GABA: Gamma-aminobutyric acid; Glu: Glutamate; Gpe: External segment of the globus pallidus; Gpi: Internal segment of the globus pallidus; M1: M1 muscarinic receptor; M4: M4 muscarinic receptor; MSN: Medium-sized spiny neurons; NMDA: N-methyl-D-aspartate receptor; SNpr: Substantia nigra pars reticulate; STN: Subthalamic nucleus.

neurotransmitters in the white matter may impair signal transmission between different areas of the brain engaged in speech motor control and result in stuttering. Moreover, in some psychiatric disorders such as schizophrenia and bipolar disorder, one of the pathological findings in the CNS is myelin loss or disruption[41]. Of cases included in the present review, 25, 5, and 6 had schizophrenia, schizoaffective disorder, and bipolar disorder, respectively. As a result, it can be suggested that drugs disrupting normal neurotransmitter balance in the white matter, which already has an underlying impairment in these patients, may exacerbate white matter dysfunction.

STUTTERING INDUCED BY DRUGS AFFECTING DOPAMINE NEUROTRANSMISSION

Increased dopamine neurotransmission in BG and stuttering

Evidence that supports the role of the dopamine excess in the pathophysiology of stuttering includes the reduction of stuttering by antipsychotic drugs, which are dopamine blockers, such as haloperidol, risperidone, olanzapine, aripiprazole, and asenapine[42], the finding of Wu *et al*[43] that showed the excessive striatal dopamine activity and increased uptake of fluoro-l-3, 4-dihydroxy-phenylalanine, a precursor of dopamine, in several parts of the brain in persons who stutter in comparison to healthy controls, and computational modeling of stuttering by Civier *et al*[44]. Furthermore, it has been shown that children aged 2.5-3 years, the age of onset of developmental stuttering in most children, have more density of D2 than D1 receptors and therefore low D1/D2 density in the striatum in comparison to older children. Therefore, drugs like haloperidol, which is a highly selective D2 antagonist, decrease this D1/D2 imbalance and the severity of stuttering. Besides the above-mentioned studies conducted in persons with developmental stuttering, cases of exacerbation of stuttering by levodopa in patients with PD[23,26,27] also propose a role for dopamine excess in the pathogenesis of NS. Chang *et al*[28] have suggested that the inhibition of the indirect pathway in the states of dopamine excess decreases the suppressing effect of this pathway on the competing motor programs. Therefore, choosing correct motor program over incorrect ones becomes difficult, which could ultimately delay the initiation of the right motor program. This delay may cause speech blockage or sound prolongation. Furthermore, in this situation, the proper signal that originated from the direct pathway and stimulates the right motor program may be initiated but suffers premature termination which may lead to the repetitions[28].

In conclusion, drugs such as levodopa, a precursor of dopamine, methylphenidate that increases the extracellular level of dopamine in the striatum[45], amphetamines that increase the release of catecholamines mainly dopamine and nerve-end particles (NEP) from presynaptic nerves and inhibit

the reuptake of dopamine and NEP into presynaptic neurons[46], and phenytoin that has been proposed as a dopamine enhancer in the BG pathways may cause stuttering by increasing the dopamine neurotransmission in BG[47,48].

Decreased dopamine neurotransmission in BG and stuttering

Reduced dopamine neurotransmission in the striatum also can cause stuttering. For example, some patients with PD, the disorder that is mainly characterized by the dopamine depletion from BG, experience new-onset NS[49], exacerbation of PDS[26,27], or re-emergence of developmental stuttering [50]. Chang *et al*[28] proposed that in this state, the decreased excitation of the direct pathway results in reduced stimulation of the correct motor program and its ability to compete other motor programs. This also may result in unstable or delayed production of signals initiating the right speech motor program.

ANTIPSYCHOTICS-INDUCED STUTTERING

Although some studies have shown the relative efficacy of antipsychotic drugs in the treatment of stuttering[42], there are case reports of antipsychotics-induced stuttering. All studies that reported efficacy of antipsychotic drugs in reducing stuttering were conducted in patients with PDS. However, all cases of antipsychotics-induced stuttering had a psychotic disorder, which was schizophrenia in the majority of them. Elevated dopamine levels and excessive dopamine activity in the striatum are present in both developmental stuttering[42,43] and schizophrenia. Therefore, the opposite effects of dopamine blockers in these disorders, improving stuttering in some cases of developmental stuttering but causing stuttering in some patients with schizophrenia, indicate that effects of these drugs on the dopamine activity in other parts of the brain and on other neurotransmitters may be responsible for their different effects on speech motor control. Furthermore, abnormalities in the brain of patients with psychotic disorders are extensive and are not comparable to persons with developmental stuttering. These differences also may justify why a dopamine blocker can be a therapeutic option in PDS but a causative agent of stuttering in the psychotic disorders.

However, it should be noted that studies by Fish *et al*[51] and Langova *et al*[52] demonstrated that not all persons with developmental stuttering respond to the dopamine blockers. In the study conducted by Fish *et al*[51], 14 out of 28 persons who stuttered Prader-Willi syndrome (PWS) and received amphetamine experienced improvement in stuttering while two got worse. Of 12 PWS who did not improve by amphetamine, eight got better on trifluoperazine, a D2 blocker. Four participants did not show any improvement neither by each medication nor by their combination. Similarly, in the study conducted by Langova *et al*[52], 88% of PWS got better on phenmetrazine, a stimulant, while 67% deteriorated using chlorpromazine. These findings have led to the suggestion of the hypothesis that persons with developmental stuttering may be classified as the dopamine blocker-responsive or stimulant-responsive[29].

In the present review and study conducted by Trenque *et al*[6], the majority of cases of DIS were caused by clozapine. Regarding the effects of antipsychotics on dopamine receptors, all antipsychotics except than clozapine, olanzapine, ziprasidone, and asenapine have a higher affinity for D2 receptors than D1 receptors. Clozapine, olanzapine, ziprasidone, and asenapine equally block both D1 and D2 receptors. Furthermore, clozapine and asenapine have a lower affinity for dopamine receptors in comparison to olanzapine and ziprasidone[53]. Clozapine is one of the most effective antipsychotic drugs[54]; however, because of its serious side effects such as agranulocytosis, seizure, and cardiovascular adverse effects[55], clozapine is considered as one of the last options in the treatment of schizophrenia and other psychotic disorders. Therefore, many patients had received several antipsychotics prior to the initiation of clozapine. Long-term blockage of D2 receptors while sparing D1 receptors caused by other antipsychotics results in the supersensitivity of D2 receptors[56]. The affinity of clozapine for blocking D2 receptors is lower than that of many other antipsychotics[53]. Therefore, after the initiation of clozapine, decreased D2 blocking combined with the supersensitivity of D2 receptors creates a state of increased D2 stimulation which finally inhibits the indirect pathway. On the other hand, antagonizing the D1 receptors inhibits the direct pathway. The inhibition of the indirect pathway impairs the suppression of the competing motor programs. Besides, the inhibition of the direct pathway decreases cerebral cortex stimulation and locomotor activity, which causes difficulties in initiating next segment in a movement sequence like speaking. Clozapine also is a $5HT_{2a}$ and $5HT_{2c}$ receptor blocker[55]. Reducing the serotonin neurotransmission increases the dopamine transmission in the prefrontal cortex, which may also cause stuttering. Although clozapine is a potent M1 antagonist [55], the effect that facilitates the dopamine neurotransmission in the direct pathway, the final result of antagonizing all above-mentioned receptors is the inhibition of both direct and indirect pathways and therefore impaired speech motor control. Moreover, changing the normal function of dopamine, serotonin, acetylcholine, and norepinephrine, by blocking α1 receptors, and histamine, by blocking H1 receptors[55], can disturb normal functions of the white matter and cause stuttering.

Other antipsychotics that are included in the present review are olanzapine, risperidone, aripiprazole, chlorpromazine, fluphenazine, and trifluoperazine. Olanzapine is very similar to clozapine regarding

the affinity for different receptors including D1, D2, $5HT_{2A}$, $5HT_{2C}$, M1, α1, and H1 receptors[57]. Other antipsychotics such as risperidone, chlorpromazine, and fluphenazine are potent inhibitors of D2 receptors without any considerable effect on D1 receptors. Chlorpromazine also is a potent M1 antagonist while risperidone and fluphenazine have no considerable effect on M1 receptor. The efficacy of risperidone in antagonizing 5HT receptors is comparable to that of olanzapine and more than the efficacy of chlorpromazine, fluphenazine, and trifluoperazine. Aripiprazole is a partial agonist of D2 and $5HT_{1A}$ receptors and antagonist of $5HT_{2A}$ receptor[57]. We suggest that these antipsychotics can cause extrapyramidal side effects (EPS) which may manifest as stuttering as well as other movement disorders by impairing the balanced and coordinated activity of the direct and indirect pathways. Furthermore, increasing the dopamine neurotransmission in the prefrontal cortex by blocking the serotonin effects as well as disturbing neurotransmitters' functioning in the white matter can be the other underlying mechanisms of the antipsychotics-induced stuttering.

The following section is focused on clozapine as the most prevalent cause of DIS.

CLOZAPINE-INDUCED STUTTERING

Clozapine is the drug with most reports of inducing a new episode of stuttering or worsening pre-existing stuttering both in the present review and analysis carried out by Trenque *et al*[6]. In the cases included in this review, clozapine induced stuttering in a wide variety of dosages ranging from 50 mg/d[10] to 700 mg/d[58,59]. However, in most cases, clozapine caused stuttering at the daily doses of 250 mg to 450 mg. It seems that stuttering is a dose-dependent adverse effect of clozapine as in 13 (43.3%) cases stuttering was significantly improved or completely vanished following dose reduction (Table 3).

We have suggested likely mechanisms of clozapine-induced stuttering in the previous section. Furthermore, based on the concomitant signs and symptoms that patients experienced with stuttering, it has been proposed that clozapine-induced stuttering may be a manifestation of the movement disorders such as focal segmental dystonia in orofacial muscles, akathisia, or dyskinesia[10,21,58,60-63] or a seizure disorder.

Although clozapine is an antipsychotic with a low potential for causing EPS[55], of 30 cases, seven experienced a type of movement disorder concomitant with stuttering[10,21,58]. Grover *et al*[61] reported a case who experienced clozapine-induced stuttering and had a history of EPS associated with other antipsychotics. Although clozapine did not cause other manifestations of EPS, they proposed that stuttering might be a symptom of movement disorders induced by clozapine. Concerning the management of clozapine-induced stuttering the dose reduction or withdrawal of clozapine resulted in significant improvement or complete relief of both stuttering and the movement disorders in two cases [58]. In contrast, in one case reported by Lyall *et al*[10], substitution of clozapine with zuclopenthixol decanoate relieved stuttering but not dyskinetic movements, and restarting clozapine resulted in reoccurrence of stuttering which responded to sodium valproate despite no electroencephalogram (EEG) abnormality. For four cases, the authors did not report whether their intervention improved the movement disorders in addition to stuttering or not[10,21].

Regarding the other likely mechanisms of clozapine-induced stuttering, it has been suggested that stuttering may be a manifestation of seizure. Clozapine-induced stuttering was associated with seizure or EEG abnormalities without typical symptoms of seizure in nine out of 30 case reports[12,25,59,60,62-66], and stuttering was significantly improved or completely relieved by addition of sodium valproate and the dose reduction of clozapine in five cases[12,59,62,64,66]. In the other four cases[25,60,63,65], anticonvulsant drugs were not tried, but discontinuation or dose reduction of clozapine resulted in complete relief of stuttering in three cases[60,63,65]. In contrast, one of the cases reported by Hallahan *et al*[58] experienced seizure after the development of stuttering. After the addition of sodium valproate, the patient had no seizure, but stuttering did not improve. It is worth mentioning that three cases had stuttering with both movement disorders and EEG abnormalities[60,62,63], which may demonstrate that some movement disorders induced by clozapine may be due to the epileptiform activity in the brain rather than EPS.

Collectively, the mechanism of clozapine-induced stuttering is multifactorial. Any of the following impairments or a combination of them can be a cause of clozapine-induced stuttering: Imbalance between direct and indirect pathways in the BG which may cause just stuttering or other movement disorders in addition to stuttering, abnormalities in the white matter neurotransmitters, and seizure or EEG abnormalities.

Finally, we suggest that in the cases of clozapine-induced stuttering at first, clinicians must do the electroencephalography to rule out any abnormal electrical activity of the brain which may progress to convulsion. If the patient has seizure or any abnormalities in EEG, the addition of sodium valproate is recommended. Even Varma *et al*[67] have recommended that one of the indications of initiating sodium valproate in patients receiving clozapine is stuttering with or without any types of seizure or EEG abnormalities. After ruling out the abnormal electrical brain activities, considering stuttering as an EPS and typical management of these side effects or dose reduction or discontinuation of clozapine may be

considered if stuttering is annoying the patient.

STUTTERING INDUCED BY DRUGS AFFECTING GLUTAMATE NEUROTRANSMISSION

As described above, as the input nucleus of the BG, the striatum receives glutamatergic projection from different parts of the cerebral cortex and thalamus. Furthermore, the STN stimulates inhibitory GABAergic neurons of the output nuclei of the BG by releasing glutamate. All ionotropic NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and kainite, and metabotropic glutamate receptors, mGlu1-8, are expressed in the BG, and glutamate is one of the important neurotransmitters that mediate signal transmission in the BG motor circuit. In addition, the computational modeling of stuttering[44] and the data of diffusion tensor imaging obtained from children who stutter[44] indicate that there is an impaired connectivity between different parts of the cerebral cortex and striatum in developmental stuttering. This impaired connection causes that BG cannot optimally detect cognitive and sensory motor context to terminate the previous phoneme and initiate the next phoneme[29] in a timely manner to produce a fluent speech. Therefore, drugs like memantine by inhibiting NMDA receptors[68] and pregabalin, gabapentin, and lamotrigine by inhibiting the release of glutamate[69,70] change the normal function of glutamate in corticostriatal pathway or in the different parts of the BG motor circuit can impair balance between the direct and indirect pathways and cause motor abnormalities like stuttering. Moreover, glutamate is the main neurotransmitter in the white matter and antagonizing its effects also disturbs signal transmission through white matter fiber tracts.

Theophylline

Theophylline increases dopamine release and transmission by inhibiting GABA receptors on the SNpc and adenosine receptors on MSNs of both direct and indirect pathways. Theophylline also increases glutamate release. Therefore, it can disturb the normal balance between the mentioned neurotransmitters in the BG and cause stuttering. Another mechanism may be impairing the normal function of neurotransmitters in the white matter by increasing glutamate, the main neurotransmitter of the white matter[5].

STUTTERING INDUCED BY OTHER DRUGS

Divalproex

Although the main mechanism of action of valproate is the blockage of voltage-dependent sodium channels[71], it has several other mechanisms of action that justify its broad anticonvulsant activity, effects in the prophylaxis of migraine headache, and mood stabilizing properties. Animal studies in rats have demonstrated that valproate increases GABA concentration in both the striatum and substantia nigra, but its effect is more pronounced in the substantia nigra[72]. Valproate also increases the firing pattern and frequency of neurons of the SNpr[73]. We propose that an increased level of GABA in the substantia nigra increases its inhibitory effects on the thalamus through the direct pathway, and therefore, reduces the brain cortex stimulation to execute the desired movement which may cause stuttering.

Atomoxetine

Atomoxetine is a selective NEP reuptake inhibitor. It increases the extracellular concentrations of NEP and dopamine in the prefrontal cortex[45]. However, studies that examined the effects of atomoxetine on the concentration of dopamine in the striatum obtained opposite results[45,74]. Because of uncertainty about the effect of atomoxetine on the dopamine levels in the striatum, we do not focus on dopamine as a mediator of likely effects of atomoxetine on speech motor control and stuttering. A study measured the blood oxygenation level dependent response using pharmacological magnetic resonance imaging in different regions of the rat brain following acute administration of atomoxetine. That study showed that atomoxetine increased SNpr and STN activity in the BG[75]. These increased activities decrease the stimulatory activity of the thalamocortical pathway. Therefore, we suggest that because of the decreased stimulation of the cerebral cortex, the favorable motor program is not executed, which can result in the inappropriate activation of the orofacial muscles and cause stuttering.

Sertraline

It is proposed that sertraline-induced stuttering may be related to the serotonergic inhibition of the dopaminergic neurons. The cell bodies of these neurons are located in the ventral tegmental area. Therefore, inhibition of the dopamine pathways in the nigrostriatum can be considered as a mechanism of promoting stuttering by sertraline or selective serotonin reuptake inhibitors drugs in general[76,77].

Bupropion

Bupropion is able to increase dopamine levels in the prefrontal cortex, which may cause stuttering[78-80].

Pyrethrin

It seems that the stuttering induced by a topical pyrethrin product in a child is related to its neurotoxicity since the metabolism of pyrethrin in children is slow. The product also had contained piperonyl butoxide, which can inhibit the hepatic metabolism of the compound and potentiate the toxicity[81].

CONCLUSION

In this review, 82 cases of DIS were collected. Most cases were related to antipsychotic drugs. Similar to the developmental stuttering, the majority of persons who experienced an episode of DIS were male. The repetitions followed by speech blocks were the most frequent core manifestations of stuttering. In 55.8% of cases, drug withdrawal was the therapeutic measure that was used to manage the stuttering.

Although we tried to provide a complete feature of the epidemiological and clinical characteristics of DIS, much information such as the core behaviors of stuttering, the interval between the initiation or increase in the dose of offending medications and the occurrence of stuttering and between the drug withdrawal or dose reduction and the improvement of stuttering, and concurrent psychological symptoms with stuttering was not reported in several cases. As a result, future cases of DIS must be reported with more detailed information since these data give others a comprehensive feature of this type of the NS.

By focusing on the cortico-BG-thalamocortical loop and the white matter fiber tracts and their neurotransmitters such as dopamine and glutamate, we suggest some likely mechanisms for DIS. However, dysfunctions in other areas of the brain like the cerebral cortex and cerebellum and other neurotransmitters are not addressed in this review. In addition, we consider stuttering as a speech motor disorder, but cognitive and sensory disorders may also play roles in the pathogenesis of DIS. Therefore, it is suggested that these subjects should be considered in the future papers discussing the underlying mechanisms of DIS. In spite of many hypotheses that can be proposed for the pathogenesis of DIS, experimental studies will provide the most robust evidence in this field. Since advanced brain imaging facilities may not be available in every setting where clinicians encounter a case of DIS to find the areas of the brain that act abnormally, animal studies evaluating the changes in the functions of the brain and different neurotransmitters are required to shed a light on the underlying mechanisms of DIS.

FOOTNOTES

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REVIEW

Insights into myelin dysfunction in schizophrenia and bipolar disorder

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Abstract

Schizophrenia and bipolar disorder are disabling psychiatric disorders with a worldwide prevalence of approximately 1%. Both disorders present chronic and deteriorating prognoses that impose a large burden, not only on patients but also on society and health systems. These mental illnesses share several clinical and neurobiological traits; of these traits, oligodendroglial dysfunction and alterations to white matter (WM) tracts could underlie the disconnection between brain regions related to their symptomatic domains. WM is mainly composed of heavily myelinated axons and glial cells. Myelin internodes are discrete axon-wrapping membrane sheaths formed by oligodendrocyte processes. Myelin ensheathment allows fast and efficient conduction of nerve impulses through the nodes of Ranvier, improving the overall function of neuronal circuits. Rapid and precisely synchronized nerve impulse conduction through fibers that connect distant brain structures is crucial for higher-level functions, such as cognition, memory, mood,

and language. Several cellular and subcellular anomalies related to myelin and oligodendrocytes have been found in postmortem samples from patients with schizophrenia or bipolar disorder, and neuroimaging techniques have revealed consistent alterations at the macroscale connectomic level in both disorders. In this work, evidence regarding these multilevel alterations in oligodendrocytes and myelinated tracts is discussed, and the involvement of proteins in key functions of the oligodendroglial lineage, such as oligodendrogenesis and myelination, is highlighted. The molecular components of the axo-myelin unit could be important targets for novel therapeutic approaches to schizophrenia and bipolar disorder.

Key Words: Myelin sheath; Oligodendroglia; Schizophrenia; Bipolar disorder; White matter

Core Tip: Schizophrenia and bipolar disorder are multifactorial neuropsychiatric entities that share clinical manifestations as well as alterations to brain structure and function, genetic characteristics, and neurobiological pathways. Among the main pathophysiological mechanisms shared by these conditions is oligodendroglial dysfunction. Scientific evidence that ranges from the microscale cellular and subcellular levels to the macroscale connectomic level strongly supports overall myelin dysfunction and brain disconnection as hallmarks of schizophrenia and bipolar disorder.

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INTRODUCTION

Currently, it is widely understood that optimal functioning of the central nervous system (CNS) depends on synaptic connections and multidirectional interactions between neuronal and glial cells. One of the closest glial-neuronal interactions in the CNS occurs between oligodendrocytes and neurons through myelination. Myelin ensheathment induces axonal compartmentalization to form nodes of Ranvier, *i.e.*, specialized domains that increase the conduction speed of action potentials. The saltatory propagation and speed of these electrical impulses depends on axon caliber, but primarily on myelin features such as the number and length of internodes as well as myelin width and compaction[1]. Therefore, myelination allows neuronal circuits to be finely tuned and synchronized and, as such, plays a key role in maintaining the proper connectivity between brain structures to support higher integrating processes, such as perception, memory, or cognition. Furthermore, through myelination, oligodendrocytes also provide metabolic support to axons[2,3], contributing to their structural and functional integrity, which is a requirement for homeostasis of the human brain.

Myelination is a neurodevelopmental process that begins during the third trimester of pregnancy and increases steadily during childhood and early youth until it reaches a slow-increasing plateau in adult life[4,5]. This process is adaptive, with neural activity being one of the main factors driving myelin plasticity[6]. Moreover, because the myelin sheath is a specialized structure made up of multiple layers of plasma membrane, from which most cytoplasm is extruded, its composition is enriched with lipids (approximately 70% of its content) and proteins[7]. These proteins have important functional roles, such as providing anchorage between myelin lamellae, attaching axons and myelin at paranodal regions, signaling and interacting with cytoskeletal elements within oligodendrocytes[7,8]. As with any other cell type, the plasma membrane in oligodendrocytes is subject to homeostatic turnover; thus, to manage this large energy requirement, their metabolic rate is higher than that of other cell types[9]. This characteristic renders myelinating oligodendrocytes more vulnerable to cellular stress and oxidative damage generated by reactive oxygen/nitrogen species[10]. In the case of injury and myelin loss (demyelination), endogenous repair mechanisms are triggered and remyelination occurs. For either developmental/adaptive myelination or remyelination to occur, oligodendrocyte precursor cells (OPCs) distributed along the brain must differentiate and mature to acquire myelinating capacity[11,12]. Oligodendrogenesis involves differential expression of proteins and other molecules and a dramatic increase in morphologic complexity, which implies crucial and extensive rearrangements of the oligodendroglial cytoskeleton[13,14].

Due to the intrinsic complexity of oligodendrocyte morphology and functioning and the importance of myelination/remyelination processes for CNS homeostasis, impairments in oligodendroglial lineage may be associated with brain disorders. Within the last two decades, great effort has been made to determine and describe neuronal and glial alterations that contribute to the etiology of mental illnesses [15-18]. Of the studied mental disorders, we focused on schizophrenia and bipolar disorder because these neuropsychiatric illnesses present a chronic and deteriorating course that imposes a large burden, not only on patients but also on society and health systems. These disorders are long-lasting, severe mental health conditions that share genetic characteristics and alterations to brain structure and function, and neurobiological pathways[19-21]. Among the main pathophysiological mechanisms shared by these conditions is glial dysfunction[22,23], specifically related to myelination, which is the focus of this text.

Taking the above information into account, the aim of this work was to gather and discuss the evidence that myelin dysfunction at the cellular and subcellular levels may underlie the white matter (WM) macroscale connectome alterations evidenced by neuroimaging in schizophrenia and bipolar disorder, thereby supporting the disconnection hypothesis that explains the symptomatic domains of these clinical entities. For this purpose, we first provide a brief overview of the main structural features of myelin. Next, we present the evidence of myelin alterations at the microscale levels (cellular and subcellular) found in postmortem samples from schizophrenia and bipolar disorder patients. Then, we briefly compare the main findings at these levels. Finally, we review evidence at the macroscale level from neuroimaging techniques and find consistent support for dysconnectivity among key brain regions in these disorders. These neuroimaging techniques are the main methods that allow us to obtain information about brain structure and function from patients during the course of their illnesses.

BRIEF OVERVIEW OF MYELIN STRUCTURAL FEATURES

Each myelin internode is a specialized structure of multiple membrane lamellae. The first membrane layer-closest to the axon-is called the adaxonal membrane. Between the axon and the adaxonal membrane is the periaxonal space[7]. Flanking each internode, paranodal loops make contact with the axon through the cell adhesion proteins neurofascin 155 (NF155; on the oligodendrocyte) and contactin-associated protein 1 (Caspr1)/contactin 1 (on the axon). In juxtaparanodal regions, myelin-axon interactions are mediated by contactin 2 and Caspr2, and the voltage-gated K^+ channels Kv1.1/1.2 are enriched at the axolemma. Contactin's cytoplasmic domains provide anchors for scaffold molecules of the paranodal-nodal-paranodal cytoskeleton, specifically for the 4.1B protein, the αII/β2SP heterotetramers (both actin-interacting proteins) and ankyrin B (AnkB)[24].

In a mature myelin internode, the adaxonal layer is relatively loose compared with the tightly compacted myelin lamellae, and its cytoplasmic content is slightly higher, which allows the functional presence of signal transduction molecules and oligodendroglial cytoskeletal components such as septin filaments[25]. These components are also present at paranodal loops. In contrast, the structure of compact myelin is almost withdrawn from the cytoplasm; thus, intracellular membranes are in tight apposition, with myelin basic protein (MBP) playing a key role in regulating the hydrophobic forces between them[7].

As previously mentioned, the molecular composition of myelin is highly enriched in lipids, which account for approximately 70% of its wet weight. Myelin membranes have a higher cholesterol content than other membranes (at approximately 1.6-fold) and are characteristically enriched with galactosphingolipids and plasmalogens, which are asymmetrically distributed among the bilayer leaflets. The extracellular leaflet is enriched in galactosylceramide and its sulfated form, sulfatide, as well as phosphatidylcholine and sphingomyelin, whereas the intracellular leaflet is rich in ethanolamine plasmalogen and other phospholipids. The lipid components of the extracellular leaflet form discrete domains known as lipid rafts, which often contain membrane proteins and are frequently involved in signaling and/or myelin component turnover. For further review of myelin lipids, see[26,27].

Myelin-specific structural proteins also are distributed according to their functions. Interestingly, at least five out of eleven CNS myelin-specific proteins are categorized as intrinsically disordered proteins. This set of physicochemical attributes accounts for their flexibility and multifunctionality, which are important for a plastic structure such as myelin[28]. An exhaustive description of the structural and functional features of every myelin-specific protein is beyond the scope of this review and has been further addressed elsewhere[8,29]. Figure 1 illustrates the main CNS myelin-specific proteins at their common locations in the myelin sheath, as well as the lipidic composition of myelin membranes.

EVIDENCE OF MYELIN ALTERATIONS AND OLIGODENDROGLIAL DYSFUNCTION IN POSTMORTEM SAMPLES OBTAINED FROM SCHIZOPHRENIA PATIENTS

The analysis of postmortem samples provides valuable information about the structural and

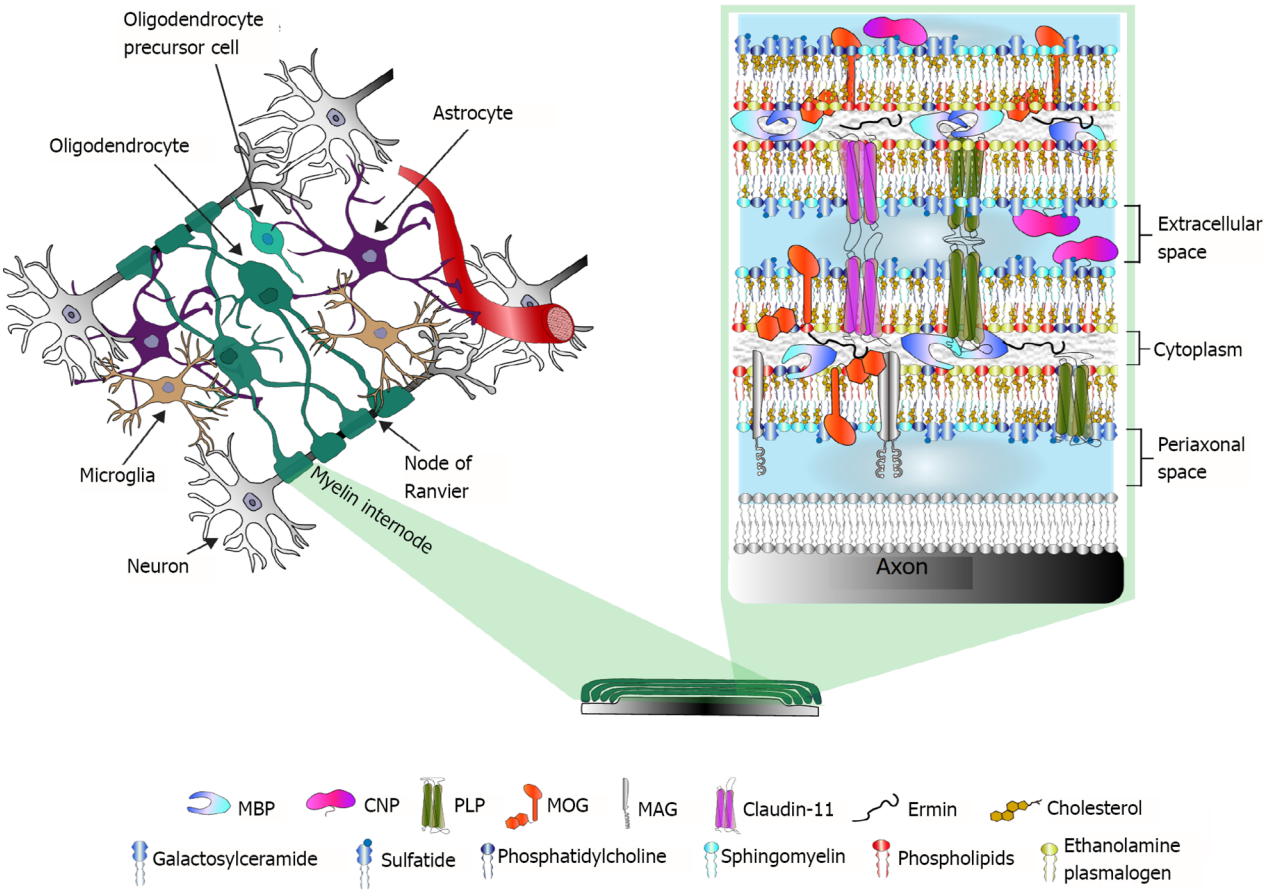

Figure 1 Myelin in the central nervous system. Left, a schematic representation of central nervous system (CNS) cells and their multidirectional interactions. Right, the main protein and lipid components of CNS myelin. Proteomic studies have revealed altered expression of myelin proteins in postmortem brain samples from patients with schizophrenia or bipolar disorder. MBP: Myelin basic protein; CNP: 2',3'-cyclic nucleotide 3'-phosphodiesterase; PLP: Proteolipid protein; MOG: Myelin-oligodendrocyte glycoprotein; MAG: Myelin-associated glycoprotein.

biochemical alterations present in the brains of patients with neuropsychiatric disorders. In the last 20 years, several reports by Uranova *et al*[30] have described the main ultrastructural alterations in oligodendrocytes and myelinated fibers found in patients with schizophrenia.

With electron microscopy and morphometry or with a stereological approach and Nissl-stained sections, they extensively analyzed the prefrontal cortex (PFC), specifically the gray matter layers of Brodmann's area 9 (BA9) and BA10[30-33] and their adjacent WM[34-36], as well as the caudate nucleus [21,33,37,38], hippocampus[33,38,39] and anterior putamen[40].

Their analysis of myelinated fibers found concentric lamellar bodies and interlamellar abnormal inclusions, swelling of periaxonal oligodendrocyte processes and ultrastructural signs of axonal atrophy [21,33,38,39]. They characterized six types of abnormal myelinated fibers that were present in patients with schizophrenia and that could correlate with the predominant presence of positive or negative symptoms, age or illness duration[35].

Oligodendrocytes showed consistent signs of dystrophia, apoptosis and/or necrosis, and in most of the studies, their numerical density was significantly reduced in patient samples[31,33,37,40]. Oligodendrocyte clusters, which are thought to be involved in activity-dependent myelination, were also consistently reduced[37,40]. In the oligodendrocytes, mitochondria were the main altered organelle, with a significant reduction in numeric and volume density and even intramitochondrial accumulation of lipofuscin granules[30,34,36,38]. These findings suggest that not only is the numerical density of oligodendrocytes affected in schizophrenia, but that their energy and redox metabolism is also compromised.

Interestingly, both perineuronal and pericapillar oligodendrocytes showed signs of dystrophy in patient samples[33,34] suggesting that oligodendrocytes may be involved both in the disrupted transmission of neuronal information and in metabolic dysregulation. In addition, these studies found dystrophic ameboid microglia adjacent to dystrophic oligodendrocytes[30,34] and myelin concentric lamellar bodies engulfed by astrocytes[21], implying the involvement of other glial cells in myelin pathology in schizophrenia patients.

Hof *et al*[41,42] found a significant decrease in both the total number of oligodendrocytes and the number of oligodendrocytes expressing the 2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNP) marker

in cortical layer III of BA9 and the WM of the superior frontal gyrus with a stereological analysis on samples from patients with schizophrenia. Additionally, the number of oligodendrocyte clusters in the WM was significantly reduced[42]. Other studies reported a decreased number of oligodendrocytes in the anterior principal thalamic nucleus[43,44], centromedian thalamic nucleus[44], thalamic internal capsule[45], hippocampus[46,47] and anterior cingulate WM[48] of schizophrenia patient samples. In the latter structure, oligodendrocytes expressing disintegrin and metalloproteinase domain-containing protein 12 (ADAM12) were examined[48]. ADAM12 is predominantly expressed in oligodendrocytes and has been suggested to play a role in myelination and neurodevelopmental processes, as well as in higher cognitive functions[49].

Not all neuropathological studies of postmortem schizophrenia brain samples showed significant differences in oligodendrocyte densities, *e.g.*, in the cingulum bundle[50], BA9 adjacent WM[23,51], and BA10 adjacent WM[34], no changes in oligodendrocyte cell densities were found between schizophrenia and control samples. In contrast, an increased density of prohibitin$^{(+)}$-oligodendrocytes was reported in the right dorsolateral prefrontal WM of schizophrenia patients[52]. The authors suggested that prohibitin may be upregulated in oligodendrocytes as a result of mitochondrial stress and/or dysfunction in schizophrenia.

mRNA expression of neural/glial antigen 2 (NG2) was augmented in the putamen of schizophrenia patients[53], suggesting that there could be an increased density of OPCs. Additionally, a study by Kerns *et al*[45] supported the hypothesis that in schizophrenia OPCs may fail to exit the cell cycle and differentiate into mature myelinating oligodendrocytes. In BA9 WM, there was no significant difference in NG2$^{(+)}$-cells but a significant reduction in cells expressing oligodendrocyte transcription factor 2 (OLIG2), suggesting an overall reduction in the oligodendroglial lineage[54].

MYELIN SUBCELLULAR/BIOCHEMICAL ALTERATIONS IN POSTMORTEM SAMPLES OF PATIENTS WITH SCHIZOPHRENIA

Proteomic approaches have been used to determine that the main myelin structural proteins are differentially expressed in schizophrenia postmortem brain samples; in most of the studies, these proteins were significantly downregulated. For most of the myelin structural proteins, altered transcriptomic levels have consistently been reported[53,55-57], and in some cases, single-nucleotide polymorphisms (SNPs) at their codifying genes have been associated with schizophrenia (Table 1). This is the case for MBP[58-61], CNP[57,60-63], proteolipid protein (PLP)[60,62,64], myelin-associated glycoprotein (MAG)[62,64,65], and transferrin[66-68]. The latter is not a structural myelin protein, but is essential for oligodendrocyte homeostasis and survival[69,70]. Downregulation of myelin oligodendrocyte glycoprotein (MOG)[58,60-62,71] and claudin-11[62,64] at the proteomic and transcriptomic levels has been reported, although no SNPs of the corresponding codifying genes have been associated with schizophrenia. Several brain regions have been analyzed by proteomic studies, such as the dorsolateral PFC BA46[59,62,71], PFC BA9 gray and WM[68], PFC BA10[60], anterior PFC[65], orbitofrontal cortex[64], anterior temporal lobe[58], corpus callosum[61], cerebellum, posterior cingulate cortex and caudate nucleus[63].

Consistent with findings of overall downregulation of myelin-specific proteins, mRNA levels of *OLIG1*[22], *OLIG2*[22,55,72-74] and *SOX10*[22,55,72], corresponding to oligodendroglial lineage transcription factors, were significantly reduced in postmortem schizophrenia brain samples. Additionally, the expression of the *NG2*, *PGDFRA* and *GALC* genes (the former two coding for markers of OPCs and the latter for a marker of immature oligodendrocytes), was consistently downregulated in patient samples[22]. Quaking (QKI), an RNA-binding protein with a key role in the posttranscriptional regulation of myelin-specific genes, mRNA levels were significantly reduced in postmortem samples of schizophrenia patients[72,75-77]. Moreover, SNPs in both *OLIG2* and *QKI* genes have been associated with this mental disorder.

In addition to the previously mentioned gene association studies, a functional glial-specific gene set analysis based on genome-wide association data reported three main oligodendroglial gene sets, *i.e.*, lipid metabolism, gene transcription and oxidation–reduction, which were strongly associated with an increased risk for schizophrenia[78]. Furthermore, gene expression profile analysis of CNP$^{(+)}$-cells revealed nine differentially regulated signaling pathways associated with oligodendrocyte differentiation[54], strongly suggesting oligodendrogenesis impairment in schizophrenia.

Proteomic studies of schizophrenia-derived postmortem brain samples have also consistently revealed that many cytoskeletal components are differentially expressed in this disorder. Dynamic cytoskeletal rearrangements are crucial for oligodendrogenesis since this process implies a dramatic increase in oligodendroglial morphologic complexity. Additionally, actin-cytoskeleton dynamic assembly and disassembly are critical for axon ensheathment during the myelination process[79-81]. Several actin-interacting proteins are involved in these rearrangements, including gelsolin and cofilin, actin filament-severing proteins that drive actin cytoskeleton disassembly, which is essential for proper myelin wrapping[79]. Gelsolin is specifically expressed in myelin-forming cells[82] and is present in the different stages of oligodendroglial lineage differentiation[83]. Transcriptomic and proteomic analyses

Table 1 Studies that reported single-nucleotide polymorphisms associated with schizophrenia in myelin/oligodendrocyte genes

Protein name	Gene	SNPs	Ref.
Myelin basic protein	*MBP*	rs12458282; rs2008323; rs721286	Baruch *et al*[185], 2009
2′,3′-Cyclic nucleotide 3′-phosphodiesterase	*CNP*	rs2070106	Peirce *et al*[186], 2006
			Voineskos *et al*[187], 2008
			Voineskos *et al*[175], 2013
Proteolipid protein	*PLP*	rs475827	Qin *et al*[188], 2005
Myelin-associated glycoprotein	*MAG*	rs720308; rs720309; rs756796; rs2301600	Wan *et al*[189], 2005
			Yang *et al*[190], 2005
			Voineskos *et al*[187], 2008
Transferrin	*TF*	rs3811655; rs448115	Qu *et al*[191], 2008
			Huo *et al*[192], 2019
Oligodendrocyte lineage transcription factor 2	*OLIG2*	rs1059004; rs9653711	Georgieva *et al*[73], 2006
			Voineskos *et al*[175], 2013
			Huo *et al*[192], 2019
			Komatsu *et al*[74], 2020
Quaking	*QKI*	rs2784865	Voineskos *et al*[175], 2013

SNP: Single-nucleotide polymorphisms.

of postmortem brain samples have shown that both gelsolin[61,68,72] and cofilin[59,63,64] are dysregulated in schizophrenia. Similarly, the oligodendrocyte-specific protein ermin, also known as juxtanodin, is downregulated in the anterior temporal lobe and upregulated in the dorsolateral PFC in patients with schizophrenia[58,59]. Ermin is an F-actin binding protein that is expressed at late stages of oligodendrocyte maturation. It may play a key role in the formation of multiple oligodendroglial processes and the dramatic changes in morphology as these cells acquire the capacity for myelination [84,85].

Septin heteromeric filaments (SEPT2/SEPT4/SEPT7/SEPT8) form at the adaxonal myelin layer and at paranodal loops. These filaments act as molecular scaffolds, mediating axo-glial signaling and compartmentalization of mature myelin. Their loss or deficit has been associated with the formation of myelin outfoldings that impair the rapid propagation of nerve impulses[25,86,87]. The four septins involved in these filaments are differentially expressed in proteomic analyses of postmortem schizophrenia brain samples[62,63].

α/β-Spectrin oligomers are important components of the membrane-bound cytoskeleton at the axolemma. At the paranodal and juxtaparanodal regions of the axon beneath a myelin internode, these oligomers interact with proteins such as 4.1B, adducin and AnkB to form a scaffold that mediates the interaction of the cytoplasmic tails of contactins and other axo-glial adhesion molecules with the actin filaments and the actin rings found along the axon. These proteins are also relevant because they are crucial for the paranodal-nodal-paranodal cytoskeleton, which is a specific arrangement of cytoskeletal protein oligomers and polymers underlying the proper assembly and plasticity of the nodes of Ranvier [24]. All of these proteins are differentially regulated in schizophrenia postmortem brain samples[58,59,62-64].

Neurofilaments are important axonal cytoskeletal components. They belong to the intermediate filament IV category, and their composition is heteromeric, with light (NEFL), medium (NEFM) and heavy (NEFH) polypeptides as their main constituents. Internexin (INA) is also a component of these axonal structural filaments. Repelling forces among negatively charged phosphorylated residues on the neurofilaments contribute to the enlargement of axon caliber, *e.g.*, at internodes (Figure 2). Thus, phosphorylation/dephosphorylation of neurofilament polypeptides is a mechanism that regulates axon caliber, which influences molecular trafficking as well as the speed of nerve impulse conduction. Proteomic studies have found that the three neurofilament polypeptides NEFL, NEFM, and NEFH, as well as INA, are differentially regulated in postmortem brain samples from schizophrenia patients[57,61-64].

As expected, the actin and tubulin monomeric components of microfilaments and microtubules, respectively, as well as various microtubule-associated proteins, are altered in schizophrenia brain samples[58,61-63]. The cytoskeleton mediates the essential functions of every cell in the organism. In the axo-myelin functional unit[88], the cytoskeleton is crucial for the following: Oligodendrogenesis; myelin

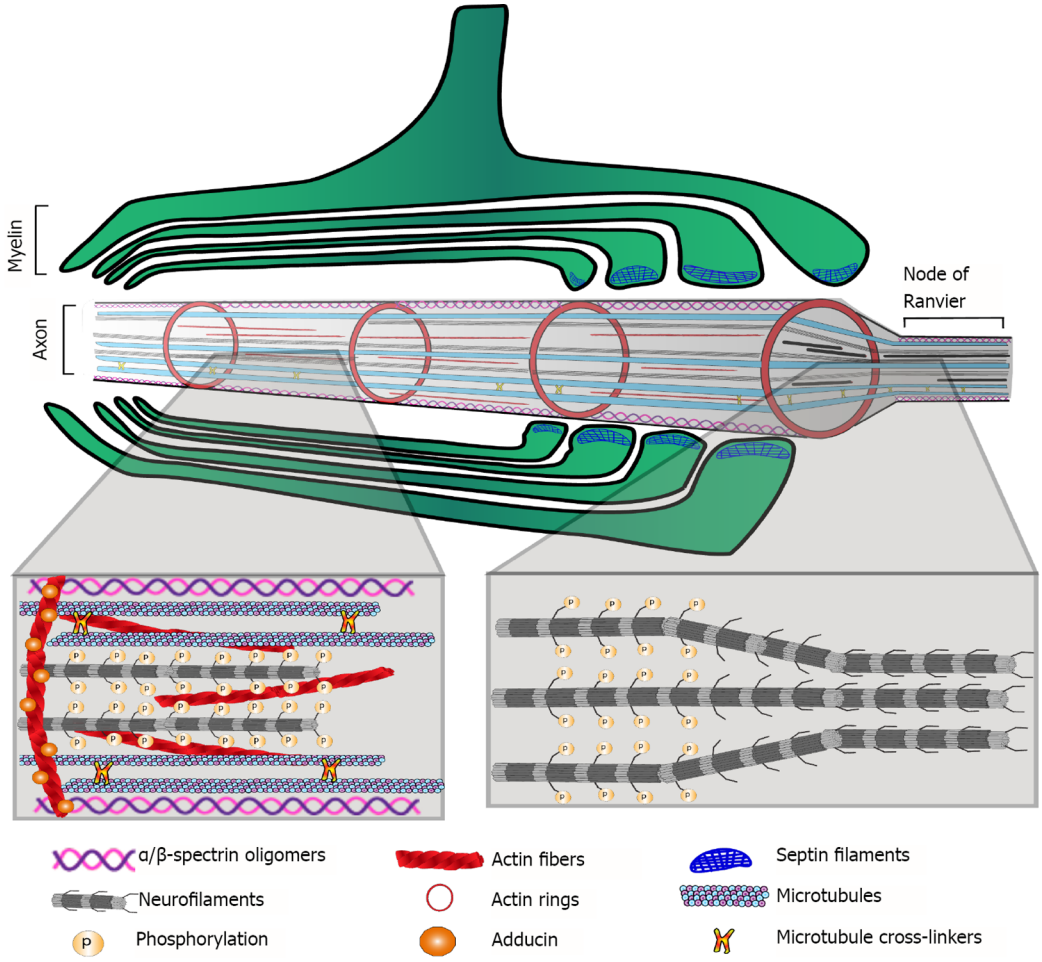

Figure 2 Main cytoskeletal components of the myelinated axon. Proteomic approaches revealed alterations in most of these components in postmortem brain samples of schizophrenia patients.

formation, turnover and plasticity; assembly and remodeling of axonal specialized domains, such as the axon initial segment and nodes of Ranvier; myelin and axonal compartmentalization; anchorage for cell adhesion molecules involved in axo-glial junctions; and scaffolds for molecules involved in signal transduction.

As most of the myelin structural proteins are affected by schizophrenia and most of the cytoskeletal components are dysregulated, it is plausible to infer that overall dysfunction of the axo-myelin unit may underlie the compromised integrity of gray and WM and thus the functional disconnection observed in schizophrenia.

Metabolic dysfunction in schizophrenia has been suggested by positron emission tomography (PET) and magnetic resonance imaging (MRI), and mitochondrial alterations have been documented as mentioned above. At the proteomic level, dysregulation in the expression of enzymes involved in energy metabolism and the antioxidant system has been observed. For example, Martins-de-Souza *et al* [59,89] found alterations in proteins involved in glycolysis (fructose-bisphosphate aldolase C and phosphoglycerate kinase 1), the Krebs cycle (citrate hydrolyase), the malate-aspartate shuttle (cytosolic malate dehydrogenase) and oxidative phosphorylation (mitochondrial ATP synthase F1 and F0 complexes) in postmortem dorsolateral PFC samples from schizophrenia patients[59,89]. In addition, four subunits of mitochondrial respiratory complex I (NADH dehydrogenase [ubiquinone] (NDU) flavoprotein 2 (NDUFV2), iron-sulfur protein 3 (NDUFS3) and 6 (NDUFS6), and 1 beta subcomplex subunit 5 (NDUFB5)) are downregulated in the anterior temporal lobe of schizophrenia patients[58,89].

Increased amounts of oxidative reactive species are produced under high energy demand or mitochondrial dysfunction, as is suggested to occur in schizophrenia. Therefore, antioxidant enzymatic systems in schizophrenia are expected to be upregulated to counteract oxidative damage. However, the expression levels of three members of the glutathione transferase (GST) family (GSTM3, GSTTLp28, and GSTP1), carbonyl reductase 1 (CBR1), carbonyl reductase 3 (CBR3) and quinoid dihydropteridine reductase (QDPR), are reduced in the thalamus and PFC of schizophrenia patients (reviewed in[89]). As these results were obtained from brain homogenates, an interesting follow-up would be to assess whether these metabolic and redox alterations are present in oligodendrocytes. For this purpose, enriched cultures of patient-derived oligodendrocytes differentiated from induced pluripotential stem

cells (iPSCs) and/or cocultures of these induced oligodendrocytes with neurons and other glial cells could be useful *in vitro* tools for studying alterations in the oligodendroglial lineage in schizophrenia.

MYELIN ALTERATIONS AND OLIGODENDROGLIAL DYSFUNCTION EVIDENCE IN POSTMORTEM SAMPLES OBTAINED FROM BIPOLAR DISORDER PATIENTS

Uranova *et al*[51] also analyzed samples from patients with bipolar disorder, examining BA9 of the PFC, layers III and VI and the adjacent WM, BA10, the caudate nucleus and the anterior putamen. A stereological approach with Nissl-stained samples revealed a significant reduction in the numerical density of oligodendrocytes in the caudate nucleus and in the gray matter layers of BA9[32,37,51]. In the adjacent WM, they found no difference between bipolar disorder samples and samples from control subjects[51]. The number of oligodendrocyte clusters was also significantly reduced in the caudate nucleus[37] and in the anterior putamen, but the latter difference was observed only in male subjects [40]. Electron microscopy analysis of the samples showed ultrastructural signs of apoptosis and necrosis of oligodendrocytes[21].

Oligodendrocyte numbers were significantly reduced in the thalamic anterior principal and centromedian nuclei, in postmortem samples from bipolar disorder patients with a clinical history of psychotic episodes[44]. The age-related increase in oligodendrocyte number observed in control subjects was attenuated in this group of patients. The latter effect was also observed by Vostrikov and Uranova[90]. Vostrikov and Uranova[90] also found significantly reduced oligodendrocyte densities in samples from BA9 Layer VI from bipolar disorder patients younger than 50 years old compared with those from corresponding age-matched controls[90]. Hayashi *et al*[91] found a significant reduction in $OLIG2^{(+)}$-cells using a flow cytometry approach in unfixed postmortem gray matter BA10 samples from bipolar disorder patients, which suggests an overall deficit in the oligodendroglial lineage. $S100B^{(+)}$-oligodendrocyte density was decreased in the left alveus of the hippocampus from bipolar disorder patients[92]. In contrast, Hercher *et al*[23] found increased oligodendrocyte density and CNP protein levels in BA9-adjacent WM in bipolar disorder patients compared with control samples. A further study also showed an increase in oligodendrocyte density along with deficits in axonal markers in prefrontal WM in bipolar disorder patients[93]. In a systematic review of postmortem brain studies in bipolar disorder, Gigase *et al*[94] found no difference in either neurons or glial cells and suggested that findings from existing studies should be validated.

Significantly less intense myelin staining of the deep prefrontal WM was shown in bipolar disorder patients than in control subjects[95]. Additionally, MBP immunostaining revealed decreased myelination of the hippocampal formation in female bipolar disorder patients than a corresponding sex-matched control group[96]. In contrast, male patients showed increased MBP staining in the superior medullary lamina, which suggests sex differences in myelin alterations[96]. To the best of our knowledge, no ultrastructural analysis of myelinated fibers has been conducted on bipolar disorder postmortem samples.

Perineuronal oligodendrocytes are located in the cerebral gray matter in close proximity to neuronal perikarya and less frequently near dendrites and neurites. Although their morphology is indistinguishable from that of other oligodendrocytes, it remains unknown whether perineuronal oligodendrocytes have a similar or different cell signature from that of typical myelinating oligodendroglial cells[97]. Bipolar disorder patients showed cytochemical abnormalities of prefrontal perineuronal oligodendrocytes, correlating with cytochemical alterations of calbindin-containing GABAergic neurons and changes in gene expression levels[98].

MYELIN SUBCELLULAR/BIOCHEMICAL ALTERATIONS IN POSTMORTEM SAMPLES OF PATIENTS WITH BIPOLAR DISORDER

Myelin structural proteins MBP, CNP, PLP and MOG were downregulated in postmortem brain samples from bipolar disorder patients[60]. Consistent downregulation at the transcriptomic level was reported for *MBP* and *CNP*, and at this level *MAG*, *PLP*, *CLDN11*, *MOG*, and *MOBP* were also downregulated[22]. Reduced mRNA levels were also reported for *TF*[22,53]. The gene expression of the oligodendroglial lineage transcription factors *OLIG1*, *OLIG2* and *SOX10* was downregulated. Additionally, transcript levels of *NG2* and *GALC*, which correspond to markers of OPCs and immature oligodendrocytes, respectively, were significantly lower in bipolar disorder samples than in control samples[22].

Differential expression of cytoskeletal components of the axo-myelin unit has been reported in postmortem brain samples of bipolar disorder patients. In the WM adjacent to BA9, the β-tubulin protein level assessed by Western blot was significantly lower in patient samples than in controls[93]. A proteomic approach found that the NEFL level was downregulated in bipolar disorder samples of BA10 [60]. Similarly, the neurofilament units NEFL and NEFM and INA, α-spectrin (SPTAN1), SEPT11 and

tubulin polymerization-promoting protein (TPPP) were downregulated, whereas β-actin (ACBT) and the ARPC5 subunit of the actin-binding Arp2/3 complex were upregulated in hippocampal samples from bipolar disorder patients[99,100]. The actin-bundling protein fascin (FASC) was also dysregulated in these samples[99]. In samples of the dorsolateral PFC, NEFL, NEFM and INA were consistently downregulated, while α- and β-tubulins as well as SEPT5, SEPT6 and SEPT11 were upregulated[67].

As in schizophrenia, alterations in metabolic and redox pathways have been described for bipolar disorder. Studies using magnetic resonance spectroscopy have found a reduction in phosphocreatine and ATP in the frontal lobes and basal ganglia, while an increase in lactate levels was reported in postmortem gray matter samples from bipolar disorder patients. In addition, mitochondrial structure is altered, and mutations or polymorphisms in mitochondrial DNA associated with the respiratory chain have been reported[101]. Furthermore, high levels of lipid peroxidation, nitric oxide concentration, and DNA and RNA oxidative damage were found in patient samples[102]. There is evidence of dysfunctional attachment of the hexokinase 1 protein to the outer mitochondrial membrane in patient samples, which results in abnormal generation of mitochondrial reactive oxygen species and cellular oxidative stress[103]. Additionally, impairment of redox modulation pathways in the frontal cortex is found in bipolar disorder patients[104]. The antioxidant molecule glutathione has been reported at low concentrations in some brain regions and could contribute to oxidative stress[105,106]; however, some patients present a significant increase in this molecule in the anterior cingulate cortex[107]. These apparently contradictory results could reflect differential redox regulation or antioxidant capacity in diverse brain regions.

Due to their high metabolic rate and high lipid content in myelin-forming membranes, oligodendrocytes are especially vulnerable to oxidative stress. Therefore, a microenvironment prone to the generation of high amounts of oxidative molecules and an impaired antioxidant capacity, which seems to be characteristic of patients with schizophrenia or bipolar disorder, would certainly contribute to the dysfunction of the axo-myelin unit and subsequently impact the proper conduction of nerve impulses.

COMPARISON OF ALTERED FEATURES OF OLIGODENDROCYTES AND MYELIN IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Several features are similarly altered by schizophrenia and bipolar disorder at the cellular level. Ultrastructural studies have revealed signs of oligodendrocyte apoptosis and necrosis[21], oligodendrocyte numerical density was significantly reduced in the caudate nucleus[37] and in BA9 gray matter layers of the PFC[32,51], and significantly fewer oligodendrocyte clusters were found in the caudate nucleus[37] and the anterior putamen[40]. In BA9-adjacent WM, a stereological analysis found no differences in oligodendrocyte numerical density in either schizophrenia or bipolar disorder patients compared to that of the control samples[51]. However, in schizophrenia, studies have reported decreased oligodendrocyte numerical density in the BA9- and BA10-adjacent WM[33,108], a significant reduction of $OLIG2^{(+)}$-cells in the former[54], and a significant decrease in both total and $CNP^{(+)}$-oligodendrocytes in the WM of the superior frontal gyrus[41,42]. Additionally, significantly fewer $ADAM12^{(+)}$-oligodendrocytes were found in the anterior cingulate WM[48]. In contrast, two different studies reported increased oligodendrocyte density in the prefrontal WM in postmortem samples from bipolar disorder patients[23,93]. One of these studies reported a concomitant decrease in axonal markers [93], which may imply axonal degeneration due to demyelination, which is consistent with an increase in oligodendrocytes at early stages of differentiation. In schizophrenia-derived samples, significantly more oligodendrocytes expressing prohibitin were found in the right dorsolateral prefrontal WM[52]. Although prohibitin proteins can be found in other cell compartments, such as the nucleus or plasma membrane, their role in the inner mitochondrial membranes is key for modulating cell proliferation or apoptosis and for overall mitochondrial homeostasis[109-112]. Therefore, altered oligodendroglial prohibitin expression is consistent with a previous work suggesting dysregulation of the cell cycle in oligodendrocytes in schizophrenia[113]. Based on the findings of that work, Katsel *et al*[113] suggested that postmitotic oligodendrocytes may abnormally re-enter the cell cycle, while a significantly increased level of NG2 in the putamen of schizophrenia patients suggested that OPCs failed to exit the cell cycle. Dysregulation of p57Kip2 gene expression in schizophrenia patient samples[113] could also be related to impaired oligodendrocyte maturation, since this protein has been characterized as an oligodendroglial differentiation competence marker[114-116].

At the subcellular level, proteomic analyses have revealed that the four most abundant myelin structural proteins[117] (PLP, MBP, CNP, and MOG) are significantly reduced in schizophrenia and bipolar disorder. At the transcriptomic level, almost all myelin structural proteins, as well as the main oligodendroglial lineage markers and OPC markers, were significantly downregulated. This evidence strongly suggests that the oligodendroglial lineage is compromised at all differentiation stages in these disorders. Moreover, several axonal and oligodendroglial cytoskeletal components and cytoskeletal-interacting proteins are dysregulated in both schizophrenia and bipolar disorder. A deficit of myelin structural and cytoskeletal proteins in the axo-myelin functional unit may compromise myelin formation, compaction, remodeling and its overall integrity and functionality, which may imply a

concomitant compromise in the assembly and functioning of the nodes of Ranvier and other axonal functional rearrangements. If nervous impulses are not properly conducted in terms of speed and precise timing, some connections would not be reinforced and could be lost, influencing the local connectome. At the macroscale connectomic level, which comprises long-range tracts, fine-tuning and synchronization of nervous impulse conduction is crucial, and even subtle alterations of myelin structural and functional features may have a detrimental impact on information processing and thus on cognitive functions and behavior.

These findings suggest that altered myelination, loss of oligodendrocytes and compromised energy and redox metabolism in oligodendrocytes of schizophrenia and bipolar disorder patients could correlate with the WM alterations observed by neuroimaging techniques. These mechanisms could explain, at least partially, the clinical manifestations observed in schizophrenia and bipolar disorder patients. The relationship between myelin and oligodendrocytes, WM and symptom domains can be systematically studied. In the following sections, we will address the evidence from imaging studies on dysfunctions in the nervous tracts and how the main symptoms correlate with these alterations, giving rise to the hypothesis of disconnection in mental disorders.

EVIDENCE OF WM ALTERATIONS IN SCHIZOPHRENIA AND BIPOLAR DISORDER IN BRAIN IMAGING STUDIES

Structural and functional neuroimaging findings provide evidence of connectivity alterations that might be related to myelin dysfunction; the most extensive evidence comes from MRI studies[118]. In the field of structural magnetic resonance imaging (sMRI), WM volume and density have been measured using techniques such as voxel-based morphometry (VBM)[119]. VBM studies have found diminished WM volume and density in several brain regions of patients with schizophrenia, with main decreases in the frontal and temporal regions. A meta-analysis of VBM studies reported decreased WM in 150 foci. The affected tracts included the corpus callosum, internal capsule, fornix, anterior commissure, and an additional sixteen tracts[120].

Additionally, WM alterations have been detected by diffusion tensor imaging (DTI); this method evaluates subtle changes in WM, determining fractional anisotropy (FA). FA expresses the diffusion of water molecules along neural fibers. Water movement is inhibited when myelin sheaths are thick and well preserved (FA = 1); in contrast, water moves easily along fibers in any direction when the myelin sheath is damaged (FA = 0)[118]. Although FA can indeed reflect changes in myelination, it could also reflect other tract properties, such as axonal ordering and axonal density[121]. Therefore, Jones *et al*[121] urge caution when interpretating DTI-based measurements and not assume that they are direct indicators of WM integrity[121]. Bearing this in mind, DTI studies have reported that patients with schizophrenia have a widespread decrease in FA[122]. For instance, the ENIGMA-Schizophrenia DTI group analyzed 4321 individuals and found widespread FA reductions in 20 of the 25 analyzed regions in schizophrenia patients when compared with those of the controls[123]. In addition, at least three meta-analyses have reported reduced FA in schizophrenia patients; they conclude that the tracts more frequently affected in these patients are the anterior corona radiata, the corpus callosum, the cingulate bundle, and the uncinate and arcuate fascicles[120,123,124] (Figure 3). Furthermore, functional MRI (fMRI) studies have also reported connectivity alterations in several circuits connecting frontal, limbic, temporal, and parietal regions in schizophrenia subjects, as well as alterations to the default network [125,126].

As the evidence is extensive and complex, we will discuss the neuroimaging evidence of WM alterations in schizophrenia based on each of its main clinical domains. This will integrate the findings and highlight the importance of WM. The structural and functional WM alterations associated with the psychotic domain of schizophrenia include tracts and circuits that connect the frontal, temporal, and parietal cortexes[127]. For instance, the arcuate fasciculus (AF) is frequently studied in regard to the psychotic domain; the AF connects temporal and parietal regions with the frontal lobe and is considered the main language processing tract of the brain because it connects Wernicke's and Broca's areas[128]. DTI studies on schizophrenia patients have reported diminished FA on the AF when compared with that of controls[123]. Additionally, some studies have related the decrease in AF integrity with thought disturbances, language alterations, and auditory hallucinations[129-131].

Furthermore, psychotic symptoms are related to functional connectivity alterations in the fronto-striatal, frontotemporal, and frontoparietal circuits[132]. The frontostriatal circuit comprises the connections between the PFC and basal ganglia[128]. These regions have been extensively studied in relation to the dopaminergic hypothesis of schizophrenia[133]. Some studies of resting-state fMRI analysis have indicated functional dysconnectivity between the dorsolateral PFC and basal ganglia in patients with schizophrenia, which is related not only to psychotic symptoms but also to cognitive alterations[134]. In contrast, the frontotemporal circuit comprises connections from the PFC to temporal structures, including the auditory cortex and Wernicke's area[128]. Functional connectivity alterations in this circuit have been related to auditory hallucinations and the perceived reality of those hallucinations [134].

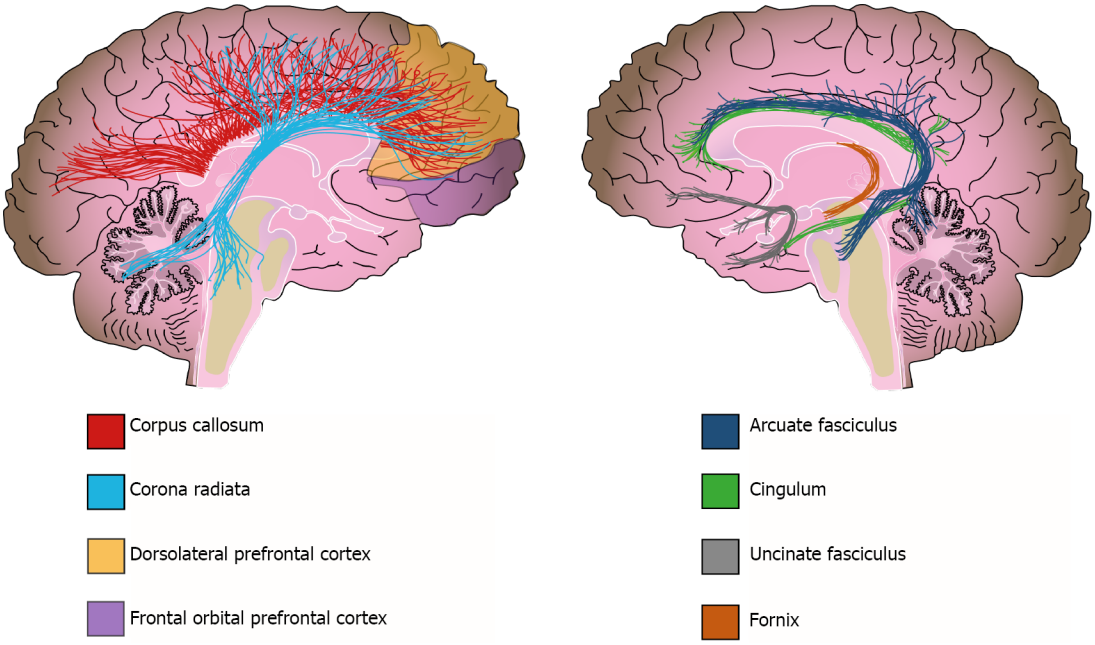

Figure 3 White matter alterations in schizophrenia. Solid lines represent the path of the affected white matter tracts, whereas shadowed areas (purple and yellow) show brain regions with diminished white matter density.

Alterations to the cingulum bundle, fornix, and inferior fronto-occipital fascicle are related to cognitive symptoms of schizophrenia[127,135]. The cingulum bundle is a major connector between limbic, paralimbic, and neocortical structures, including the dorsolateral PFC, amygdala, paralimbic gyrus, and cingulate gyrus. This tract is implicated in self-monitoring, spatial orientation, and memory [128]. Subjects with schizophrenia have lower FA on the cingulum bundle than controls, which has also been linked with executive dysfunction and impaired working memory in these same patients[136,137]. The fornix is another WM structure implicated in cognitive function; this tract connects the hippocampus with other cortical structures and is implicated in memory and spatial learning[128]. Patients with schizophrenia have compromised fornix integrity and disrupted functional connectivity between the PFC and the hippocampus[138,139]. Further analysis of functional connectivity has provided evidence of alterations in the frontostriatal and frontoparietal circuits that are also related to cognitive dysfunctions in schizophrenia subjects[132].

Connectivity alterations have been associated with altered tract integrity of the uncinate fascicle; this tract connects the orbitofrontal and anterior dorsolateral cortex with the temporal lobe and is related to negative symptoms[128]. At least two studies have demonstrated an association between low FA of this tract and flattened affect and lack of social engagement[140,141]. As WM decline can be a consequence of demyelination, all of these neuroimaging results (that report WM reduction in important tracts underlying highly integrative brain functions) support the hypothesis that demyelination may be a key factor in explaining, at least in part, the symptoms of schizophrenia.

There are also extensive data on gray and WM changes that are associated with clinical characteristics, genetics, functional impairment, and treatment response for bipolar disorder[142,143]. Currently, one of the main hypotheses about the neurobiology of this disease centers on the disconnection of prefrontal-subcortical networks and limbic structures associated with mood regulation[144]. Diverse prefrontal-striatal-thalamic circuits that regulate the expression of sensorial, cognitive, and emotional data from cortical regions are altered in bipolar disorder patients. It is believed that the dysfunction of these networks explains the cognitive, behavioral, and affective manifestations of this disorder[145]. The current fronto-limbic circuit disconnection model highlights the importance of WM in bipolar disorder. Evidence of WM alterations can be provided through structural or functional findings from neuroimaging techniques, with the most extensive evidence coming from MRI studies.

White matter hyperintensities (WMHs) are evident bright areas on T2 MRI sequences. These alterations are one of the most replicated findings in bipolar disorder[144]. WMHs are lesions that are associated with vascular anomalies and neurodegenerative processes, such as demyelination, axon loss, or necrosis[146]. These lesions are frequently found around the lateral ventricles (periventricular), deep WM, and subcortical gray matter (basal ganglia, thalamus)[147,148]. At least three meta-analyses have linked the presence of WMHs with bipolar disorder, and it is estimated that approximately 39% of bipolar disorder patients have these lesions, compared with 18% of controls[149-151]. The presence of WMHs in patients has been associated with the worst outcomes of the disease, such as hospitalizations, psychotic symptoms, suicide attempts, cognitive impairment, and treatment resistance[151-155].

In addition to WMH, there is also extensive evidence about WM volume alterations from different methodologies[156]. Two meta-analyses that used a region-of-interest (ROI) approach reported a volume reduction in the corpus callosum of bipolar disorder patients, which is a structure of crucial importance for interhemispheric connectivity and is implicated in higher cognitive functions such as attention, memory, and language[124,156,157]. However, no clear association was found between altered corpus callosum volumes and psychotic symptoms or suicidal ideation in patients[157-159]. In contrast, Lavagnino *et al*[160] reported an association between volume reduction of the posterior corpus callosum and a higher number of affective episodes, hospitalizations, and incomplete remission of symptoms in female patients[160]. Other studies and meta-analyses used VBM to evaluate the whole brain and reported a reduction in WM volume of the corpus callosum, corona radiata, posterior cingulum, and inferior longitudinal fasciculus in bipolar disorder[142,161] (Figure 4).

DTI studies of bipolar disorder have reported diffuse WM microstructural alterations[124,162,163], which are evident when tract integrity and WM volume are measured. Recent meta-analyses have found FA reductions in all major classes of WM tracts (commissural, association and projection fibers) with frequent reports of alterations in temporoparietal WM, the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and left cingulum[124,164]. A mega- and meta-analysis of the ENIGMA group revealed decreased FA in 29 ROIs, with the greatest effect sizes in the corpus callosum and cingulum of patients compared with those of controls[162]. Voxel-based analysis of DTI (VBA-DTI) data has also found clusters of decreased FA and WM volume in prefrontal, temporal and parietal regions [164-166]. Emsell *et al*[165] conducted a study on euthymic bipolar disorder patients and found a cluster extending from the prefrontal WM to the splenium of the corpus callosum and posterior cingulum bundle[165], whereas a VBA-DTI meta-analysis reported another two clusters in areas involved in emotional processing[164]. Nortje's meta-analysis identified a large cluster of decreased FA and mean diffusivity in the right temporoparietal WM, a region that is crossed by the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus[164]. The evidence suggests that the posterior WM contributes to cognitive deficits, while the alterations of anterior fibers are associated with affective symptoms of bipolar disorder[164,167]. In conclusion, the previously discussed evidence suggests not only alterations to fronto-limbic connectivity but also dysfunction in parietal, fronto-occipital and interhemispheric connections, which may explain the cognitive and emotional manifestations of this disorder[167].

THE DISCONNECTION PARADIGM AND WM DYSFUNCTION IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Taken together, the evidence discussed above highlights the importance of oligodendroglial cells for brain function; through myelin formation, they are involved in the precise synchronization of electrical impulses that propagate along nerve fibers connecting brain structures[168-170]. Most long-distance connecting tracts in the CNS are heavily myelinated and comprise the WM. Although structural and functional WM alterations have been described in other mental illnesses, such as major depression, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, autism spectrum disorders, Alzheimer's disease, and drug addiction[16,171], in this review, we focused on schizophrenia and bipolar disorder because these two neuropsychiatric illnesses share several clinical and patho-physiological features.

As can be inferred from the previously mentioned findings, the focus of investigations on the pathophysiology of schizophrenia and bipolar disorder has changed from alterations in specific regions to dysfunction in the connectivity of brain structures. This shift occurred first for schizophrenia, when the disconnection hypothesis was postulated more than twenty years ago, in response to the fact that several manifestations of schizophrenia, such as negative symptoms, cannot be fully explained by structural alterations to a specific cortical area[172-174]. Researchers subsequently hypothesized that the clinical domains of schizophrenia might be due to widespread network dysfunction instead of only specific morphological alterations of specialized cortical regions[125]. This paradigm shift in schizophrenia research quickly translated to other psychiatric conditions, and many studies have since tested the disconnection hypothesis in bipolar disorder[153]. Functional MRI and DTI studies have reported an association between compromised WM integrity and clinical manifestations of these disorders[126,167].

In the following years, many neuroimaging studies have associated WM alterations found in psychiatric patients with executive function, functional impairment, affective symptoms, treatment response or resistance, suicidal thoughts and attempts, and the severity of symptoms, to name only a few traits[123,145,161,175]. This overwhelming evidence has helped researchers to frame schizophrenia and bipolar disorder as multidimensional conditions with strong brain correlates at the macroscale connectomic level[125]. Undoubtedly, further research from a neuroglial integrative perspective is necessary to unravel the anomalies at the cellular/subcellular level, *i.e.*, the microscale connectomic level that may underlie the complex clinical manifestations of these patients.

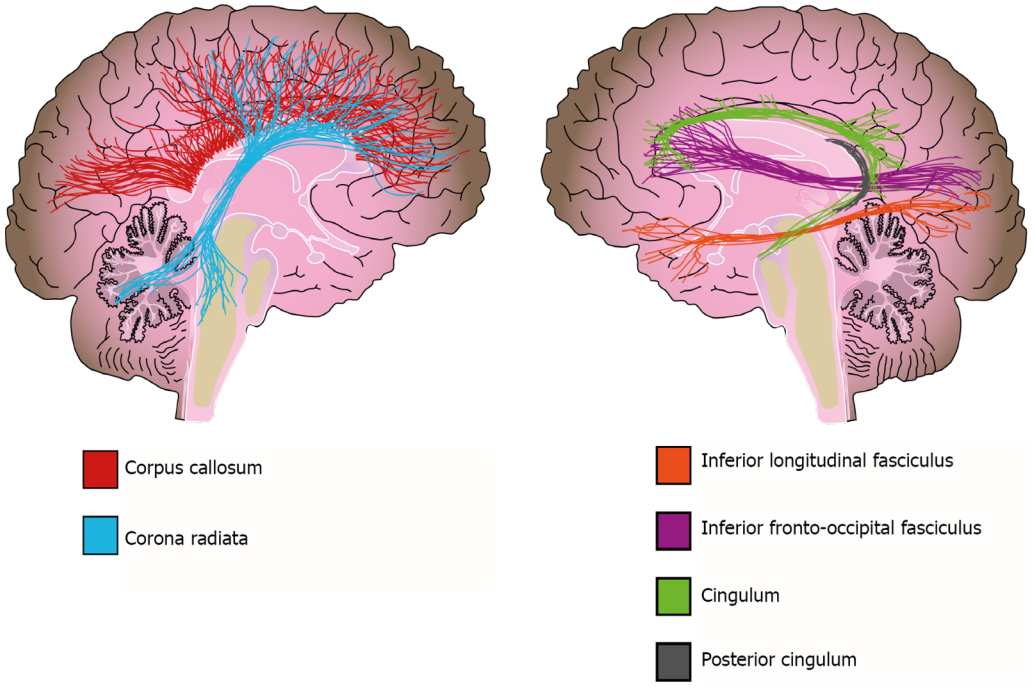

Figure 4 White matter alterations in bipolar disorder. Solid lines represent the path of the affected white matter tracts.

PERSPECTIVES: MYELINATION IS NOT AN EXCLUSIVE OLIGODENDROGLIAL-NEURONAL RELATIONSHIP

The axo-myelin interaction is so close that, by itself, it constitutes a functional unit with a complex and deeply intermingled physiology. However, both astrocytes and microglia interact with axo-myelin units and influence their function[176-179]. Metabolic homeostasis and *de novo* formation or plasticity of myelin internodes and nodes of Ranvier are modulated by astrocytes and microglia. The main glial-mediated modulatory mechanisms of myelin homeostasis include physical intercellular interactions through gap junctions, secretion of soluble factors and clearance of myelin debris. Dysregulation of these modulatory mechanisms may also underlie the pathophysiology of mental illnesses such as schizophrenia and bipolar disorder; however, scientific research on this topic is still limited.

During the last two decades, great advances have been made in our understanding of human CNS physiology and pathophysiology, and glial cells have been recognized as key players in neuropsychiatric disorders[15,180-182]. Nevertheless, scientific psychiatry and patients with mental disorders would definitely benefit from a more integrative point of view at all research levels.

CONCLUSION

Schizophrenia and bipolar disorder are multifactorial neuropsychiatric illnesses that share clinical manifestations and alterations to brain structure and function, genetic characteristics, and neurobiological pathways. Both are chronic and severe conditions that cause disability, reduce lifespan and impose a high burden on patients and society. The disconnection hypothesis of the pathophysiology of these two disorders is supported by alterations in WM tracts revealed by neuroimaging techniques. Alterations at the macroscale connectome level strongly correlated with the multidimensional clinical manifestations of these disorders; however, to better understand the correlates at the cellular and subcellular levels, it is necessary to obtain deeper insight into the main components of WM, *i.e.*, myelinated axons. Therefore, the pathophysiology of both the neuronal and oligodendroglial components of neural circuits and networks needs to be investigated. Twenty years since the first hypothesis implying oligodendrocyte/myelin failure as a hallmark of schizophrenia[183], a large amount of evidence at the connectomic, microscopic, proteomic, transcriptomic and genomic levels has accumulated for overall dysfunction of the axo-myelin functional unit in these patients. Although oligodendrocyte/myelin dysfunction has also been consistently reported in bipolar disorder, the same amount of scientific knowledge about axo-myelin pathophysiology in this psychiatric disorder is lacking, at least at the cellular and subcellular levels. Further research on schizophrenia and bipolar disorder is needed to better understand the axo-myelin molecular pathways that are dysregulated and to identify potential targets for the development of novel therapeutic alternatives. Several recent studies

have focused on the effects of commonly prescribed antipsychotic drugs on oligodendrocytes/myelin [184]. However, testing the effects of novel compounds intended to induce oligodendrogenesis and (re)myelination[116] in preclinical models of schizophrenia and bipolar disorder could also hold great promise for future research.

FOOTNOTES

Author contributions: Valdés-Tovar M contributed to the overall conception and design of the study; all authors carried out comprehensive literature search and wrote the first draft; Rodríguez-Ramírez AM contributed to the clinical perspective and figure design; Sotelo-Ramírez CE contributed to figure creation; Solís-Chagoyán H critically revised the manuscript; Valdés-Tovar M and Camarena B obtained funding; all authors assisted in a thorough revision of the manuscript and approved its final version.

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MINIREVIEWS

Common outcome, different pathways: Social information-processing deficits in autism spectrum disorder and attention-deficit/hyperactivity disorder

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Abstract

Social functioning is a key domain of impairment in both autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). This review adopts the social information-processing model as the theoretical framework to compare and contrast the deficits of ASD and ADHD at each of the six steps of social information-processing. Both disorders show deficits at each step, but the nature and origins of the deficits are different. Thus, while both disorders exhibit a common outcome of social impairment, the exact pathways that each disorder traverses along the six steps of social information-processing are different. For ASD, there is a social knowledge/behaviour deficit arising from difficulties in social/emotional cue detection, encoding, and interpretation, leading to problems in joining and initiating social interaction. For ADHD, there is a performance deficit incurred by disruption arising from the ADHD symptoms of inattention and hyperactivity/impulsivity, while its acquisition capacity on social knowledge is relatively intact. The inattentive, intrusive, and impulsive behaviours of ADHD unsettle social interaction. Finally, this review proposes training targets for intervention along the six steps of the social information-processing model for ASD and ADHD, as well as areas for future research in further elucidating the social impairment of the two disorders.

Key Words: Autism spectrum disorder; Attention deficit/hyperactivity disorder; Social information-processing; Social impairment; Social skills training; Social outcome

Core Tip: Both autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) show deficits in social information-processing, but their nature and origins are different. While both disorders exhibit a common outcome of social impairment, the exact pathways that each disorder traverses along the social information-processing steps are different. For ASD, there is a social knowledge/behaviour deficit arising from difficulties in social/emotional cue detection, encoding, and interpretation, which lead to problems in joining and initiating social interaction. For ADHD, there is a performance deficit incurred by disruption arising from the ADHD symptoms of inattention and hyperactivity/impulsivity. The inattentive, intrusive, and impulsive behaviours of ADHD unsettle social interaction.

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INTRODUCTION

Social functioning is a key domain of impairment in both autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD)[1]. For the diagnosis of ASD, social impairment is a defining feature and a core diagnostic criterion. Findings consistently indicate significant deficits in fundamental aspects of social cognition including weakness in emotion recognition skills and theory of mind compared to typically developing peers. These in turn are significant contributing factors for suboptimal social behaviour and social outcome in ASD.

Social impairment is also well-documented in children with ADHD and has often been conceptualized as a manifested outcome of its core symptoms of inattention, hyperactivity, and impulsivity. Children with ADHD demonstrate a failure to modulate behaviour according to the social contexts and more frequently engage in inappropriate social behaviours such as paying less attention to peers (inattention) or interrupting others out of turn (impulsivity) during their social interactions[2,3]. These problems in social behaviours are seen as contributed by ADHD symptoms, giving rise to inconsistent or inappropriate behavioural responses and regulation[2,4], and often result in higher rates of peer rejection and friendship failures.

Since both children with ASD and those with ADHD present with social impairment, it is important to better understand the processes that underlie this common outcome between the two disorders. A recent review by Mikami *et al*[1] extensively examined the characteristics and aetiologies of social impairment in these two disorders. Across the broad domains of social functioning including social cognition, social behaviour, and peer regard, it was found that both ASD and ADHD shared transdiagnostic impairment in all of these areas, yet were also distinct in the different areas of difficulties. For instance, while both disorders exhibited problems in peer regard, the social difficulties of ADHD were characterized by disruptive and negative behaviours in peer situations, while ASD children might lack the positive or prosocial behaviours to initiate and maintain peer relationships. In other words, there is a distinctiveness of deficiency in knowledge and skills in ASD compared to relatively intact skills but problematic performance in ADHD. While this recent review describes well the potential different bases of deficits leading to impairment in overt social behaviours across the two disorders, it has not organized the underlying deficits under a coherent and comprehensive theoretical framework of social information-processing that characterizes in sequential steps how an individual first attends and processes incoming stimuli in a social situation, including the thoughts and feelings of others, to be followed by decision-making, and then choice and enactment of an appropriate social response at the end. These underlying social cognitive processes are the mechanisms and pathways that translate a social situation into a social outcome. A social information-processing model, proposed by Crick and Dodge[5], has been put forward to explain social behaviours with a series of hierarchical, stepwise cognitive processes that serve the above-described cognitive functions in responding to social situations or events. This series of cognitive processes, which are based largely on biologically determined capabilities in social cognition, as well as past learning experiences, shape the eventual social interaction. Thus, any deficits along this hierarchy of sequential steps can contribute to social impairment[4].

This review will adopt the social information-processing model by Crick and Dodge[5] as its theoretical framework, which is well-defined and well-tested, to elucidate the social cognitive processes that underlie the common outcome of social impairment in ASD and ADHD. The identified deficits can become viable training targets to be alleviated for enhancement of social behaviours in ASD and ADHD.

THE SOCIAL INFORMATION-PROCESSING MODEL

The social information-processing model proposed by Crick and Dodge[5] describes a hierarchy of covert, mental mechanisms that are employed to translate external social cues (inputs) to overt behavioural responses (outputs). It provides a theoretical framework to better understand the social cognitive abilities and social adjustment of children. The model includes five cognitive steps followed by the sixth step of behavioural response enactment: (1) Encoding of internal and external social cues; (2) Interpretation and mental representation of cues; (3) Clarification or selection of goals; (4) Response construction; (5) Response decision; and (6) Behavioural enactment[5,6]. Each step is guided by biologically determined capabilities in cognitive functioning, as well as a memory database of learned social experiences, which informs of social rules, schemas, and knowledge/skills of social behaviours.

Upon encountering a social situation, children enter the initial steps of social information-processing, whereby they selectively attend to, encode, and interpret social cues (steps 1 and 2). Essentially, steps 1 and 2 help the children create a mental representation of the presenting social situation or event - what is happening (attend and encode) and why it is happening (interpretation), including inferences about the perspectives and intentions of others involved. Deficits in these early stages of social information-processing, such as inaccurate encoding and interpreting of social cues, can create a biased mental representation of the social situation upon which behavioural responses are chosen for.

After creating a mental representation, children clarify and select a goal or desired outcome for the social situation in step 3. For instance, if they encode aggressive cues and interpret the situation as provocative or hostile, the children may determine whether their goal is to get even or avoid the provocation; whilst if they interpret the situation as friendly, the children may then consider more pro-social goals. The intention is to produce certain desired outcomes in a social situation.

After the children clarify their goals, they then need to construct a range of potential behavioural responses (step 4), either selecting from their existing pool of behaviour repertoire or generating a new piece of behaviour if the situation calls for it due to its novelty. Subsequently, at step 5, children evaluate their response choices and decide upon the most appropriate behaviour based on various expectations, including outcomes expectation, sense of self-efficacy and response appropriateness. Finally, at step 6, the chosen response is behaviourally enacted, producing a social outcome. Yet, children may produce suboptimal social responses should they have very limited behaviour repertoire, bad judgement on evaluating and deciding on the appropriateness of the responses, or over/underestimation of their self-efficacy in enacting the responses to the social situation. All these lead to impairment in social interaction.

Role of emotions in social information-processing

Crick and Dodge[5]'s model also recognizes the importance that emotions play in social information-processing by highlighting the interactions between emotions and cognitions[7]. Each step of the social information-processing is intertwined with emotional processes. The biologically determined cognitive capabilities and the memory database of past learning experiences that guide social information-processing also include a predisposition to emotionality. The emotional states will affect the children's mood-congruent cued recall of past experiences, for instance, which in turn affects the information-processing. In encoding and interpreting cues, emotion recognition ability can play an important role in which emotion cues become encoded and interpreted; as such, inaccurate or selective encoding and interpretation of others' emotions, such as the tendency to encode and interpret ambiguous cues as anger, may generate more hostile responses than if the cues were encoded and interpreted as more neutral. The encoding and interpretation of cues can also be influenced by pre-existing mood states and levels of emotional arousal during the interaction, such that children are more likely to notice and recall mood-congruent information. Emotions can also have an impact in the determination of goals and the construction and choice of behavioural responses, whereby children with high emotional reactivity may choose goals and responses that primarily help to reduce emotional arousal, such as avoidant or hostile goals and actions. Children who are weak in reading and interpreting others' emotional cues, on the other hand, may tend to determine goals and choose responses that are less considerate of others' emotions and less likely to maintain relationship. Overall, while the social information-processing model describes primarily a social cognitive mechanism to explain social outcomes, there is a strong interplay with emotional processing, such that differences in emotionality or emotion recognition can influence each step of social information-processing toward the outcomes.

Studies of social information-processing in children

Children with both externalizing and internalizing problems have been found with deficits along each step of the social information-processing model. For example, children with externalizing problems such as aggression were more likely to attend and encode cues related to aggressive or aversive acts in social situations (step 1)[8]. When interpreting social cues (step 2), aggressive children, as compared to non-aggressive peers, also showed hostile attributional biases and viewed others' actions and motivation as driven by hostile intent even when the situations were presented as ambiguous[5,8]. Research comparing behavioural responses of children with and without externalizing problems also

found differences in the quality and quantity of responses/solutions generated, whereby aggressive boys produced fewer assertive responses to solve social difficulties, but with an increased likelihood to engage in direct aggressive actions if the situations involved hostile provocation (steps 4-6).

Children with internalizing problems are also found with ineffective social information-processing patterns when compared to socially adjusted children. Depressed children, for instance, were less accurate in encoding relevant social cues and showed hostile attribution biases when interpreting social cues in unfamiliar situations (steps 1 and 2)[5,9]. In terms of behavioural responses, depressed children viewed assertive responses as associated with less positive and more negative outcomes, and thus tended towards constructing fewer assertive responses (steps 4 and 5)[10].

Conversely, social information-processing patterns for prosocial behaviour in children showed that they were more likely to interpret social cues positively, with a preference for maintaining positive relationship in the goal clarification step (step 3) even in face of provocation. Children who were accepted by their peers provided more prosocial and effective solutions and responses than children of lower peer status (step 4)[11].

Overall, the literature demonstrates that the social information-processing model by Crick and Dodge [5] is a helpful theoretical framework for understanding the underlying cognitive and behavioural processes contributing to differences in social behaviours and outcomes in children. It highlights the hierarchical nature as well as the interconnectedness of each step of the processes in contributing to the effectiveness and appropriateness of social responses to social situations, and how deficits in any of the steps can culminate into problematic social behavioural outcomes. It has proven validity in explaining and predicting externalizing, internalizing, and prosocial behaviours. This review will adopt this model to elucidate how the social information-processing deficits of children with ASD or ADHD can lead to their social impairment in six steps.

SOCIAL INFORMATION-PROCESSING DEFICITS IN ASD AND ADHD

Although the social information-processing model by Crick and Dodge[5] has been applied to study the social deficits in ASD and ADHD, the number of available studies has not been plentiful. Furthermore, most studies conduct their investigation separately with ASD and ADHD; studies directly comparing the social information-processing patterns of the two disorders remain sparse to date. One general consensus emerging in the literature is that social information-processing deficits do emerge in ASD and ADHD, and they in turn contribute to the social impairment of both disorders. However, as we systematically review below studies at each step of social information-processing, the deficits identified are of different nature for ASD and ADHD, providing insight into how these disorder-specific deficits, though traversing different pathways along the hierarchically determined steps of social information-processing, eventually cumulate into a final common outcome of social impairment for both disorders.

Step 1: Encoding of social cues

Cue encoding and detection: Cue encoding is the first step in social information-processing. A commonly used assessment tool for examining cue encoding is the social information processing interview (SIPI). It is a structured interview based on a series of vignettes or stories depicting negative peer social interactions (peer rejection or provocation). Children with ASD were found to score significantly lower on the efficient coding score of the SIPI, which measured the average level of details that could be accurately recalled by the children regarding the presented vignettes[6]. This indicated that children with ASD were encoding social information less accurately. This could potentially be due to their remembering fewer details (*i.e.*, encoding fewer cues) or remembering the details inaccurately (*i.e.*, tendency to code irrelevant cues), or both. Unfortunately, such error patterns were not captured by the SIPI and thus not reported. Nonetheless, the inefficiency in cue encoding by children with ASD means that they will in turn generate a less accurate mental representation of the social situations.

Children with ADHD were consistently found to encode fewer cues compared to control children when presented with the social vignettes[12]. Furthermore, they encoded lower percentages across positive, negative, and neutral cues, indicating that the inefficiency was non-specific and present across all valences[13]. Difficulties in attention and working memory, two fundamental deficits underlying ADHD symptomatology, were suggested for this non-specific pattern of inefficiency in cue encoding[12, 13]. It was hypothesized that children with ADHD might miss noticing cues due to inattentiveness or might fail to encode all relevant cues due to working memory deficit (*i.e.*, forgetting or failing to recall details of the social vignettes). Once again, the inefficiency in cue encoding in children with ADHD hinders them from developing a more balanced and accurate mental representation of the social situations.

Overall, cue encoding deficit is identified in both ASD and ADHD. However, since these findings are from separate studies, which use different (though similar) measures of cue encoding, it is difficult to conclude if the findings are directly comparable. Researchers also seem to speculate different origins of the encoding inefficiency in the two disorders. For the children with ASD, it is a fundamental deficit of ASD in encoding social cues, while the cue-encoding inefficiency of children with ADHD is a by-

product or a result of interruption arising from their ADHD symptoms, *i.e.*, inattention and working memory deficit.

Social perception/cognition: Those rare studies which directly compared social perception/cognition between ASD and ADHD suggested a more severe social perception/cognition deficit in ASD but a milder deficit in ADHD[14,15]. In particular, the evidence seems to suggest a larger contributing role of neurocognitive factors in social perception/cognition deficit in ADHD than ASD. Baribeau *et al*[15] compared the social perception/cognition abilities of children with ASD, ADHD, or obsessive-compulsive disorder and typically developing children using the Reading the Mind's Eyes test (RMET), a standardized test on decoding mental states which was based upon matching photographs of eyes with corresponding emotions and mental states being portrayed. Children with ASD were found to exhibit the most significant social perception/cognition deficit compared to other groups, while children with ADHD were found to display an intermediate level of social perception/cognition deficit, falling between the ASD and control groups in their performance. Furthermore, after controlling for intelligence quotient (IQ), there was a narrowing in the performance gap between the clinical groups and typically developing children. In particular, the accuracy scores of ADHD children became comparable to those of typically developing children. Drawing from these results, it seems that a large part of the social perception/cognition deficit in ADHD can be explained by lower general cognitive abilities, since ADHD children do have a lower IQ compared to typically developing peers[16]. For ASD, however, the effect of IQ can only explain part of the deficit. In the same study, features of hyperactivity and impulsivity were also found to be associated with deficit in social perception/cognition for all participant groups regardless of diagnosis; ADHD traits as measured by the strength and weaknesses of ADHD and normal behaviour rating scale had a significant negative effect on the RMET scores. The adverse impact of ADHD features in social perception/cognition was further substantiated by findings indicating that stimulants improved social perception/cognition in ADHD [14].

Another important differentiating factor when comparing social perceptual/cognitive deficits in ASD and ADHD is age. While paediatric samples demonstrated moderate effect sizes in social perception/cognition deficits for both ASD and ADHD, the effect sizes became smaller for adult ADHD samples, suggesting age-related improvement and catching-up in social perception/cognition for ADHD as they aged. Conversely, this age-related improvement was not found among the ASD population[14]. These differential findings across age support the speculation that social information-processing deficits of ADHD may be by-products of ADHD symptomatology whose age-related improvement also results in correspondingly age-related improvement in social perception/cognition.

Facial emotion recognition: Emotion recognition has been included as a fundamental process in social information-processing within the first step of cue encoding[7]. The encoding and interpretation of others' affective cues are an important source of information for processing. Facial emotion recognition has been studied extensively in ASD. The ability to recognise and discriminate facial emotional expressions is present in infants as young as 10 wk of age, but it is a key generalized deficit or delayed ability in children with ASD across all facial expressions, and may vary in magnitude for specific emotions, with more difficulty in the recognition of negative emotions, particularly fear and anger[17-19]. It persists through to adulthood[20]. This suggests a failure to develop specialization and expertise in emotional processing in ASD, and despite investing in efforts and resources to compensate, children with ASD are still unable to catch up in adulthood.

Findings on emotion recognition in ADHD also suggest weaker emotion recognition capability[19]. Yet, it has been speculated that emotion recognition deficit in ADHD may be due to a failure to attend to the appropriate cues of affect incurred by the inattention symptom of ADHD. In a study examining emotion recognition, it was found that boys with ADHD showed poorer performance across all tasks regardless of whether facial emotions were involved, indicating a more generalized difficulty involving deficit in attention control[21]. Furthermore, other studies found random error patterns and increased performance variability on emotion recognition performance for children with ADHD as well, which further implicated the role of inattentiveness in emotion recognition performance (*e.g.*, momentary lapses of attention characteristics of ADHD)[12,19]. Conversely, among children with ASD, performance in emotion recognition tasks was less variable with no random or variable error patterns[19], suggesting a performance profile less affected by momentary lapses of attention as in ADHD. These findings suggest a more pertinent role of inattentiveness in emotion recognition performance in children with ADHD, but not in children with ASD.

Yet, some studies do find inattention or distractibility as an important covariate for explaining facial emotion recognition deficits in both ASD and ADHD. However, it should be noted that in some of these studies, children with ASD were included regardless of the presence or absence of comorbid ADHD symptoms. For instance, in one study, up to one-third of the cases with a primary ASD diagnosis also fulfilled the criteria for ADHD[19]. Furthermore, the presence of ADHD aggravated the facial emotion recognition performance, including increased variability, in comorbid ASD and ADHD children, highlighting once again the negative role of inattentiveness in emotion recognition performance[22].

Step 2: Interpretation of cues

Interpretation of cues involves attribution processes in which children make inferences about causal relationships, intents of others, *etc.* Children with ASD or ADHD have been suggested to show attributional biases in cue interpretation. A common and well-researched cognitive bias is the hostile attribution bias, which is the tendency to attribute malevolent or hostile intents when interpreting ambiguous or neutral social scenarios. For instance, preschool children with ASD were found to frequently interpret actions of others as hostile, which then led to the enactment of more aggressive responses[6]. However, the same bias was not consistently found among school-aged children and adolescents with ASD[23]. Instead, adolescents with ASD were more likely to show a negative, global attribution style in which they were more likely to view social outcomes as independent of their responses, making them less likely to assert prosocial responses but avoid or withdraw from interaction when faced with social situations[24]. The study reasoned that those repeated experiences of negative social interaction experienced by children with ASD, due to the well-known weakness in theory-of-mind in ASD, could lead to this negative, global attributional bias.

Attribution bias has also been studied among children with ADHD. They appeared to rely more heavily on their own opinions on what was happening in the social situations rather than on the observable, factual information[13]. This was suggested to be related to attentional problems, which hampered upstream cue encoding, contributing to fewer cues being encoded. Having less factual information to rely on, children with ADHD subsequently had to rely more on personal opinions. They were also more likely to show a recency effect when interpreting social situations by using the most recent contextual information[12]. This shallow interpretative process might also be related to attentional problems and working memory deficits, such that they were unable to hold and mentally manipulate all of the social cues, thus only relying on their most recent memories. Furthermore, a hostile attribution bias was generally not found in children with ADHD by comparison to typically developing peers[25,26]. Instead, children with ADHD were suggested to have a positive illusory attribution bias, whereby they tended to overestimate their abilities, leading them to choose unattainable or overly ambitious behavioural responses, as well as to underestimate their problems in the actual social situations. Such bias made the children with ADHD to be rated as less friendly, more inattentive, and less engaged in social situations[12].

Overall, in terms of cue interpretation, both ASD and ADHD show attribution biases, though the type of attribution biases and the underlying contributors differ between the two disorders. Children with ASD are more likely to show a negative, global attribution style contributed by repeated negative social experiences, which in turn drives withdrawal-based responses in social interaction. Children with ADHD are found to show positive illusory bias, making them less likely to consider the full impacts of their responses and outcomes, but more likely to engage in impulsive and overly ambitious responses with socially inappropriate behaviours. Also, the role of inattention and working memory deficits appears to be more relevant for cue misinterpretation in ADHD.

Step 3: Goal clarification

In step 3 of the social information-processing model, children need to clarify their goals for the social situations. Social goals can be relationship enhancing or building, or conversely, can also be relationship damaging or retaliatory.

Unfortunately, this current review has not identified studies specific to goal clarification in ASD and ADHD. Some inferences can be made from some indirect findings. Adolescents with ASD were found to rate withdrawal as a preferred response compared to typically developing peers[24]. This may reflect a tendency to adopt a non-social, withdrawal/avoidant goal orientation. Given their positive illusory bias, as described above, children with ADHD might be overly confident of their competency and adopted the overly ambitious goal of confronting their problems in social situations[13].

Steps 4 and 5: Response construction and decision

Findings on response construction and decision in adolescents with ASD found that the reduced breadth of social experiences and a higher proportion of harsh social experiences might be leading to limited availability of social problem-solving responses in their memory database. Consequently, adolescents with ASD were more likely to evaluate withdrawal responses as preferable in social scenarios and generate non-social withdrawal responses to avoid problems in social interaction[24]. These findings may be reflective of the real-life difficulties in initiating and responding to social situations experienced by individuals with ASD.

Children with ADHD tended to generate a lower proportion of positive responses and higher proportion of negative responses in social situations[13]. Children with ADHD had significantly higher rates of negative interactions with peers, including a higher rate of peer rejection. Thus, they were less likely to have positive responses in store in their memory database, but instead, they had many negative responses.

Step 6: Behavioural enactment

Behavioural enactment is the last step of the social information-processing model and is generally

conceptualized as the behavioural outcomes of the five previous cognitive steps upstream. Naturally, the culmination of deficits in those previous steps will lead to suboptimal behaviours being enacted, thus impairing social functioning in children with ASD or ADHD.

Children with ASD show deficits in observable social behaviours, including less social play and fewer social initiation, as well as poorer verbal and nonverbal social communication that reduces the effectiveness of their social interactions[1]. This absence of positive social behaviours in ASD can be seen as the result of upstream social cognitive and emotion recognition deficits, creating an inappropriate mental representation of the social situations combined with a tendency to choose and positively evaluate non-social withdrawal responses.

It has been suggested that children with ADHD may have adequate social knowledge but experience difficulty in enacting social behaviours appropriately[27,28]. This suggestion collaborates well with findings that children with ADHD are noted with relatively milder deficits in social perception/cognition compared to children with ASD[14,15]. Instead, they showed more inconsistency and variability in their social behaviours which appeared to be more strongly influenced by the core features of ADHD - inattention, hyperactivity, and impulsivity[12,19]. For example, children with ADHD were found to show elevated negative social behaviours such as barging in and poor sportsmanship, which were contributed by the core symptoms of hyperactivity/impulsivity. Due to inattentiveness, they were also found to demonstrate an absence of positive behaviours such as missing the pace and content of conversation[1]. One study demonstrated that social problems in ADHD primarily reflected inconsistent performance rather than the lack of knowledge and skills[2]. Using the social skill improvement system, a parent-rated measure of observable social behaviours, Aduen *et al*[2] found that children with ADHD exhibited more social performance problems than children without, while rates of social acquisition problems were relatively rare and idiosyncratic. These findings suggested that children with ADHD failed in fact to perform learned social skills consistently across settings. Another study also pointed to a social performance deficit in ADHD, as opposed to the lack of social knowledge and inherent social communication deficits seen in ASD[3]. For instance, while both ASD and ADHD groups exhibited significant social behavioural difficulties, deficits in children with ASD were characterized by significantly less adaptive and appropriate social behaviours, which was a reflection of a knowledge deficit, while children with ADHD were found to have more inappropriate assertiveness, a reflection of impulsivity. Table 1 summarizes the social information-processing deficits in ASD and ADHD.

COMMON OUTCOME, DIFFERENT PATHWAYS

Both ASD and ADHD have been well known for social impairment, exhibiting difficulties in relating with others. This is the common social outcome for the two disorders. However, the above review organized under the social information-processing model by Crick and Dodge[5] suggests different pathways traversing along the six steps of information-processing for children with ASD or ADHD to arrive at the common outcome.

Children with ASD start with an inefficiency in cue encoding and deficits in facial emotion recognition. They also exhibit a more severe deficit in social perception/cognition, which persists into adulthood without any sign of abatement. These encoding deficits, *e.g.*, well known as theory-of-mind deficits in the literature of ASD, consequently lead ASD children to generate a less accurate mental representation of the social situations in which they find themselves.

Regarding the interpretation of cues, children with ASD develop over time a negative, global attribution style in which they see themselves as helpless in effecting the social outcome. With this interpretation, they tend to opt for withdrawn and avoidance responses. There goes a vicious cycle in which these withdrawn/avoidance responses limit the breadth and positivity of the social experiences. These in turn reduce the availability or construction of positive social problem-solving responses to cope with the challenges in social situations. In the end, children with ASD, harbouring a withdrawn and avoidant response tendency, display less social play and fewer social initiation which thwart their social interaction.

Children with ADHD also start with a cue encoding deficit. This is followed by difficulties in social perception/cognition and facial emotion recognition. However, researchers speculate different origins of these encoding difficulties. For children with ASD, these encoding difficulties are cognitive deficits to social and emotion stimuli inherent to ASD, while for children with ADHD, they are by-products originating from interruption incurred by ADHD symptoms of inattention and hyperactivity/impulsivity. The latter suggestion is based on the observation that the encoding difficulties are random, non-specific, or variable across all valences, reflective of those momentary lapses of attention typical of ADHD. Children with ADHD thus display a performance deficit due to interruption by ADHD symptoms, but little acquisition problems on social knowledge. When the symptoms of ADHD are treated with stimulant medication, performance in social perception/cognition improves. Furthermore, an age-related improvement is also seen, in parallel with the age-related improvement in ADHD symptoms. All these point to an influential role of ADHD symptoms in hindering social information-processing. In the interpretation of social cues, children with ADHD also show a positive illusory bias,

which is of a different type from that of children with ASD. Such bias eventually leads to overly ambitious responses of confronting their problems in social situations. Once again, as in the case of children with ASD, children with ADHD are also locked in a vicious cycle in which inadequate social responses and negative social experiences are reinforcing each other and thus hinder the choice and construction of proper behaviour responses. Eventually, children with ADHD enact impulsive and inattentive behaviour, disrupting their social interaction with others.

In short, both disorders, ASD and ADHD, show social information-processing problems right from the very beginning and end with behaviour enactment that disrupts social interaction. However, as described above, the common social outcome is arrived at from different pathways that traverse along the six steps of social information-processing, invoking two cascading chains of deficits along the six steps. These eventually cumulate in suboptimal responses that hinder social relating, namely, withdrawn/avoidant responses from children with ASD, but intrusive/impulsive responses from children with ADHD. In brief, ASD does display inherent encoding deficits in social and emotion processing (*e.g.*, theory-of-mind deficits), while ADHD symptoms mar performance in social information-processing, despite a fairly intact pool of social knowledge acquired, *i.e.*, a social performance deficit rather than a knowledge deficit in ADHD.

CLINICAL IMPLICATIONS ON SOCIAL SKILL TRAINING FOR ASD AND ADHD

Social information-processing has been a focus of intervention to reduce aggressive and violent behaviours and increase prosocial behaviours in children[8]. The social skill training programs thus devised involve explicit teaching of social problem-solving steps using developmentally appropriate teaching strategies such as skill modelling, role play, and feedback. These programs are well studied with positive findings in relation to increased prosocial behaviours and reduced aggressive behaviours [8].

Fewer studies are conducted using specifically social information-processing as a model for social skill training with ASD and ADHD. One study that did so in a small group of five children with ASD found post-intervention improvement across multiple domains of social skills[29]. Another study with 27 children with ADHD also found improvement in social competency[30]. The scarcity and the small sample size of these studies mean that further intervention studies should be conducted to explore the usefulness of the social information-processing model in guiding the design and implementation of intervention programs for children with ASD or ADHD.

Proposed social information-processing treatment targets

The current review identifies in the social information-processing framework viable treatment targets for ASD and ADHD. At the early steps of social information-processing, children with ASD or ADHD both show reduced cue detection and encoding efficiency, specifically for detecting and recognizing emotion cues. Treatment that brings attention to and teaches the detection of relevant social cues (keeping attention on relevant and appropriate social and emotional cues, while screening out irrelevant cues) should be considered. Particularly for children with ASD, which show specific deficits in cue-encoding, strategies to increase their motivation to attend to and encode emotion-specific cues are more warranted, while for children with ADHD, maintaining overall attentiveness to social and emotion cues in social situations should be one overarching goal.

This review finds that children with ASD tend to show a more negative, depressive attributional style, while children with ADHD a positive illusory bias. Overall, both groups of children suffer from a biased interpretation of social cues contributing to an inaccurate mental representation of the social situations, and training should be targeted at improving the accuracy of interpretation, with consideration on the different biases that are more prevalent for the two disorders separately.

With respect to response generation and evaluation, children with ASD or ADHD both show a tendency to generate more negative responses, the former tending toward withdrawn/avoidant responses, while the latter toward more impulsive/intrusive responses. A common limiting factor for both groups of children is the absence of positive social experiences that allow these children to practice, evaluate, and receive feedback on generating and enacting positive social responses. Thus, the provision of positive social experiences should be incorporated in social skill training to expand the breadth of the social exposure of children with ASD or ADHD, in which more pro-social behaviours can be modelled/constructed, enacted, evaluated, and thus stored in the memory database for future use.

Finally, at the last step of behavioural enactment, the social difficulties of ASD and ADHD are of a social knowledge deficit *vs* a performance deficit. For children with ASD, the cumulative effects of deficits in cue encoding, interpretation, and response construction have produced a void in social knowledge and behaviour repertoire in coping with the demands of various social situations. Thus, knowledge-based social skill training to increase the pool of social knowledge and behaviours is essential to address the social impairment of children with ASD. For children with ADHD, the social impairment is of a performance deficit, caused by disruption arising from the inherent ADHD-related deficits in attention, working memory, and behavioural inhibition, as well as a generally lower IQ in

Table 1 Summary of social information-processing deficits in autism spectrum disorder and attention-deficit/hyperactivity disorder

Social information processing steps	ASD	ADHD
Step 1: Encoding of social cues		
Cue encoding and detection	Children with ASD found to be less accurate in cue encoding in social situations	Children with ADHD found to encode fewer social cues, and this inefficiency non-specific across all valences, suggesting involvement of attention and working memory difficulties
Social perception/cognition	Children with ASD showing more severe social perception/cognition deficits than children with ADHD and typically developing children	A larger contributing role of neurocognitive factors in social perception/cognition deficits in ADHD, including lower intelligence and ADHD symptomatology
Facial emotional recognition	Children with ASD showing generalized deficits in facial emotion recognition across all emotions with difficulties persisting into adulthood, suggesting a failure to develop specialization and expertise in facial emotional processing	Children with ADHD showing weaker emotion recognition but with increased performance variability and random errors, suggesting contributory role of inattentiveness in failure to attend to the appropriate cues of affects
Step 2: Interpretation of cues	Children with ASD showing a negative, global attribution style contributed by repeated negative social experiences, driving in turn withdrawal-based responses in social interaction	Children with ADHD showing a positive illusory bias to engage in impulsive and overly ambitious responses; inattention and working memory deficits playing an important role in cue misinterpretation
Step 3: Goal clarification	Adopting a non-social, withdrawal/avoidant goal orientation	Adopting an overly ambitious goal of confronting problems in social situations
Steps 4 and 5: Response construction and decision	Adolescents with ASD evaluating withdrawal responses as preferable and generating such responses to avoid problems in social interaction; reduced breadth of positive social experiences limiting availability of appropriate social responses in their memory database	Children with ADHD generating a lower proportion of positive responses and a higher proportion of negative responses in social situations; higher rates of negative interactions with peers resulting in fewer positive responses stored in their memory database
Step 6: Behavioural enactment	Children with ASD showing a social knowledge deficit affecting the enactment of social responses, resulting in social responses consistently less adaptive and appropriate	Children with ADHD showing a performance deficit with increased inconsistency and variability in enactment of social behaviours, incurred by the core symptomatology of ADHD

ASD: Autism spectrum disorder; ADHD: Attention-deficit/hyperactivity disorder.

each step of social information-processing. Thus, there is a strong argument for the need to address attention and behavioural control in the management of social deficits in ADHD. Given the proven efficacy of stimulant medication on ADHD[31], such intervention should also produce beneficial effects on the social performance in children with ADHD. Indeed, there is evidence for this[14], but existing studies are few and some are inconclusive or inconsistent[32]. Behavioural training and scaffolding techniques that are also proven to manage ADHD symptoms[33] are the alternatives to be considered to deal with deficits in attention and working memory as well as behavioural disinhibition during social interaction. A recent meta-analytic review has indeed demonstrated the similar efficacy of both stimulant medication and behavioural treatment on the core ADHD symptoms[34]. Thus, future study should further examine if the social information-processing deficits of ADHD can be improved upon the alleviation of the core ADHD symptoms by existing efficacious medication and behavioural treatment.

CRITIQUES AND FUTURE DIRECTIONS

The social information-processing model is initially theorized and applied to explain aggressive behaviours in children independent of any specific clinical groups. As such, many assessment methods are specifically designed to elucidate social cognitive mechanisms underlying aggressive behaviours. For example, the SIPI which is designed specifically to assess social information-processing patterns of aggressive behaviours mainly includes negative social scenarios of peer provocation or peer rejection [6]. Furthermore, the vignettes and the interview-based method are not designed in consideration of the special needs of individuals with mentalistic functioning or language deficits such as those with ASD. As such, the interview-based SIPI and similar tools which rely on verbal comprehension and expression abilities to provide responses to the questions, and which require respondents to 'imagine' their involvement in hypothetical situations may prove difficult for children/youths with ASD and confound the assessment[24]. There is also concern on the limited ecological validity of these measures, using hypothetical situations; development and the use of more ecologically valid measures are thus suggested[13].

Despite the view that children with ADHD display a performance deficit in social functioning due to the impact of ADHD symptoms and a lower general IQ, not many studies have actually investigated or controlled the impact of these variables. Future studies should consider doing so, including the invest-

igation of whether the efficacious stimulant medication and behavioural treatments of ADHD symptoms can in turn also improve the social functioning of ADHD children, as hypothesized above.

A sizable subgroup of children with ADHD (25%-75%) have comorbid oppositional defiant disorder (ODD)[35], which is also well known to be associated with social functioning deficits. Previously, treatment of ODD has been challenging, relying mainly on behavioural treatment. However, a recent study has suggested potential beneficial medication treatment[36]. Once again, it is intriguing to examine if the successful alleviation of comorbid ODD in children with ADHD may also help their social functioning.

This review finds few studies that directly compare children with ASD against children with ADHD. This makes exact comparison of the deficits of the two clinical groups difficult. For those few studies which include both clinical groups, more exacting group differences are revealed. For example, Baribeau *et al*[15] found that children with ASD had the worst social perception/cognition deficits, while those of children with ADHD were milder. Furthermore, the social perception/cognition deficits of children with ADHD improved with age, while those of children with ASD did not[14]. Thus, more future studies should involve direct comparison between the two disorders in order to provide more exacting contrast to uncover the common and differentiating deficits contributing to their social impairment.

The social information-processing model has been applied successfully in a wide range of prevention and intervention programs to reduce aggression and promote prosocial behaviour[8]. Yet, few studies apply the social information-processing model to social skill training for ASD and ADHD. This review has made a series of suggestions above to identify viable targets for intervention. They should inform the design and implementation of potentially beneficial intervention programs for ASD and ADHD, respectively.

Finally, there is a recent concern regarding misdiagnosis of some medical conditions, *e.g.*, autoimmune encephalitis, for ASD[37]. Unfortunately, most existing literature in ASD does not address this disorder in the definition and recruitment of participants in their study so that we cannot estimate how far the conclusion of this current review is affected by the inclusion of participants with autoimmune encephalitis.

CONCLUSION

ASD and ADHD are both characterized by social impairment. This review applies the social information-processing model by Crick and Dodge[5] to define and compare the underlying deficits in the social cognitive mechanisms that contribute to the common outcome of social impairment in both disorders. It is found that both disorders show deficits at each step of social information-processing, but the nature and origins of the deficits may be different for the two disorders. In other words, the same outcome in social impairment may be arrived at by different pathways along the six steps of social information-processing. For ASD, there are difficulties in social/emotion cue detection, encoding, and interpretation, leading to a social knowledge/behaviour deficit that limits the availability and construction of behaviours to join or initiate social interaction. For ADHD, there is a performance deficit caused by disruption arising from ADHD symptoms of inattention and hyperactivity/impulsivity, leading to intrusive and impulsive behaviours that unsettle social interaction. Our conclusion essentially matches well with that of a recent review by Mikami *et al*[1], but our current review is framed under a coherent, well-developed model of social information-processing[5]. Social skill training that targets different loci of the social information-processing deficits of ASD and ADHD is well advised.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Associated mortality risk of atypical antipsychotic medication in individuals with dementia

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Abstract

BACKGROUND

Antipsychotic medications such as risperidone, olanzapine and aripiprazole are used to treat psychological and behavioural symptoms among dementia patients. Current evidence indicate prescription rates for antipsychotics vary and wider consensus to evaluate clinical epidemiological outcomes is limited.

AIM

To investigate the potential impact of atypical antipsychotics on the mortality of patients with dementia.

METHODS

A retrospective clinical cohort study was developed to review United Kingdom Clinical Record Interactive Search system based data between January 1, 2013 to

December 31, 2017. A descriptive statistical method was used to analyse the data. Mini Mental State Examination (MMSE) scores were used to assess the severity and stage of disease progression. A cox proportional hazards model was developed to evaluate the relationship between survival following diagnosis and other variables.

RESULTS

A total of 1692 patients were identified using natural language processing of which, 587 were prescribed olanzapine, quetiapine or risperidone (common group) whilst 893 (control group) were not prescribed any antipsychotics. Patients prescribed olanzapine showed an increased risk of death [hazard ratio (HR) = 1.32; 95% confidence interval (CI): 1.08-1.60; $P < 0.01$], as did those with risperidone (HR = 1.35; 95%CI: 1.18-1.54; $P < 0.001$). Patients prescribed quetiapine showed no significant association (HR = 1.09; 95%CI: 0.90-1.34; $P = 0.38$). Factors associated with a lower risk of death were: High MMSE score at diagnosis (HR = 0.72; 95%CI: 0.62-0.83; $P < 0.001$), identifying as female (HR = 0.73; 95%CI: 0.64-0.82; $P < 0.001$), and being of a White-British ethnic group (HR = 0.82; 95%CI: 0.72-0.94; $P < 0.01$).

CONCLUSION

A significant mortality risk was identified among those prescribed olanzapine and risperidone which contradicts previous findings although the study designs used were different. Comprehensive research should be conducted to better assess clinical epidemiological outcomes associated with diagnosis and therapies to improve clinical management of these patients.

Key Words: Dementia; Antipsychotics; Mortality; Vascular; Alzheimer's disease; Frontotemporal dementia; Lewy bodies; Parkinson's and mixed

Core Tip: Antipsychotic medication is widely prescribed to patients with dementia displaying neuropsychiatric symptoms. Treatment with olanzapine and risperidone was associated with an increased mortality risk. In comparison, quetiapine showed a relatively lower, non-significant association with the mortality risk in those with dementia. Clinicians need to be aware of the potential heterogeneous relationship between dementias, antipsychotic medication, and mortality when creating a psychopharmacological treatment plan for their patients.

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INTRODUCTION

Antipsychotic prescribing in older adults must be made with caution as there are age related changes in pharmacokinetics and pharmacodynamics that can result in an increased sensitivity to drugs and their side effects. This is evident in both typical and atypical antipsychotic prescribing within this population. Thus, Landi *et al*[1] demonstrated a 47% elevation of falls in elderly adults being prescribed typical antipsychotics, whilst atypical antipsychotic drugs have been associated with higher hospitalisation rates with acute kidney injury[2] and an increased 90 d risk of non-vertebral osteoporotic fracture, hip fracture and various other fractures and falls[3]. Similarly, the concerns around the safety and effectiveness of aripiprazole, olanzapine, quetiapine and risperidone (four specific antipsychotics) have been also raised for older patients in a clinical trial setting[4].

Antipsychotics are also used to treat anxiety, agitation and psychotic experiences presenting in dementia, the majority of whom are elderly. Patients with dementia are considered particularly vulnerable to the effects of antipsychotics[5]. In particular, those using antipsychotics extensively would have an increased susceptibility to venous thrombolytic episodes, hip fractures and strokes[6].

Due to the perceived risk of mortality and of side-effects, typical antipsychotics have begun to be replaced by atypicals in the last decade[5]. However, whilst there appears strong evidence for an associated risk of adverse events of both typical and atypical antipsychotic medication in the elderly, and in those with dementia, the evidence around increased mortality is less clear. Some of the literature suggests that there is an increased morality risk in dementia patients from both typical and atypical

antipsychotics accounting for an additional 1800 deaths per year[5]. However, others have argued that typical antipsychotics have a greater mortality risk than atypicals for those individuals with dementia[7] yet a meta-analysis of all cause dementia, indicated that there was a small increased risk of death from atypical antipsychotics compared to those on a placebo[8]. Furthermore, a retrospective study on a cohort of vascular dementia patients have found that there was no significant increases of mortality risk with those exposed to atypical antipsychotics to those with no exposure[9].

The present study investigates the risk of antipsychotics on mortality in all forms of dementia including vascular dementia. We hope this will help inform clinical practice and contribute to the development of training packages on prescribing antipsychotics in dementia.

MATERIALS AND METHODS

Study design

A retrospective clinical cohort study was designed to review data gathered over a 5-year period (January 1, 2013 to December 31, 2017) in a National Health Service (NHS) setting. The aim of the study was to investigate the potential impact of atypical antipsychotics on the mortality of patients with dementia. Health Research Authority (HRA) provided guidance to the Akrivia Health and all data controllers that neither ethics nor HRA approval (legal & governance) is required for the establishment of the Clinical Record Interactive Search (CRIS) system or using de-identified data (from the system) for research purposes in March 2020. Local approvals were obtained from the Southern Health NHS Foundation Trust (SHFT) patient-led oversight committee.

Cohort inclusion and exclusion criteria

The CRIS platform was used to identify suitable participants for this study as per the inclusion/exclusion criteria. Patient records in the SHFT database were filtered to only include those: Older than 30 years at the beginning of the study period (January 1, 2013); having a first diagnosis of either Alzheimer's disease (G30), vascular dementia (F01), frontotemporal dementia (G31.0), unspecified dementia (F03) or dementia in other diseases (F02); have been assigned this first diagnosis between January 1, 2013 and December 31, 2016; and to never had a diagnosis of either schizophrenia (F20), schizoaffective disorder (F25) or bipolar disorder (F31). A total of 1770 patients were deemed eligible for this study.

Data extraction

Akrivia Health provides the CRIS system to analyse de-identified data from the Southern Health NHS Foundation Trust Electronic Health Records (EHR). There are currently 14 NHS Mental Health Foundation Trusts in the United Kingdom using CRIS with 3.2 million anonymised patients' record. Each site has its own CRIS access port that ingests data from their own EHRs that is managed within a robust governance model in the form of an independent oversight committee. The SHFT CRIS system includes records of the Trust's patients except those that have opted out from having their de-identified records used for research and evaluation purposes that could improve clinical benefit. The accessible data include notes that are written by clinicians as a report on a patient's progress, including comments on medication. The CRIS platform extracts the free text (progress notes) in a de-identified format to enable researchers with appropriate approvals to conduct research. Given the scale of the cohort, it was not feasible to compile a medication history manually. Natural language processing (NLP) was employed to identify medications within the patient's notes using the Med-7 algorithm[10]. This data was used to refine the cohort into three groups; medication group prescribed olanzapine, quetiapine or risperidone, comparison group (not prescribed any antipsychotic), and exclusion group (prescribed an antipsychotic other than olanzapine, quetiapine or risperidone). Additional variables were obtained from CRIS, including: Mortality status, date of death, age at diagnosis, gender, and ethnicity.

Data analysis

The CRIS database supports the Med-7 NLP algorithm[10]. The algorithm indicates phrases with medications. Both the de-identified patient electronic healthcare records and the Med-7 medication outputs were searched using Structured Query Language and the relevant data tables were then exported into Python 3.8[11]. Python was then used to carry out all the analyses and generate the figures, using the following packages: Pandas[12], Numpy[13], Lifelines[14] and Matplotlib[15].

Proportional hazards assumption

To assess the relationship between survival since diagnosis and the other variables, a cox proportional hazard (CPH) model was built. This model used the 'death flag' as an event of interest, 'survival since diagnosis' as the duration, 'age at diagnosis' as a continuous covariate, and one-hot encoded covariates of 'gender', 'ethnicity' and 'MMSE Score'.

CPH models assume the time-independence of the proportional hazards, consequently assuming the hazard ratios (HR) are constant with time. In our case, a violation of this assumption would mean the HR are dependent on the time since diagnosis. For example, a specific medication could be associated with a temporary survival risk but be relatively safe in the long-term (or vice versa). Rulli *et al*[16] provide a detailed explanation of this issue. Particular care should be taken when comparing the results of multiple studies (*i.e.*, including our study in an aggregate), as the time dependence of results may vary across datasets.

The time-independence assumption of the proportional hazards was tested using scaled Schoenfeld residuals and a rank transformation of time[17-18]. The statistical significance of the deviation from time-independence was calculated using an approximation developed by Davidson-Pilon[14] with a *P*-value threshold of 0.01. All variables were above the threshold, with 'age at diagnosis' having a *P*-value of 0.0102 (see Figure 1). To address the possible violation, we model the CPH as a stratified model, using 'age at diagnosis' as a stratifying variable, separating patients into 5-year strata intervals.

RESULTS

Descriptive statistics

The NLP algorithm identified a total of 1692 patients with at least one medication entry. Of these, 587 patients were prescribed either olanzapine, quetiapine or risperidone (medication group), 893 were not prescribed any antipsychotic medication (comparison group) and 290 were prescribed an antipsychotic other than olanzapine, quetiapine and risperidone (exclusion group). Olanzapine was prescribed to 155 patients, quetiapine to 144 and risperidone to 450 patients. There were 153 patients who were prescribed at least two of the three antipsychotics over the study period. The demographic profiles and the MMSE scores for the study groups are shown in Table 1.

Outcomes

MMSE scores from the time of first diagnosis were also obtained using NLP (regular expression search). Patient records were followed for up to 5 years after the first diagnosis, retrieving the date of death if present.

Survival duration

1097 (74%) patients had a recorded death within 5 years of their first diagnosis (*i.e.*, patients with a 'death flag'). For these patients, the 'survival since diagnosis' was calculated, representing the duration in months between the first diagnosis and the date of death. The mean survival since diagnosis was 26.7 mo (SD = 19.9).

CPH model

The stratified CPH model had a concordance of 0.60, with six of the included covariates showing a significant HR. The variable-level results are listed in Table 2. Specifically, patients prescribed olanzapine showed an increased risk of death within the study period [HR = 1.32; 95% confidence interval (CI): 1.08-1.60; $P < 0.01$]. Those prescribed risperidone showed a similar increased risk of death (HR = 1.35; 95%CI: 1.18-1.54; $P < 0.001$). Quetiapine showed no significant association with an increased risk of death (HR = 1.09; 95%CI: 0.90-1.34; $P = 0.38$).

Patients with a high MMSE score (20-30) at diagnosis showed a lower risk of death (HR = 0.72; 95%CI: 0.62-0.83; $P < 0.001$). Interestingly, the MMSE Score HR always trend in a negative direction, suggesting that patients with any mention of an MMSE score in their clinical notes, regardless of its value, have a decreased risk of death. To better understand this effect, a follow-up CPH model was built, with 'MMSE Missing' as a covariate instead of the 'MMSE Score' groups. In this model, patients who do not have any mention of an MMSE score in their clinical notes ($n = 872$) show a significantly higher risk of death (HR = 1.30; 95%CI: 1.14-1.47; $P < 0.001$).

Those identifying as female ($n = 766$) had a significantly lower HR (HR = 0.73; 95%CI: 0.64-0.82; $P < 0.001$) than those identifying as male ($n = 714$). Patients of the White-British ethnicity showed a significantly lower risk of death (HR = 0.82; 95%CI: 0.72-0.94; $P < 0.01$), suggesting better outcomes for patients in this group.

DISCUSSION

The results show a significantly higher mortality risk for those prescribed olanzapine and risperidone. This supports previous findings of Gerhard *et al*[19], who showed that quetiapine had a lower mortality risk than risperidone, while olanzapine had a similar mortality rate to risperidone within the elderly population. Gerhard *et al*[19] argued that their findings could be due to less variance in dosing of quetiapine. In addition, higher doses of both olanzapine and risperidone were thought to have been

Table 1 Demographic information for the two study cohorts

Demographic	Category	Total	Medication group	Comparison group
Number of patients		1480	587	893
Age (mean ± SD)		82.6 ± 8.1	81.7 ± 8.4	83.3 ± 7.9
Gender	Male	714 (48.2%)	294 (50.1%)	420 (47.0%)
	Female	766 (51.8%)	293 (49.9%)	473 (53.0%)
	Other/NA	0	0	0
Ethnicity	White-British	1033 (69.8%)	451 (76.8%)	582 (65.2%)
	White-Irish	5 (< 1%)	4 (< 1%)	1 (< 1%)
	White-Any other	17 (1.1%)	6 (1.0%)	11 (1.2%)
	Mixed-White and Asian	1 (< 1%)	1 (< 1%)	0 (< 1%)
	Asian-Indian	6 (< 1%)	2 (< 1%)	4 (< 1%)
	Asian-Bangladeshi	1 (< 1%)	0 (< 1%)	1 (< 1%)
	Asian-Any other	10 (< 1%)	5 (< 1%)	5 (< 1%)
	Black-Caribbean	2 (< 1%)	1 (< 1%)	1 (< 1%)
	Black-African	2 (< 1%)	1 (< 1%)	1 (< 1%)
	Any other ethnic group	2 (< 1%)	2 (< 1%)	0 (< 1%)
	Not stated/NA	401 (27.1%)	114 (19.4%)	287 (32.1%)
MMSE	Number of patients with MMSE	608 (41.1%)	226 (38.5%)	382 (42.8%)
	Number of patients without MMSE	876 (58.9%)	361 (61.5%)	511 (57.2%)
MMSE score	20-30	369 (60.7%)	101 (44.7%)	268 (70.2%)
	10-19	199 (23.7%)	98 (43.4%)	101 (26.4%)
	< 10	40 (6.56%)	27 (11.9%)	13 (3.4%)

The percentages listed are of the column totals (number of patients) for the respective group. The only exception is the Mini Mental State Examination (MMSE) Score percentages, which are a proportion of the 'number of patients with MMSE' count. The 'Ethnicity-Asian' and 'Ethnicity-Black' groups include the Asian British and Black British ethnicity groups. MMSE: Mini Mental State Examination.

linked to a higher risk of mortality.

Aside from dosing, the differences in mortality rate could be due to the risk of cerebrovascular events. Risperidone and olanzapine have been associated with greater risks of cerebrovascular events[20-24]. The mechanism by which risperidone and olanzapine may increase the risk of cerebrovascular adverse events could be related to high levels of prolactin. Olanzapine and risperidone have been associated with high levels of prolactin[25-26]. High levels of prolactin have been associated with cerebrovascular events[27]. Furthermore, hyperprolactinaemia has been reported to frequently complicate antipsychotic treatment[28].

It is worth noting that risperidone has not been reported to cause anticholinergic side effects in the elderly unlike other atypicals[29]. Within this population, anti-psychotics are used to treat agitation and psychotic phenomenon often presented in dementia. Olanzapine and risperidone as atypical antipsychotics are commonly prescribed due to their favourable side-effect and safer metabolic profiles [5,30] age related changes in pharmacokinetics and pharmacodynamics can lead to increased sensitivity to drugs and their side effects[31] consequently impacting on mortality rates.

Polypharmacy is another facet observed within this population of patients that could attribute to the findings of our study. A recent scoping review on the sex and gender differences in polypharmacy in this population could support this theory[32] notably for women with dementia, in comparison to men [32]. Similarly, dementia is implicated in the increased risk of polypharmacy within the elderly population with rates varying from over 65 years taking from 6 medications to more than 10 medications in those older than 85 years across the world.

This study results contradict the previous findings of Sultana *et al*[9], who found no increase in risk hazard across olanzapine, quetiapine and risperidone, there are several differences in our study design that may account for the differing outcomes.

Table 2 Results of the cox proportional hazard model, with survival since diagnosis as the duration variable

Covariate	Total	Alive	Dead	Hazard ratio	*P* value
Medications					
Olanzapine	155	33 (21.3%)	122 (78.7%)	1.32[a] (1.08-1.60)	< 0.01
Quetiapine	144	29 (20.1%)	115 (79.9%)	1.09 (0.90-1.34)	0.38
Risperidone	450	82 (18.2%)	368 (81.8%)	1.35[b] (1.18-1.54)	< 0.001
Gender					
Male	714	165 (23.1%)	549 (76.9%)	Baseline	
Female	766	218 (28.5%)	548 (71.5%)	0.73[b] (0.64-0.82)	< 0.001
Ethnicity					
White-British	1033	275 (26.6%)	758 (73.4%)	0.82[a] (0.72-0.94)	< 0.01
White-Irish	5	2 (40.0%)	3 (60.0%)	0.51 (0.16-1.62)	0.26
White-Any other	17	6 (35.3%)	11 (64.7%)	0.62 (0.34-1.13)	0.12
Mixed-White and Asian	-	-	-	-	-
Asian-Indian	6	1 (16.7%)	5 (83.3%)	1.49 (0.61-3.63)	0.38
Asian-Bangladeshi	-	-	-	-	-
Asian-Any other	10	6 (60.0%)	4 (40.0%)	0.17[a] (0.05-0.53)	< 0.01
Black-Caribbean	-	-	-	-	-
Black-African	-	-	-	-	-
Any other ethnic group	-	-	-	-	-
MMSE score					
20-30	369	123 (33.3%)	246 (66.7%)	0.72[b] (0.62-0.83)	< 0.001
10-19	199	45 (22.6%)	154 (77.4%)	0.87 (0.73-1.04)	0.12
< 10	40	11 (27.5%)	29 (72.5%)	0.81 (0.56-1.19)	0.28

[a]Hazard ratio significant at the $P < 0.01$ level.
[b]Hazard ratio significant at the $P < 0.001$ level. The 'Alive' and 'Dead' percentages are a proportion of the 'Total' count. The hazard ratio is listed along with the 95% confidence interval. MMSE: Mini Mental State Examination.

The cohort in the present study covers five different International Classification of Diseases diagnosis sub-groups (G30, F01, G31.0, F03, F02), rather than vascular dementia (F01) exclusively. As such, the present results are representative of the shared patterns observed across differing dementias. Patients with Alzheimer's disease (G30) are known to show an increased mortality risk associated with long-term antipsychotic use[33]. This is a plausible finding observed across the dementia diagnoses, in particular among vascular dementia patients. A direct comparison of the individual dementia diagnosis sub-groups could assist establishing the homogeneity/heterogeneity of the mortality risk effect in future studies.

The geographical differences between the Southampton and South London population also play a vital role in our findings, given the variations in ethnicities and races. The non-medication results are comparable across both studies with women demonstrating a lower risk in comparison to men. In addition, the Caucasian group demonstrated a relatively lower risk compared to most other groups. Consistent with other studies[34], patients with high MMSE scores were also associated with lower risk of mortality. This may either mean the MMSE test is not used in patients with advanced dementias, or that there are systematic patterns due to missing data issues within electronic healthcare records in primary and secondary care organizations. These possible theories could be substantiated with prospective research studies.

Strengths and limitations

A study design using de-identified EHR has implicit strengths and limitations. The study provides a direct look into patient-level effects without influencing the clinical trajectory of the participants. Similarly, this design enables the analysis of the whole patient population in the NHS Trust (except for those opting out of NHS research) which would be prohibitively time consuming using traditional

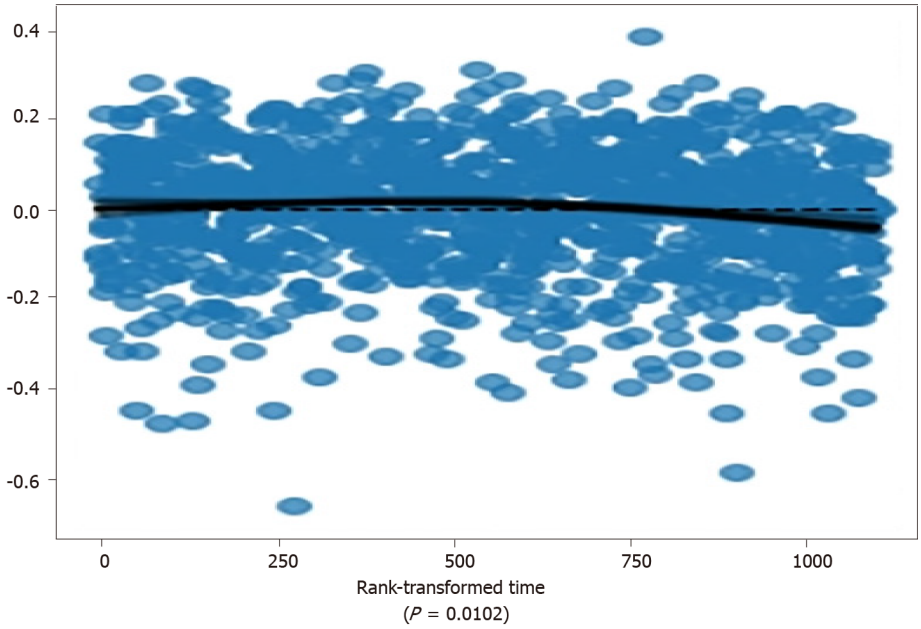

Figure 1 Scaled Schoenfeld residuals for age at diagnosis, plotted against time ranks.

patient recruitment methods. The use of NLP allows for the estimation of prescribed medication despite the fact that this information is rarely recorded in a structured format.

The strengths of using CRIS is that key features of the older adult population could be reviewed for this disease. Validating an original dataset by way of a secondary independent analysis is valuable to further future research within this area. On the other hand, it is important to appreciate that any retrospective EHR study is descriptive in nature. It is representative only of the cohort at hand, and any attempts at generalization should be accompanied by a robust theoretical underpinning of the observed effects. These are out of the scope of the current study, whereby the presented results aim to stimulate areas of further research, not inform clinical practice.

However, to strengthen the outcomes of this study, it was not feasible to develop an aggregated dataset which would have benefited the outcomes of this study. It is therefore recognized; future research should consider expanding the data collection during patient visits to better understand key clinical features and standardized scores in relation to the disease. A key data limitation is the under-representation of certain ethnic groups. Specifically, the 'White-British' group accounts for 95.7% of the patients who have an ethnicity on record. This makes it impossible to accurately estimate any ethnicity-related effects of the model, especially in the ethnicity groups that only include 1-5 patients. Gianfrancesco *et al*[35] provide a useful discussion on the potential bias associated with underrepresentation in EHRs. To investigate these effects, studies may benefit from specifically approaching the under-represented groups in order to generate more balanced cohorts.

A further limitation is that the method used within our paper is used in limited research papers due to differences with data gathering time points which impact the patients at risks at differing time points. Parmar *et al*[36] demonstrated similar methods could be used to estimate censored data along with a number of events at specific intervals although, the limitation with this is further assumptions would be made to generate estimates. The correlation tests based on Schoenfeld residuals is a positive step to assess the proportionality of hazards in standard cox models. Pseudo-likelihood was used to define Schoenfeld residuals at event times. Additionally, Kaplan-Meier estimates could have been completed if the event times and a ranking system was available at the point at which the dataset was furthered to assess the performance in a better way. Similarly, it would be beneficial to conduct simulation studies to address this issue although, this is a step to be completed as part of future research.

CONCLUSION

The study showed an increased mortality risk associated with olanzapine and risperidone whilst quetiapine showed a relatively statistically insignificant association. This study reports a heterogeneous relationship between dementias, antipsychotic medication, and mortality, with some medication classes being more problematic than others. Antipsychotic use especially in the elderly population with dementia should only be prescribed when absolutely necessary given that such medication related adverse effects remain a significant source of mental and physical distress. Evidentiary argument implicates long-term antipsychotic use to progressive reduction in brain volume. As such, regulatory

warnings from the Food and Drug Administration and the European Medicines Agency on antipsychotics in population seem to be ineffective as usage has increased. Future comprehensive investigation is imperative, especially in understanding how the sub-diagnoses of dementias differ in their medication interactions and the effect of biological differences in sex and ethnicity that many intervene and further elucidate our findings. Further investigation to better assess clinical epidemiological outcomes associated with diagnosis and non-pharmacological therapies to improve clinical management of these patients is warranted.

ARTICLE HIGHLIGHTS

Research background

Antipsychotic medication is widely prescribed to patients with dementia displaying neuropsychiatric symptoms. The present study investigated the risk of antipsychotics on mortality in all forms of dementia including vascular dementia. It is anticipated the findings will help inform clinical practice and contribute to the development of training packages on prescribing antipsychotics in dementia.

Research motivation

Antipsychotic prescribing in older adults must be made with caution as there are age related changes in pharmacokinetics and pharmacodynamics that can result in an increased sensitivity to drugs and their side effects. Similarly, the concerns around the safety and effectiveness of aripiprazole, olanzapine, quetiapine and risperidone (four specific antipsychotics) have been also raised for older patients in a clinical trial setting. Usage of antipsychotics in this population has increased despite regulatory warnings from the Food and Drug Administration and the European Medicines Agency.

Research objectives

This study was developed with a primary objective to evaluate the impact of atypical antipsychotics associated with mortality in a dementia cohort.

Research methods

A retrospective clinical cohort study was designed to review data from electrical health records (RIO system) gathered over a 5-year period (January 1, 2013 to December 31, 2017) in a National Health Service setting.

Research results

Treatment with olanzapine and risperidone was associated with an increased mortality risk. In comparison, olanzapine showed a relatively lower non-significant association with the mortality risk in those with dementia.

Research conclusions

Clinicians within primary and secondary care need to be aware of the potential heterogeneous relationship between dementia, antipsychotic medication and mortality when creating a psychopharmacological treatment plan for their patients.

Research perspectives

Future comprehensive investigation is imperative, especially in understanding how the sub-diagnoses of dementias differ in their medication interactions and the effect of biological differences in sex and ethnicity that many intervene and further elucidate our findings.

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FOOTNOTES

Author contributions: Phiri P and Carr H drafted the study protocol; Phiri P wrote the first draft of the manuscript version; Engelthaler T conducted the data extraction and analysis; all authors contributed to the critical revision of the manuscript and have approved the final manuscript.

Institutional review board statement: Health Research Authority (HRA) provided guidance to the Akrivia Health and all data controllers that neither ethics nor HRA approval (legal & governance) is required for the establishment of the Clinical Record Interactive Search (CRIS) system or using de-identified data (from the system) for research purposes in March 2020. Local approvals were obtained from the Southern Health NHS Foundation Trust (SHFT) patient-led oversight committee.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: Phiri P has received other, educational from Queen Mary University of London, Stanford University School of Medicine and other from John Wiley and Blackwell, outside the submitted work. Rathod S reports other from Janssen, Otsuka and Lundbeck outside the submitted work. All other authors report no conflict of interest.

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ORIGINAL ARTICLE

Observational Study

Reduced paraoxonase 1 activities may explain the comorbidities between temporal lobe epilepsy and depression, anxiety and psychosis

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Abstract

BACKGROUND

Temporal lobe epilepsy (TLE) is the most common focal epilepsy subtype in adults and is frequently accompanied by depression, anxiety and psychosis. Aberrations in total paraoxonase 1 (PON1) status may occur in TLE and these psychiatric conditions.

AIM

To examine PON1 status, namely Q192R PON1 genotypes and PON1 enzymatic activities, in TLE.

METHODS
We recruited 40 normal controls and 104 TLE patients, 27 without comorbidities and 77 with comorbidities including mood disorders (n = 25), anxiety disorders (n = 27) and psychosis (n = 25).

RESULTS
Four-(chloromethyl)phenyl acetate hydrolysis (CMPAase) and arylesterase activities were significantly lower in TLE and mesial temporal sclerosis (MTS) with and without psychiatric comorbidities than those in normal controls. The areas under the receiver operating characteristic curve of CMPAase were 0.893 (0.037) for TLE and 0.895 (± 0.037) for MTS. Partial least squares path analysis showed that there were specific indirect effects of PON1 genotype on TLE severity (P < 0.0001) and psychopathology (P < 0.0001), which were both mediated by lowered CMPAase activity, while arylesterase activity was not significant. The severity of TLE was significantly associated with psychopathology scores. Furthermore, PON1 CMPAase activity was inversely associated with Mini Mental State Examination score.

CONCLUSION
The severity of TLE and comorbidities are to a large extent explained by reduced PON1 enzyme activities and by effects of the Q192R genotype, which are mediated by reduced CMPAase activity. Total PON1 status plays a key role in the pathophysiology of TLE, MTS and psychiatric comorbidities by increasing the risk of oxidative toxicity. PON1 enzyme activities are new drug targets in TLE to treat seizure frequency and psychiatric comorbidities.

Key Words: Antioxidants; Oxidative stress; Neuroimmune; Major depression; Mood disorders; Affective disorders

Core Tip: The severity of temporal lobe epilepsy (TLE) and mesial temporal sclerosis and their psychiatric comorbidities including depression, anxiety and psychosis are largely explained by lowered paraoxonase 1 (PON1) enzyme activities, which mediate the effects of the Q192R PON1 genotype on psychopathology and epilepsy severity. It is argued that PON1 status may play a key role in the pathophysiology of TLE, mesial temporal sclerosis and its psychiatric comorbidities by increasing the risk of neuro-oxidative toxicity. It is concluded that PON1 enzyme activities are new drug targets to treat seizure frequency and psychiatric comorbidities in patients with TLE.

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INTRODUCTION

Patients with epilepsy suffer from recurrent seizures originating from excessive and synchronous firing of groups of neurons in the brain[1,2]. Temporal lobe epilepsy (TLE) is the most common focal epilepsy subtype in adults, with a 40% incidence in relation to all types of epilepsy[3]. Hippocampal sclerosis or mesial temporal sclerosis (MTS), which is associated with neuronal loss and gliosis, is the most common primary pathology, accounting for 36% of all focal pathologies of epilepsy[4,5].

Neuropsychiatric disorders such as mood, anxiety and psychotic disorders are observed in about 30%-70% of TLE patients, and these comorbidities have a significant impact on the patient's quality of life[6-8]. In TLE, comorbid depression has the highest prevalence (42.9%) followed by anxiety disorders (18.4%), especially generalized anxiety disorder (GAD), while psychosis (PSY) shows a lower prevalence (around 5%-7%)[9,10].

In epilepsy, the first seizure may induce reactive oxygen and nitrogen species (ROS/RNS), and when these reactive species are produced in large quantities and exceed the antioxidant defense mechanisms, they may cause oxidative damage to lipids, proteins, DNA and mitochondria, excitotoxicity and neuroinflammation[11,12]. Oxidative neurotoxicity is particularly important in the central nervous system, since the brain is sensitive to oxidative stress due to its high energy and aerobic metabolic

demand[13-15]. Mitochondrial dysfunctions arising from ROS/RNS and the consequent oxidative lesions are frequently observed after seizures and during epileptogenesis and, additionally, are associated with neurodegeneration[13]. During seizures, performant antioxidant defenses are extremely important to protect brain tissues against oxidative damage ensuing from lipid peroxidation and aldehyde formation[15]. Experimental studies suggest that these oxidative pathways play an important role in the pathophysiology of TLE and TLE progression[16,17]. In addition, TLE is associated with decreases in antioxidant defenses as indicated by lowered superoxide dismutase[18] and glutathione levels in the hippocampus[19].

The enzyme paraoxonase 1 (PON1) is of particular importance because it is bound to high density lipoprotein (HDL) and has the ability to catalyze the hydrolysis of organic phosphates and lipid peroxides, protecting lipids, HDL and low density lipoprotein (LDL) from oxidation[20]. The PON1 Q192R single nucleotide polymorphism determines in part the catalytic activity and antioxidant properties of PON1 enzymes[21]. The alloenzyme R has a higher efficiency in detoxifying substrates such as paraoxon and 4-(chloromethyl) phenyl acetate (CMPA), and homozygous RR carriers metabolize lipids more efficiently than alloenzyme Q carriers, explaining their stronger protection against lipid peroxidation[22]. Nevertheless, there are only few studies that have examined total PON1 status (that is enzymatic activities and PON1 genotypes) in epilepsy. Dönmezdil *et al*[23] and Calik *et al*[24] found significantly lowered serum PON1 and arylesterase activities in patients with epilepsy, although these authors did not measure total PON1 status, which should include total enzyme activities and PON1 genotypes[25]. Moreover, no studies examined the associations between PON1 status and psychiatric comorbidities in TLE, although PON1 status is significantly associated with major depression, anxiety disorders and subtypes of PSY[25].

Hence, the objective of this study was to evaluate PON1 status, namely CMPAase and arylesterase activities as well as PON1 Q192R genotypes, in patients with TLE and MTS with and without comorbid PSY, depression and anxiety.

MATERIALS AND METHODS

Participants

For this case-control study, 104 patients with TLE and 40 normal controls were recruited. Patients with TLE were admitted to the outpatient clinic of the Comprehensive Epilepsy Unit of King Chulalongkorn Memorial Hospital, Bangkok, Thailand from December 2013 to December 2014. The patients were diagnosed with TLE by a senior neurologist specializing in epilepsy. The latter diagnosis was based on the history of clinical characteristics of seizures, electroencephalography records and magnetic resonance imaging scans performed in all patients. The patients with TLE were subdivided into four subgroups based on the presence of psychiatric comorbidities according to the criteria established in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), namely: (1) Mood disorders due to TLE with depressive characteristics (n = 25); (2) Anxiety Disorder Due to TLE with panic attacks, GAD or obsessive-compulsive symptoms (n = 27); (3) Psychotic disorder due to TLE with delusions or hallucinations (n = 25); and (4) "Pure TLE" when there were no psychiatric comorbidities (n = 27).

Exclusion criteria for healthy controls were a diagnosis of epilepsy, febrile seizures in childhood and any other axis 1 psychiatric disorder and a positive family history of epilepsy, mood disorders or psychotic disorders. Exclusion criteria for TLE patients were: (1) Any other axis 1 disorder, except mood, anxiety and psychotic disorders due to TLE; and (2) Interictive dysphoric disorder. Exclusion criteria for patients with mood disorders due to TLE were anxiety and psychotic disorders. In the patient group with anxiety disorders due to TLE, we excluded patients with mood disorders or PSY, and, in the patient group with psychotic disorder due to TLE, we excluded patients with mood and anxiety disorders. In addition, patients with "pure TLE" did not suffer from any of the above-mentioned psychiatric comorbidities. Exclusion criteria for patients and controls were: (1) (Auto)immune diseases including diabetes, psoriasis, chronic obstructive pulmonary disease, inflammatory bowel disease; (2) Neurodegenerative and neuroinflammatory disorders, such as multiple sclerosis, Parkinson's disease and Alzheimer's disease; (3) Immune, inflammatory or allergic response 3 mo before the start of the study; (4) A lifetime history of treatment with immunomodulatory drugs; (5) Use of therapeutic doses of antioxidants or supplements containing ω3-polyunsaturated fatty acids 3 mo before inclusion in the study; and (6) Pregnant or lactating women.

Prior to participation in the research, all individuals signed a written informed consent form. The Institutional Review Board of the Faculty of Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand, gave their approval to this research (IRB number 305/56) in accordance with the International Guideline for the Protection of Human Research, as established by the Declaration of Helsinki, The Belmont Report, International Conference on Harmonization of Good Clinical Practice and Council for International Organizations of Medical Sciences Guideline.

Measurements

Semi-structured interviews were conducted by a senior neurologist and a senior psychiatrist specialized in epilepsy. The neurologist collected sociodemographic data and TLE characteristics including family history of epilepsy, age at onset of TLE, type of epilepsy, location of the lesion, seizure frequency, seizure control (seizure free, fairly and poorly controlled seizures); history of post-ictal confusion, type of seizures and use of antiepileptic drugs (AEDs). The diagnosis of TLE was made based on the history of partial seizures and electroencephalography records of epileptiform activities in one or both temporal regions. In addition, the senior neurologist and a radiologist used results of magnetic resonance imaging scans to make the diagnosis of MTS or other types of TLE. Patients and controls were evaluated by the senior psychiatrist to identify psychotic symptoms, anxiety and depression, using DSM-IV-TR criteria. The diagnosis of mood disorders due to TLE comprises major depression in an acute episode or in partial remission and ictus-related depression. The diagnosis of anxiety disorder due to TLE comprises patients with panic, GAD, obsessive-compulsive symptoms and ictus-related anxiety such as fear and horror. Psychotic disorders due to TLE comprise delusions (persecutors, possessed, paranoid and reference ideas), hallucinations (auditory, taste, visual and olfactory) and ictus-related psychoses, as described by Kanchanatawan *et al*[26]. These psychoses can be ictal, pre-ictal, post-ictal, psychotic aura, peri-ictal, interictal or schizophrenic-like PSY. In this context, fear, horror, forced thoughts, out-of-body experiences and going crazy were not considered to be psychotic.

The senior psychiatrist (BK) also assessed the Brief Psychiatric Rating Scale (BPRS), the Hamilton Depression (HAM-D) and Anxiety (HAM-A) Rating Scale[27-29] and also assessed the Mini Mental State Examination (MMSE)[30] in patients and controls. The body mass index (BMI) was calculated using the ratio between body weight in (kg) and height (m^2) and tobacco use disorder was evaluated using the DSM-IV-TR criteria.

PON1 assays

Blood samples were collected at 8:00 am, after an overnight fast, and serum was aliquoted and stored at -80 °C until thawed for PON1 status. Total PON1 activity was determined by the formation of phenyl acetate hydrolysis[22]. The rate of phenylacetate hydrolysis was determined on a Perkin Elmer® EnSpire model microplate reader (Waltham, MA, United States) at a wavelength of 270 nm measured over 4 min (16 readings at 15 s between readings) with the temperature maintained at 25 °C. Activity was expressed in U/mL based on the phenyl acetate molar extinction coefficient, which is 1.31 mmol/Lol/Lcm-1. For the stratification of the functional genotypes of the PON1Q192R polymorphism (PON1 192Q/Q, PON1 192Q/R, PON1 192R/R), we used CMPA (Sigma, St. Louis, MO, United States) and phenyl acetate (PA, Sigma). PON1 polymorphism confers differences in hydrolysis capacity, and this allows to stratify the genotypes after phenotypic analysis of enzyme activity. Isoform R has high hydrolysis activity on CMPA, whilst alloenzyme Q has lower hydrolytic activity on CMPA, and both alloforms hydrolyze PA with similar efficacy. Therefore, the reaction with PA is performed with high salt concentrations, which partially inhibits the activity of R allozyme, thereby providing a better distinction between the three functional genotypes. The rate of PA hydrolysis in low salt concentration by arylesterase was also measured.

Statistics

We used analysis of variance to assess differences in scale variables between diagnostic groups and analysis of contingency tables (χ^2-tests) to assess associations among categorical variables. We used multivariate general linear model (GLM) analysis to ascertain the associations between diagnosis and biomarkers while controlling for possible background variables including sex, age, BMI, smoking and the drug state. Consequently, tests for between-subject effects were employed to examine the associations between diagnosis and each of the biomarkers. Model-generated estimated marginal mean values were computed, and protected pair-wise comparisons among treatment means were employed to delineate the differences among the study groups. We used *P*-corrections for false discovery rate to control for multiple statistical tests[31]. Automatic binary regression analysis was employed to delineate the best biomarker prediction of TLE (controls as reference group). We employed automatic stepwise (step-up) multiple regression analysis to assess the most significant biomarkers predicting the BPRS, HAM-D, HAM-A and MMSE scores. Regression analyses were double-checked for collinearity and bootstrapped using 5000 samples, and the bootstrapped results are shown in case of discrepant results. All tests were two-tailed and a *P* value of 0.05 was used for statistical significance. IBM SPSS25 (Armonk, NY, United States) (for windows was used to analyze the data. The number of participants was established *a priori* using GPower: At least 138 people were required to achieve a power of 0.8 (effects size: 0.3; alpha = 0.05; four groups and four covariates) (analysis of covariance).

To examine the causal associations between PON1 genotype and PON1 enzyme activities and TLE characteristics and psychopathology, we performed partial least squares (PLS) path analysis employing SmartPLS[32]. SmartPLS is a structural equation modeling technique that allows to examine causal pathways explaining the effects of input variables (PON1 genotype) on output variables (PON1 activities and clinical aspects of TLS and comorbidities), whereby variables are entered as single indicator variables (PON1 genotype and enzyme activities) or as latent vectors (LV) extracted from TLE

features (TLE; aura; postictal confusion; TLE frequency; seizure free, fairly and poorly controlled seizures); and the three psychopathological rating scale scores (BPRS, HAM-A, HAM-D)[32]. We conducted PLS path analysis when the model complied with quality criteria, *i.e.* model SRMR < 0.080 and when the LVs showed adequate reliability validity as indicated by composite reliability > 0.7, rho_A > 0.8, Cronbach's alpha > 0.7 and average variance extracted (AVE) > 0.5; while the outer model factor loadings were > 0.6 with $P < 0.001$[32]. Consequently, we conducted complete and consistent PLS path analysis using 5.000 bootstrap samples to compute path coefficients (with P values) and the significance of total, total indirect and specific indirect effects.

RESULTS

Demographic and clinical data

Table 1 shows the socio-demographic data of the participants in this study. There were no significant differences in age, BMI, marital status, or tobacco use disorder between the study groups. There was a trend towards more females in TLE patients with depression and anxiety. Subjects with TLE were somewhat less educated than the healthy controls. Therefore, we have statistically controlled for education in regressions with psychopathology ratings and MMSE as dependent variables. There were no significant differences in seizure frequency, age of onset of TLE, a history of aura, postictal confusion and control of seizures (free of seizures, fair and poor control) between the four TLE subgroups. Patients with psychotic disorder due to TLE showed a higher incidence of status epilepticus as compared with those with "pure TLE". Table 1 also shows the rating scale scores and MMSE scores in the five subgroups. The BPRS and HAM-A scores were significantly different between the five subgroups, with the lowest levels in controls and highest values in patients with TLE + PSY and TLE + anxiety, respectively. The HAM-D score was significantly higher in patients with TLE + depression than in all other study groups, while the MMSE was significantly lower in TLE patients than in controls, with the lowest scores being established in TLE + PSY.

Associations between TLE with and without comorbidities and PON1 genotypes

The total study group (patients and controls) was at Hardy-Weinberg equilibrium ($\chi^2 = 1.086$, df = 1, $P = 0.297$), while also the control ($\chi^2 = 1.2013$, df = 1, $P = 0.273$) and the TLE ($\chi^2 = 0.530$, df = 1, $P = 0.467$) subgroups were at Hardy-Weinberg equilibrium. There was no significant association between PON1 Q192R genotypes and TLE subgroups ($\psi = 0.137$, $P = 0.251$), namely in controls: 1/17/22 *vs* 10/51/47 in TLE for the QQ, QR and RR genotypes, respectively. There were no significant associations between TLE and different genetic models of the *PON1* gene, including allelic, dominant, recessive and overdominant models.

Associations between PON1 activity and diagnosis

We examined the associations between the activities and diagnosis using multivariate GLM analysis while adjusting for sex, age and BMI. We examined four PON1 activity indices namely PON1 CMPAase and AREase enzyme activities as measured in this study and their residualized values after covarying for PON1 genotypes. The latter explained 70.0% of the variance in PON1 CMPAase and arylesterase activities (F = 173.88, df = 2/145, $P < 0.001$), with the lowest CMPAase activities and the highest arylesterase activities in QQ carriers.

Multivariate GLM analysis showed that there was a significant association between PON1 activity and diagnosis (Table 2). Tests for between-subjects effects showed significant associations between diagnosis and CMPAase and the residualized CMPAase activities with an explained variance of around 43.7%-45.0%. The associations with arylesterase and the residualized arylesterase activity shared around 24.8%-33.0% of the variance. Table 3 shows the model-generated estimated marginal mean values, indicating that all PON1 activities were significantly lowered in TLE patients than in controls. These differences were highly significant, with a distance of around 1.586 standard deviations between controls and patients with TLE + PSY in residualized PON1 CMPAase activity. Figure 1 shows the box-plot of CMPAase activity values in controls, pure TLE and TLE with psychiatric comorbidities.

Binary logistic regression analysis with TLE as dependent variable (controls as reference group) showed that the residualized PON1 CMPAase activity was the most significant biomarker discriminating TLE from controls, with a sensitivity of 70.4%, specificity of 90.0% and accuracy of 75.7% ($\chi^2 = 69.74$, df = 1, $P < 0.001$, Nagelkerke = 0.546). The odds ratio was 0.111 (95% confidence interval: 0.053-0.230; Wald = 29.41, $P < 0.001$; B = 1.515, SE = 0.279).

Table 4 shows that CMPAase and arylesterase activities were significantly lower in MTS (with psychiatric comorbidities), "pure" TLE and "pure" MTS (both without psychiatric comorbidities) than those in controls. The strongest impact was established for CMPAase activity in MTS. The area under the receiver operating characteristic curve using reduced CMPAase activity as discriminatory variable was 0.893 (0.037) for TLE and 0.895 (± 0.037) for MTS.

Table 1 Sociodemographic and clinical data of healthy controls and patients with temporal lobe epilepsy and patients with psychosis, depression and anxiety due to temporal lobe epilepsy (mean ± SD)

Variables	HC[1]	TLE[2]	TLE + PSY[3]	TLE + DEP[4]	TLE + ANX[5]	F/X[2]	df	*P* value
Age (yr)	37.4 (12.8)	40.0 (12.8)	37.9 (10.5)	39.0 (10.7)	37.0 (8.2)	0.34	4/141	0.849
Sex (♂/♀)	10/30	11/16	13/14	4/21	5/22	10.31	4	0.036
BMI (kg/m^2)	24.0 (4.3)	24.1 (4.0)	23.5 (3.7)	23.9 (4.3)	22.4 (4.3)	0.79	4/140	0.535
Married (No/Yes)	26/14	18/9	20/7	20/5	15/11	3.58	4	0.466
Education (yr)	14.2 (4.9)[2,3,4,5]	11.4 (4.7)[1]	9.4 (4.4)[1]	10.3 (5.4)[1]	10.8 (4.5)[1]	5.14	4/141	0.001
TUD (No/Yes)	38/2	24/3	23/4	21/4	23/4	Ψ = 0.136	-	0.607
Frequency seizures	-	29.1 (84.7)	19.1 (40.7)	8.0 (17.0)	9.7 (11.0)	0.99	3/89	0.402
Age onset TLE (yr)	-	17.8 (12.6)	12.2 (10.1)	17.6 (8.9)	16.1 (8.8)	1.75	3/100	0.162
Hx Aura (No/Yes)	-	6/21	5/22	7/18	8/19	1.15	3	0.766
Hx Postictal confusion (No/Yes)	-	8/19	10/16	9/16	11/15	0.97	3	0.808
Hx Status epilepticus (No/Yes)	-	24/3[3]	14/11[2]	21/4	13/9	10.75	3	0.013
Seizure control	-	7/8/8	7/8/8	5/4/0	5/5/10	Ψ = 0.309	-	0.307
BPRS	18.3 (1.1)[2,5]	23.6 (3.3)[1,3,4,5]	41.3 (5.9)[1,2,4,5]	32.9 (6.7)[1,2,3,5]	29.4 (50.)[1,2,3,4]	115.64	4/141	< 0.001
HAM-D	0.6 (2.0)[2,5]	4.8 (2.5)[1,4,5]	5.8 (2.9)[1,5]	19.8 (4.9)[1,2,3,5]	10.3 (3.8)[1,2,3,4]	145.21	4/140	< 0.001
HAM-A	2.6 (5.4)[2,5]	7.8 (3.9)[1,3,4,5]	11.6 (6.7)[1,2,3,5]	18.9 (8.8)[1,2,3,5]	23.8 (5.4)[1,2,3,4]	59.69	4/141	< 0.001
MMSE	28.3 (2.4)[2,5]	25.1 (4.4)[1,3]	22.4 (5.4)[1,2,4,5]	25.7 (2.4)[1,3]	25.8 (8.9)[1,3]	11.06	4/140	< 0.001

[1-5]Results of post-hoc comparisons among the five diagnostic groups.

[1]Indicates HC and "1" associated with column figures indicates that this value is different from HC.

[2]Indicates TLE and "2" associated with column figures indicates that this value is different from TLE.

[3]Indicates TLE + PSY and "3" associated with column figures indicates that this value is different from TLE + PSY.

[4]Indicates TLE + DEP and "4" associated with column figures indicates that this value is different from TLE + DEP.

[5]Indicates TLE + ANX and "5" associated with column figures indicates that this value is different from TLE + ANX.

BMI: Body mass index; TUD: Tobacco use disorder; Control seizures: Seizure free and fairly and poorly controlled seizures; BPRS: Brief Psychiatric Rating Scale; HAM-D: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; MMSE: Mini Mental State Examination; HC: Healthy controls; TLE: Temporal lobe epilepsy; TLE: TLE without ant psychiatric comorbidities; TLE + PSY: Psychotic Disorder due to TLE; TLE + DEP: Mood Disorder due to TLE with depressive features; TLE + ANX: Anxiety Disorder due to TLE.

Effects of possible confounding variables

As shown in Table 2, there were no significant effects of possible confounders including sex, age and BMI. There were also no significant effects of smoking (F = 0.48, df = 4/135, P = 0.748) and the Fagerstrom score (F = 0.16, df = 4/135, P = 0.960). We have also examined the possible effects of treatments with valproate (n = 34), carbamazepine (n = 61), phenytoin (n = 38), levetiracetam (n = 38), lamotrigine (n = 27), phenobarbital (n = 26), clonazepam (n = 10), clobazam (n = 58), topiramate (n = 12), gabapentin (n = 8), antipsychotics (n = 9), antidepressants (n = 16), anxiolytics (n = 10), CaCo3 (n = 13) and folic acid (n = 27). These drug state variables were examined as dummy variables entered altogether in multivariate GLM analysis or one by one in univariate GLM analyses. However, both types of GLM analyses showed no significant effects, even without P-correction for multiple testing. There was no significant association (Spearman rank order correlation) between the number of AEDs and either CMPAase (-0.086, P = 0.398, n = 102) or arylesterase (r = 0.052, P = 0.605, n = 102) activity.

Prediction of rating scale scores using biomarkers

In order to examine the effects of biomarkers on the rating scale scores, we performed automatic multiple regression analysis with the rating scales as dependent variables and the four PON1 measurements (residualized and non-residualized CMPAase and AREase activities), the PON1 genetic models, age, sex as well as education (Table 5). Firstly, we examined associations with the BPRS and two symptoms profiles namely PSY that is sum of BPRS items 4 (conceptual disorganization), 11 (suspiciousness), 12 (hallucinations) and 15 (unusual thought disorders), and negative symptoms namely the sum of BPRS symptoms 3 (emotional withdrawal) and 16 (blunted affect). We found that 29.1% of the variance in the BPRS total score and 11.8% of the variance in PSY was predicted by PON1 CMPAase activity and education (both inversely). Figure 2A shows the inverse association between

Table 2 Results of multivariate general linear model analysis examining the differences between diagnostic groups (diagnosis), namely healthy controls, temporal lobe epilepsy with and without comorbidities including depression, psychosis, and anxiety

Tests	Dependent variables	Exploratory variables	F	df	*P* value	Partial Eta squared
	All 4 biomarkers					
Multivariate	CMPAase	Diagnosis	6.49	16/410	< 0.001	0.158
	Arylesterase	Sex	1.22	4/134	0.306	0.035
	Res CMPAase	Age	0.61	4/134	0.654	0.018
	Res Arylesterase	BMI	1.07	4/134	0.375	0.031
Between-subject effects	CMPAase	Diagnosis	28.06	4/137	< 0.001	0.450
	Res CMPAase	Diagnosis	26.60	4/137	< 0.001	0.437
	Arylesterase	Diagnosis	11.31	4/137	< 0.001	0.248
	Res Arylesterase	Diagnosis	16.90	4/137	< 0.001	0.330

Diagnosis: Five diagnostic groups, namely Psychotic Disorder due to temporal lobe epilepsy (TLE), Mood Disorder due to TLE with depressive features, Anxiety Disorder due to TLE, "Pure TLE" (without any comorbidities) and healthy controls. PON1: Paraoxonase; CMPAase: 4-(chloromethyl)phenyl acetate hydrolysis; Res: Residualized (after regression on PON1 genotype); BMI: Body mass index.

Table 3 Model-generated estimated marginal means of paraoxonase 1 levels in healthy controls and patients with temporal lobe epilepsy and psychosis, depression and anxiety due to temporal lobe epilepsy

Variables	HC[1]	TLE[2]	TLE + PSY[3]	TLE + DEP[4]	TLE + ANX[5]
CMPAase (U/mL)	42.1 (1.3)[2,3,4,5]	28.5 (1.6)[1]	24.5 (1.6)[1]	24.8 (1.7)[1]	27.3 (1.7)[1]
Res CMPAase (z scores)	1.041 (0.128)[2,3,4,5]	-0.196 (0.150)[1]	-0.545 (0.163)[1]	-0.545 (0.163)[1]	-0.375 (0.159)[1]
Arylesterase (U/mL)	212.4 (9.0)[2,3,4,5]	156.4 (10.5)[1]	144.2 (10.4)[1]	143.7 (11.4)[1]	137.3 (11.2)[1]
Res Arylesterase (z scores)	0.920 (0.140)[2,3,4,5]	-0.193 (0.163)[1]	-0.425 (0.162)[1]	-0.400 (0.177)[1]	-0.434 (0.174)[1]

[1-5]Results of post-hoc comparisons among the five diagnostic groups.
[1]Indicates HC and "1" associated with column figures indicates that this value is different from HC.
[2]Indicates TLE and "2" associated with column figures indicates that this value is different from TLE.
[3]Indicates TLE + PSY and "3" associated with column figures indicates that this value is different from TLE + PSY.
[4]Indicates TLE + DEP and "4" associated with column figures indicates that this value is different from TLE + DEP.
[5]Indicates TLE + ANX and "5" associated with column figures indicates that this value is different from TLE + ANX.
TLE: Temporal lobe epilepsy; TLE: TLE without psychiatric comorbidities; TLE + PSY: Psychotic Disorder due to TLE; TLE + DEP: Mood Disorder due to TLE with depressive features; TLE + ANX: Anxiety Disorder due to TLE; HC: Healthy controls; PON1: Paraoxonase; CMPAase: 4-(chloromethyl)phenyl acetate hydrolysis; Res: Residualized values after regression on PON1 genotype.

total BPRS score and CMPAase activity (partial regression based on the first regression in Table 5). The best predictors of negative symptoms were the residualized CMPAase activity, age and education (all inversely correlated) and male sex. We found that 25.4% of the variance in the HAM-D score was predicted by PON1 CMPAase activity, education (both inversely), female sex and being a QQ or RR carrier. Figure 2B shows the partial regression of the total HAM-D score on CMPAase activity. A large part of the variance in suicidal ideation (item 3 of the HAM-D) was explained by QQ genotype and residualized CMPAase activity (inversely associated) combined. We also computed the associations between physiosomatic symptoms, namely the sum of the HAM-A items 11 (anxiety somatic), 12 (somatic symptoms GIS), 13 (somatic symptoms general), 14 (genital symptoms) and 15 (hypochondriasis) and found that 12.2% of its variance was explained by PON1 CMPAase activity (inversely associated). Consequently, we have computed an index of psychomotor retardation (PMR) as z values of item 8 of the HAM-D and item 13 of the BPRS (both PMR) and found that 29.5% of the variance in PMR was explained by residualized CMPAase activity, age and education (all inversely associated) and male sex. CMPAase activity combined with female sex predicted 15.3% of the variance in the total HAM-A score. We have computed an overall psychopathology index as the sum of the z values of the BPRS, HAM-D and HAM-A. This index was best predicted by PON1 CMPAase activity, education (both inversely), female sex and PON1 genotype. We found that 43.4% of the variance in the MMSE score was predicted by education and CMPAase activity (both positively associated).

Table 4 Measurement of paraoxonase enzymatic activity in healthy controls and subgroups of temporal lobe epilepsy patients

PON1 activities	HC	Pure TLE	F	df	*P* value	Partial eta squared
CMPAase (U/mL)	42.8 (1.7)	28.8 (1.9)	30.61	1/62	< 0.001	0.331
Arylesterase (U/mL)	215.4 (10.8)	156.4 (12.2)	13.47	1/62	0.001	0.178
		MTS				
CMPAase (U/mL)	41.7 (1.5)	25.6 (1.2)	81.44	1/100	< 0.001	0.449
Arylesterase (U/mL)	209.8 (9.4)	139.4 (7.5)	36.98	1/100	< 0.001	0.270
		Pure MTS				
CMPAase (U/mL)	42.2 (1.8)	27.3 (2.6)	22.61	1/52	< 0.001	0.303
Arylesterase (U/mL)	213.0 (10.8)	139.5	14.65	1/52	< 0.001	0.220

Data are results of univariate general linear model analysis and are shown as model-generated marginal estimated mean (SE) values after covarying for age, sex and body mass index. Pure TLE: Temporal lobe epilepsy without any psychiatric comorbidity; MTS: Established mesial temporal lobe sclerosis (thus including psychiatric comorbidities); Pure MTS: Established mesial temporal lobe sclerosis without any psychiatric comorbidity; TLE: Temporal lobe epilepsy; HC: Healthy controls; MTS: Mesial temporal sclerosis.

Results of path analysis

Figure 3 shows the results of a consistent and complete PLS path analysis with the PON1 genotype (additive model) as input variable and a LV extracted from the three rating scale scores (BPRS, HAM-D and HAM-A) as final outcome in a multi-step mediation model with PON1 activities (CMPAase and arylesterase) and a LV extracted from TLE features (frequency, aura, controlled epilepsy and postictal confusion) as mediators. There were no significant effects of arylesterase (after considering the effects of CMPAase), and, therefore, only the latter are shown in this figure. The fit of the model was adequate with SRMR = 0.053, while the construct reliability validity of both LVs was adequate with composite reliability values of 0.890 and 0.855; Cronbach α values of 0.847 and 0.805, rho_A values of 0.898 and 0.810 and AVE values of 0.620 and 0.719 were determined for TLE and psychopathology LVs, respectively. All outer loadings of the indicators of both LVs were > 0.694 (all at $P < 0.0001$). We found that 46.0% of the variance in the psychopathology index was explained by the TLE LV (positively associated) and PON1 CMPAse activity (inversely associated), while 25.3% of the variance in the TLE LV was explained by CMPAase activity. Finally, the PON1 genotype additive model explained 9% of the variance in CMPAase activity. There were specific indirect effects of PON1 genotype on: (1) The TLE LV, which were mediated by CMPAase activity ($t = 4.07$, $P < 0.0001$); and (2) The psychopathology LV mediated by CMPAase activity ($t = 1.97$, $P = 0.048$) and the path from PON1 genotype→CMPAase activity→TLE LV→psychopathology LV ($t = 3.74$, $P < 0.0001$). Likewise, the PON1 genotype had significant total (indirect) effects on TLE LV ($t = 4.07$, $P < 0.0001$) and psychopathology LV ($t = 3.87$, $P < 0.0001$). We have also examined the total effects of the QQ, QR and RR genotypes on the TLE and psychopathology LVs and found that QQ ($t = 3.39$, $P = 0.001$ and $t = 3.20$, $P = 0.001$) and RR ($t = -3.35$, $P = 0.001$ and $t = -3.26$, $P = 0.001$), but not QR, had significant total effects on the TLE and psychopathology LVs, respectively.

DISCUSSION

The first major finding of this study is that PON1 CMPAase and arylesterase activities were significantly decreased in patients with TLE, especially MTS, as compared with healthy controls. In our study, reduced levels of CMPAase yielded an area under the receiver operating characteristic curve of around 0.893 for TLE and MTS. These findings extend those of previous publications reporting significantly reduced levels of PON1 and arylesterase in patients with epilepsy when compared to healthy controls [24,33].

The second major finding of this study is that there were no significant differences in PON1 status between TLE without any comorbidities and depression, anxiety or PSY due to TLE, although severity of depression, PSY and anxiety were strongly associated with CMPAase activity. As such, CMPAase and, to a lesser degree, arylesterase activity are important in predicting the severity of psychopathology in TLE. We also observed that the severity of TLE predicts a general index of psychopathology.

Psychiatric comorbidities such as depression and anxiety are prevalent in patients with epilepsy and occur 2 to 3 times more frequently in this group of patients than in people who do not have the disease [34,35]. Some authors found a strong association between low levels of PON1 and CMPAase activities and major depression[36,37], whilst reduced activity of CMPAase was additionally associated with lower quality of life, increased disability and staging of illness[36,38], suggesting that reduced total

Table 5 Results of multiple regression analysis with rating scales as dependent variables and paraoxonase status as explanatory variables

Dependent variables	Explanatory variables (model)	β	*t* value	*P* value	F model	Df	*P* value	Partial Eta squared
BPRS	CMPAase	-0.444	-6.09	< 0.001	29.35	2/143	< 0.001	0.291
	Education	-0.213	-2.93	0.004				
Psychosis	CMPAase	-0.260	-3.20	0.002	9.56	2/143	< 0.001	0.118
	Education	-0.167	-2.06	0.041				
Negative symptoms	Education	-0.329	-4.52	< 0.001	12.75	4/141	< 0.001	0.226
	Sex	-0.329	-4.29	< 0.001				
	Res CMPAase	-0.189	-2.56	< 0.011				
	Age	-0.172	-2.30	0.023				
HAM-D	CMPAase	-0.347	-4.51	< 0.001	11.95	4/140	< 0.001	0.254
	Education	-0.231	-3.02	0.003				
	Overdominant model	-0.227	-3.06	0.003				
	Sex	0.170	2.31	0.023				
Suicidal ideation	Dominant model	0.354	4.61	< 0.001	13.21	2/143	< 0.001	0.156
	Res CMPAase	-0.173	-2.26	0.025				
Physiosomatic symptoms	CMPAase	-0.349	-4.47	< 0.001	19.94	1/144	< 0.001	0.122
PMR	Education	-0.386	-5.13	< 0.001	14.75	4/141	< 0.001	0.295
	Sex	-0.252	-3.54	0.001				
	Res CMPAase	-0.243	-3.36	0.001				
	Age	-0.186	-2.53	0.013				
HAM-A	CMPAase	-0.350	-4.80	< 0.001	12.93	2/143	< 0.001	0.153
	Sex	0.163	2.10	0.037				
Psychopathology index	CMPAase	-0.430	-5.83	< 0.001	19.94	3/141	< 0.001	0.298
	Education	-0.250	-3.41	0.002				
	Overdominant model	-0.148	-2.07	0.040				
MMSE	Education	0.593	9.09	< 0.001	54.48	2/142	< 0.001	0.434
	CMPAase	0.175	2.69	0.008				

BPRS: Brief Psychiatric Rating Scale; HAM-D: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; MMSE: Mini Mental State Examination; PMR: Psychomotor retardation; Res CMPAase: Residualized (after regression on PON1 genotype); CMPAase: 4-(chloromethyl)phenyl acetate hydrolysis; Dominant and overdominant model: PON1 Q192R genotype models.

PON1 and CMPAase activities may play a role in the pathophysiology and progression of mood disorders[36]. In patients with anxiety disorders, decreased levels of PON1 are accompanied by high levels of lipid hydroperoxides as compared with individuals without anxiety[39,40]. CMPAase activity is also inversely associated with symptoms characteristic of (deficit) schizophrenia including PSY, negative symptoms and PMR[37]. The latter authors reported that CMPAase activity was significantly reduced in patients with schizophrenia and that this effect was, to a large extent, determined by increased frequency of the QQ genotype. Noto *et al*[41] reported a significant decrease in PON1 activity in drug-naïve patients with first-episode PSY.

Our results show that PON1 CMPAase activity is positively associated with the MMSE score, which is significantly reduced in TLE patients, suggesting that PON1 activity protects against cognitive decline in TLE. In this regard, epilepsy *per se* is accompanied by a neurocognitive decline[42]. In patients with schizophrenia, reduced PON1 activity is strongly associated with neurocognitive deficits[37], whilst in mood disorders, reduced PON1 status is associated with staging of the disorder, which is characterized by increased neurocognitive deficits[43].

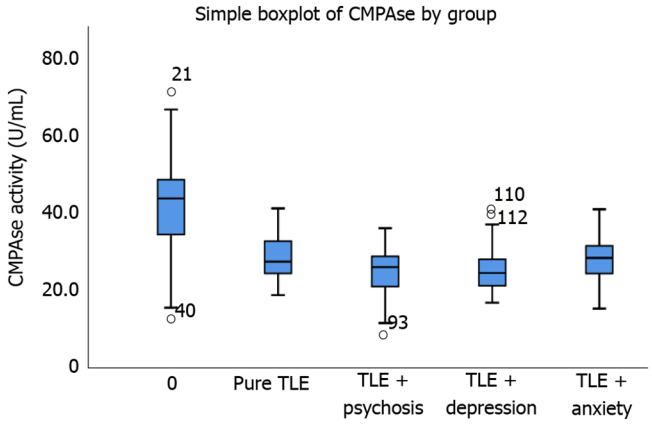

Figure 1 Box plot of 4-(chloromethyl) phenyl acetate hydrolysis activity in controls (0), pure temporal lobe epilepsy (temporal lobe epilepsy: No comorbidities are present) and temporal lobe epilepsy with psychiatric comorbidities. TLE: Temporal lobe epilepsy; CMPAase: 4-(chloromethyl)phenyl acetate hydrolysis.

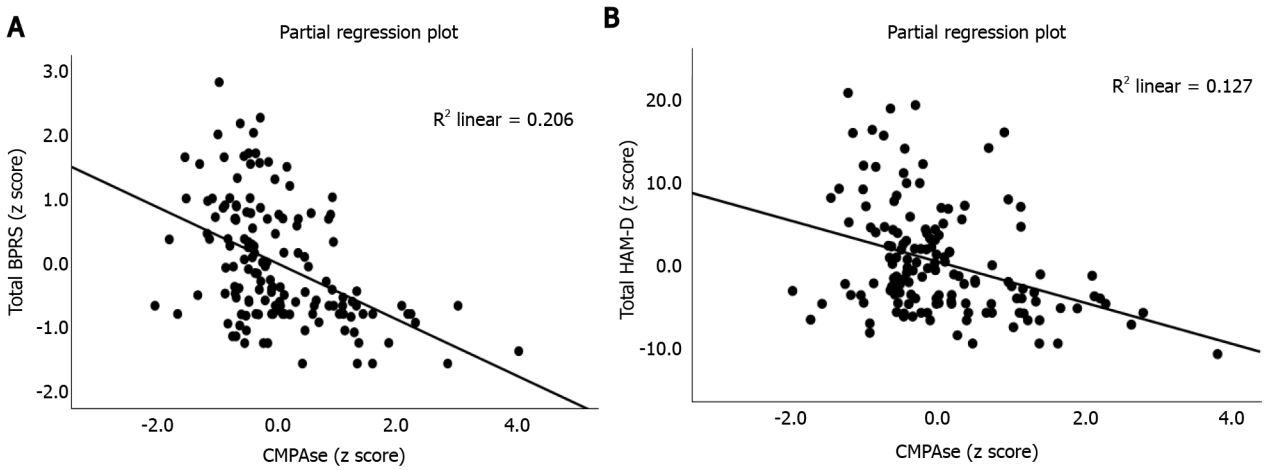

Figure 2 The Brief Psychiatric Rating Scale score and total Hamilton Depression Rating Scale score on 4-(chloromethyl) phenyl acetate hydrolysis activity in 104 patients with temporal lobe epilepsy with and without comorbidities and 40 healthy controls. A: Inverse association between the Brief Psychiatric Rating Scale score and 4-(chloromethyl) phenyl acetate hydrolysis activity in 104 patients with temporal lobe epilepsy with and without comorbidities and 40 healthy controls; B: The partial regression of the total Hamilton Depression Rating Scale score on 4-(chloromethyl) phenyl acetate hydrolysis activity in 104 patients with temporal lobe epilepsy with and without comorbidities and 40 healthy controls. BPRS: Brief Psychiatric Rating Scale; CMPAase: 4-(chloromethyl)phenyl acetate hydrolysis; HAM-D: Hamilton Depression Rating Scale.

The third major finding of this study is the significant association between the PON1 genotype and TLE features including seizure frequency, aura, postictal confusion, uncontrolled seizure type and TLE-associated psychopathology including severity of PSY, depression and anxiety. Thus, PLS path analysis revealed that the PON1 genotype, especially the QQ but also the QR, variants increase risk and severity of TLE and TLE-associated psychopathology and that the RR genotype is protective. Our study indicates that genetically determined decreases in PON1 CMPAase activity as well as reduced PON1 enzyme activities, which occur independently of the PON1 genotype, may be causally related to TLE and its psychiatric comorbidities. As such, alterations in CMPAase and PON1 activities, which are secondary to oxidative stressors[25,43], or environmental factors including nutritional factors and smoking may also be involved[25]. Nutritional factors that may affect PON1 activity include polyphenols, oleic acid, a Mediterranean diet, chokeberry and pomegranate juice, lipids, vitamin C and vitamin A[25]. Interestingly, tobacco use, which lowers PON1 activity, is associated with focal or generalized seizures[44,45], indicating that chemicals in tobacco smoke may have pro-convulsive effects [46]. Harmful and potentially harmful constituents in tobacco that may trigger seizures are carbon monoxide, toluene, cresol, arsenic, acetone, ammonia, lead and hexane[46].

PON1 is a detoxifying enzyme that is associated with HDL[40] and has anti-inflammatory[25] and antioxidant properties, including hydrolyzing lipid peroxides[47]. PON1 activity may protect against lipid, LDL and HDL oxidation and increase HDL's ability to increase cholesterol efflux from macrophages[48]. Furthermore, PON1 protects against macrophages' pro-oxidative effects, which produce free radicals and myeloperoxidase, resulting in the highly toxic peroxynitrite and hypochlorous

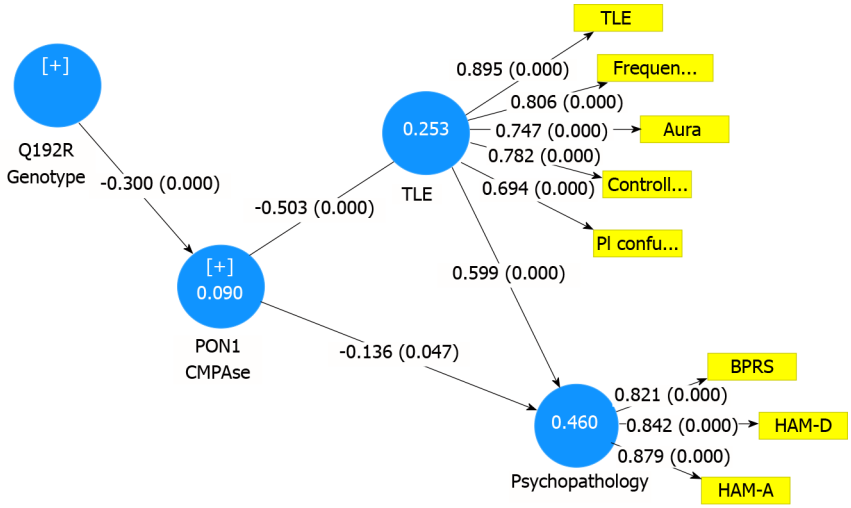

Figure 3 Results of partial least squares path analysis with a latent vector extracted from three psychopathology dimensions as outcome variable and a latent vector extracted from temporal lobe epilepsy features, paraoxonase 1 activity and the Q19R paraoxonase 1 genotype (additive model) as input variables. Shown are path coefficient with *P* value (between brackets). Frequency: Seizure frequency; Aura: Aura present or not; Controlled: Seizure free and fairly and poorly controlled seizures; PI confusion: History of post-ictal confusion; BPRS: Brief Psychiatric Rating Scale; HAM-D/HAM-A: Hamilton Depression and Anxiety Rating Scale scores; TLE: Temporal lobe epilepsy; CMPAase: 4-(chloromethyl)phenyl acetate hydrolysis.

acid[40]. Moreover, Borowczyk *et al*[49] reported that PON1 may hydrolyze homocysteine thiolactone, a toxic metabolite that can induce epileptic seizures in rats and is implicated in neurodegenerative disorders. Importantly, in oxidative stress conditions, PON1 may be damaged by increased myeloperoxidase activity and elevated production of peroxynitrite and hypochlorous acid, leading to reduced antioxidant defenses and thus an increased vulnerability to oxidation of LDL and HDL, which in turn will lower the protective effects of HDL[43]. Therefore, a well-functioning antioxidant system is important to prevent lipid peroxidation and conditions characterized by PON1 gene-associated decreases in PON1 activity (like TLE and MTS) are accompanied by increased risk to develop lipid oxidation.

There is now some evidence of increased oxidation of lipids[50,51] and lipid peroxidation occurring during TLE progression[15]. Moreover, experimental epilepsy/TLE models show increased hydroxyl radicals in the CNS[52], increased lipid peroxidation and reduced antioxidant defenses[15,15,53]. For example, Mojarad and Roghani[18] found increased lipid peroxidation and decreased superoxide dismutase activity in a kainic acid induced TLE model. The latter model is also accompanied by a decrease in the reduced form of glutathione in the hippocampus[19] and increased malondialdehyde, the end product of lipid peroxidation, in the piriform cortex[17]. Moreover, elevated malondialdehyde is associated with a greater vulnerability of the piriform cortex to seizure-induced damage. Lipid peroxidation can alter the permeability of the mitochondrial membrane and enzymes present in the membrane, possibly leading to neurodegenerative processes[12]. Therefore, the results of the current study suggest that reduced PON1 CMPAase activity, which is in part genetically determined, participates in the pathophysiology of TLE and MTS and the onset of comorbid psychopathology through increased oxidative stress. This mechanistic explanation may, at least in part, underpin the strong comorbidity between TLE and psychiatric symptoms. Moreover, the decrease in serum PON1 activity may explain the cognitive impairments in TLE/MTS. Previously, it was reported that reduced PON1 CMPAase activity is associated with cognitive deficits in schizophrenia and dementia[37]. For example, increased ROS levels may cause loss of inhibitory neurons in the hippocampus in patients with epilepsy and induce a hyperexcitability state, which can initiate reactive gliosis and, consequently, mitochondrial dysfunction leading to neurodegeneration[12].

Limitations

Our results were adjusted for possible effects of sex, age, BMI and smoking, which may affect PON1 enzymatic activity and oxidative biomarkers[25]. All patients in the current study were medicated (AEDs or psychotropic drugs). Some studies, but not all, suggested that AED treatment may influence lipid peroxidation[54]. For example, treatment with levetiracetam may be accompanied by a decrease in serum PON1 and arylesterase activity and a significant increase in oxidized LDL[55]. Nevertheless, in our study, there were no significant effects of AEDs, antipsychotics or mood-stabilizing drugs on PON1 activity, and we found no associations between the number of AEDs patients were taking and PON1 enzymatic activity. Nevertheless, in the present study we did not control for duration of treatment with AEDs or antipsychotics on PON1 activities. Moreover, other studies found no significant differences in oxidative stress indicators between treated and untreated epilepsy patients[56,57]. Arylesterase activity

is not significantly different between chronically polymedicated psychiatric patients and controls, suggesting that treatment with psychotropic medications does not induce changes in arylesterase activity[25].

CONCLUSION

The activities of CMPAse and arylesterase enzymes are significantly decreased in patients with TLE, especially MTS, as compared with healthy controls. The detrimental effects of the PON1 genotype on the severity of TLE, depression, PSY and anxiety are mediated by reduced CMPAase. The aberrations in PON1 status may play a key role in the oxidative pathophysiology of TLE, MTS and psychiatric comorbidities. PON1 enzymatic activity is a new drug target in TLE to treat seizure frequency and psychiatric comorbidities.

ARTICLE HIGHLIGHTS

Research background

Hippocampal sclerosis, also known as mesial temporal sclerosis (MTS), is the most common primary epileptic pathology, accounting for 36% of all focal epileptic pathologies. Depression, anxiety, and psychosis (PSY) affect between 30%–70% of temporal lobe epilepsy (TLE) patients. The pathophysiology of TLE, TLE progression, depression, anxiety and PSY is heavily influenced by oxidative pathways and decreased antioxidant defenses.

Research motivation

The enzyme paraoxonase 1 (PON1) protects against lipid peroxidation, and its activity is influenced in part by a single nucleotide polymorphism in PON1. There has been no research that examined the links between PON1 status and mental comorbidities in TLE.

Research objectives

The goal of this research was to look at PON1 status, namely 4-(chloromethyl) phenyl acetate CMPAase and arylesterase activities, as well as PON1 Q192R genotypes, in patients with TLE and MTS who had comorbid PSY, depression and anxiety.

Research methods

This is a case-control study that examined 104 patients with TLE and 40 normal controls. TLE patients were divided according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision criteria into: (1) Mood disorders due to TLE with depressive features (n = 25); (2) Anxiety disorders due to TLE (n = 25); (3) Psychotic disorder due to TLE (n = 25); and (4) "Pure TLE" when there were no psychiatric comorbidities. After an overnight fast, blood samples were obtained at 8:00 a.m., and serum was aliquoted and kept at -80 °C until thawed for total PON1 activity (PON1Q192R polymorphism, and arylesterase and CMPAase activities). Data were analyzed using partial least squares pathway analysis.

Research results

PON1 activities were significantly lower in TLE patients than those in controls. The area under the receiver operating characteristic curve using lower CMPAase activity as discriminatory variable was 0.893 (0.037) for TLE and 0.895 (± 0.037) for MTS. We found that 46.0% of the variance in the severity of depressive, anxiety and psychotic symptoms was explained by the severity of TLE features and PON1 CMPAse activity while 25.3% of the variance in TLE severity was explained by CMPAase activity. PON1 QQ and RR, but not QR, had significant effects on severity of TLE and comorbid psychopathology.

Research conclusions

In individuals with TLE, particularly MTS, the activity of CMPAse and arylesterase enzymes are much lower than in healthy controls. Reduced CMPAase mediates the negative effects of the PON1 genotype on TLE, depression, PSY and anxiety severity.

Research perspectives

Changes in PON1 status play a role in pathophysiology of TLE, MTS and mental comorbidities. PON1 enzymatic activity is a novel therapeutic target in TLE for the treatment of seizure frequency and mental comorbidities.

FOOTNOTES

Author contributions: All the contributing authors have participated in the manuscript; Kanchanatawan B and Maes MHJ designed the study; Kanchanatawan B and Limothai C recruited patients and completed diagnostic interviews and rating scale measurements; Maes MHJ carried out the statistical analyses; all authors contributed to interpretation of the data and writing of the manuscript and approved the final version of the manuscript; Kanchanatawan B and Barbosa DS shared senior authorship.

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Informed consent statement: All participants in this study gave written informed consent form before participating in the study.

Conflict-of-interest statement: The authors have no conflict of interest with any commercial or other association in connection with the submitted article.

Data sharing statement: The dataset generated during and/or analyzed during the current study will be available from the corresponding author upon reasonable request and once the dataset has been fully exploited by the authors.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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ORIGINAL ARTICLE

Observational Study

Importance of communication in medical practice and medical education: An emphasis on empathy and attitudes and their possible influences

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Abstract

BACKGROUND

Healthcare professionals need to be prepared to promote healthy lifestyles and care for patients. By focusing on what students should be able to perform one day as clinicians, we can bridge the gap between mere theoretical knowledge and its practical application. Gender aspects in clinical medicine also have to be considered when speaking of personalized medicine and learning curricula.

AIM

To determine sets of intellectual, personal, social, and emotional abilities that comprise core qualifications in medicine for performing well in anamnesis-taking, in order to identify training needs.

METHODS

An analysis of training clinicians' conceptions with respect to optimal medical history taking was performed. The chosen study design also aimed to assess gender effects. Structured interviews with supervising clinicians were carried out in a descriptive study at the Medical University of Vienna. Results were analyzed by conducting a qualitative computer-assisted content analysis of the interviews.

Inductive category formation was applied. The main questions posed to the supervisors dealt with (1) Observed competencies of students in medical history taking; and (2) The supervisor's own conceptions of "ideal medical history taking".

RESULTS

A total of 33 training clinicians (n = 33), engaged in supervising medical students according to the MedUni Vienna's curriculum standards, agreed to be enrolled in the study and met inclusion criteria. The qualitative content analysis revealed the following themes relevant to taking an anamnesis: (1) Knowledge; (2) Soft skills (relationship-building abilities, trust, and attitude); (3) Methodical skills (structuring, precision, and completeness of information gathering); and (4) Environmental/contextual factors (language barrier, time pressure, interruptions). Overall, health care professionals consider empathy and attitude as critical features concerning the quality of medical history taking. When looking at physicians' theoretical conceptions, more general practitioners and psychiatrists mentioned attitude and empathy in the context of "ideal medical history taking", with a higher percentage of females. With respect to observations of students' history taking, a positive impact from attitude and empathy was mainly described by male health care professionals, whereas no predominance of specialty was found. Representatives of general medicine and internal medicine, when observing medical students, more often emphasized a negative impact on history taking when students lacked attitude or showed non-empathetic behavior; no gender-specific difference was detected for this finding.

CONCLUSION

The analysis reveals that for clinicians engaged in medical student education, only a combination of skills, including adequate knowledge and methodical implementations, is supposed to guarantee acceptable performance. This study's findings support the importance of concepts like relationship building, attitude, and empathy. However, there may be contextual factors in play as well, and transference of theoretical concepts into the clinical setting might prove challenging.

Key Words: Medical history taking; Attitude; Empathy; Training; Physicians' view

Core Tip: The findings in this study underline the importance of paying attention to core competencies in medicine and medical students' socialization and training. Enriching self-assessments with observer-based reflections, as carried out in this investigation, seems to be a valid approach to identify training needs. Tolerance of ambiguity and openness to self-reflection, as demonstrated by the participants in our study, might be relevant in this context. Empathic relationships shape embodied empathy, result in embodied skills, and shift an individual's perception.

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INTRODUCTION

Freud's advice for physicians practicing psychoanalysis was to not concentrate on details and rather surrender one's attention- the optimal mental state of an analyst: "withhold all conscious influences from his/her capacity to attend, and give himself/herself over completely to his/her 'unconscious memory'"[1].

This attitude differs a great deal from most clinical settings nowadays, due to necessary domain-based medical skills. The rapid medical technology developments in the last decade (*e.g.*, digital innovations like remote monitoring/mobile apps, medical devices, and robotic systems/machines controlled by a doctor and mixed reality in education) shape all healthcare fields. Nevertheless, as medicine is practiced for and by human beings, human factors are predominant in all interactions. To infer the workings of a patient's mind is a challenging task, and accepting uncertainty and incompleteness of our understanding is an unavoidable recognition[1,2]. Thus, personal and interpersonal competencies are relevant in meeting the needs of the health system, together with expert

knowledge and skills[3].

Interpersonal skills are especially relevant when taking a patient's history[4]. Guidelines for general medical history taking skills usually include a semi-structured interview manual that suggests a structured approach, in order to ensure professionalism[5,6]. In addition, communication components, such as relationship-building, trust, and respect, are established as markers for quality care[4]. The level of evidence supporting methods of developing these abilities, as well as medical professionalism, is limited[7,8]. Frameworks for communication-oriented curricula have been developed because the importance of building a relationship was found to be one of the core competencies in the physician-patient interaction[9-13].

An essential concept with a great impact on the quality of communication and professionalism is empathy. Empathy has been shown to be trainable but might depend on personality[14-18]. Through empathy, it is possible to improve the patients' compliance, satisfaction, clinical outcome, and decrease (interestingly enough) the possibility of a lawsuit[17-26]. Empathy describes a semi-voluntary, and in some conceptualizations, innate ability to share affective states with others, and requires a certain curiosity. Definitions of empathy overlap with another important concept, that of mentalization. Mentalizing (Theory of Mind) is the ability to interpret one's own and others'' mental states (*i.e.* intentions, beliefs)[27,28]. Key dimensions of empathy have been widely enumerated: emotive, cognitive, behavioral, and moral[29]. Such comprehension requires differentiating between one's own and others' mental states. This ability develops in repeating social interactions that result in the development of the Self, adequate affective regulation, and attachment patterns, and that mediate prosocial behavior[30,31]. Education of medical professionalism is compromised by a decline in empathy[32-34]. Protective factors and predictors of higher empathy include: resilience against stress, social support[35,36], agreeability, and conscientiousness[37].

Competency-based training in health care puts focus on applied knowledge and thus on improving practice[38,39]. More than 50% of patients support a participative approach with shared-decision making based on transparency[40,41]. In such a patient centered approach (PCA), the patient's values, perspective, and circumstances are respected[19,42-44]. Collaboration and coordination of available services at a systems level with resource allocation continuity and improved quality of services are other features of PCA[40]. The effects of PCA have been widely researched: increased adherence to therapy among patients has been demonstrated[45], as well as reduced recovery times[25], decreased mortality [46], improved quality of life[47], and improved general health[48]. To enable the patient to be part of the decision-making process, physicians must provide understandable information[49-51]. Compassion-based interventions and a relationship built on a solid affect-cognitive level are key features[44,49].

Aim of the study

Developing core abilities in medical professionals is relevant to improving individualized medical care. The key questions are, (1) What are the core competencies in medical history taking; and (2) What are the prerequisites to ensuring a "good" anamnesis? From a theoretical point of view, we hypothesized that empathy might be one of the identifiable themes independent of specialty and that gender effects might exist.

MATERIALS AND METHODS

Study design and setting

A qualitative descriptive study was carried out at the Medical University of Vienna (MedUni Vienna) between June 2015 and April 2016. Assumptions and views of instructors regarding desirable core competencies in medical history taking were extracted from interviews with clinicians.

Study population

All attending physicians had been practicing physicians for more than 10 years and had been instructors, mentors, and/or tutors at the MedUni Vienna.

Inclusion and exclusion criteria

The exclusion criteria were (1) Missing written informed consent, and (2) Professional experience of fewer than 10 years. Health care professionals not engaged with medical student supervision and training were also excluded from the survey.

Sampling methods

More than 5000 health care professionals were invited to participate in the study *via* an internal communication listserv for teaching clinicians and university teachers *via* MedUni Vienna-list.

The instructors were chosen by Löffler-Stastka H according to the representation of medical specialties in Vienna/Austria in order to reflect this real-life distribution. Unfortunately, the original aim of equal numbers of male and female physicians interviewed could not be met due to the actual

gender distribution of physicians in Vienna/Austria.

Sample size

Thus, 33 attending physicians who both agreed to participate in the study and matched the required specialty-distribution were included.

Instruments

The interview was standardized and semi-structured, with 16 open-ended questions developed by an interdisciplinary team. The questions allowed free association in order to carry out qualitative content analysis[52]. Questions about the interviewee's own experience in communication and medical history taking and their experience with and memory of their observed medical student's performance during training at their department were investigated. The interviews were all carried out personally at the MedUni Vienna; the setting did not change considerably (interview duration: 45 min). The attending physicians' interviews were all carried out by four different female interviewers (three medical students and one educational scientist). These interviewers were instructed and supervised by Löffler-Stastka H.

The interviews were audiotaped, transcribed, and imported into the program Atlas.ti[53]. Standard background questions (age/specialization of the attendant physician) were asked at the beginning of the interview.

Analysis of the interviews

Results were analyzed by conducting a qualitative computer-based content analysis of the interviews [54] using the program Atlas.ti.

For more information about these methods and content analysis, please refer to the diploma thesis of Zervos, K[52].

Ethical issues

The study design complies with the ethical standards set forth in the Declaration of Helsinki. This study was reviewed and approved by the Ethics Committee of the Medical University of Vienna (EK-Nr. 1381/2015).

As the questions did not include questions about any individual student's performance, but rather relied on the memory and experience of the interviewee, supervised students remained anonymous to the interviewers and the authors of the current study.

RESULTS

As mentioned above, the distribution of specialties in this study is similar to the Viennese/Austrian population of clinicians[52]. Thirteen of the 33 interviewed attending physicians were female, and the remaining 20 were male. In Table 1 we present the distribution of attending physicians in terms of their specialties and sex.

The "ideal patient history"

Associations of the participating attending physicians in this study can be arranged into positive (knowledge, ability to establish a relationship/trust, structure, accuracy and attitude/empathy; Figure 1) and negative ones (language barrier, lacking trust/relationship, or time, interruptions, incomplete) (Table 2).

"Knowledge" was the requirement most often identified in experts speaking about medical history taking; 24 participants mentioned knowledge. Physicians were allowed to mention themes several times. When counting the quotes per specialty/specialty group and correcting for the number of participants per group, general practitioners, pediatricians and non-surgical subspecialties (*e.g.*, psychiatrists, anesthetists, *etc.*) scored highest, while surgical specialties, surgical subspecialties and internists scored lower (Table 3). No gender-specific difference was found. The theme "structure" was mentioned by 20 participants, often in conjunction with "knowledge".

"Establishing a relationship" was another recurrent theme; it was found in 22 of the interviews, with a total of 53 quotes about it. The "ability to create trust" was mentioned in strong association with the attachment-related category. Most quotes on relationship-building were collected from interviews with non-surgical subspecialties, general surgeons, and pediatricians (Table 4). Interestingly, internists and surgeons from surgical subspecialties (ENT, gynecology) mentioned this ability the least often.

When asked about what they considered an ideal anamnesis, 19 attending physicians mentioned the health professionals' "attitude and personality" as important, with a presumably positive impact on the quality of the patients' history-taking process.

Furthermore, in 15 interviews, "empathy" was isolated as being important (21 quotes). Representatives of general medicine and psychiatry often mentioned quotes relating to "attitude" and "empathy" in ideal history taking (Figure 2). In regards to the mention of "attitude", we saw a minor gender-

Table 1 Specialization and sex

Group	Specialty	Sex		Total (*n* =32)
		Female (*n* = 13)	Male (*n* = 19)	
Internal medicine	General internal medicine; Gastroenterology; Cardiology	3	4	7
Surgical specialties	General surgery; Neurosurgery; Visceral surgery; Thoracic surgery; Vascular surgery	2	4	6
Surgical subspecialties	Gynecology; ENT	1	2	3
Non-surgical subspecialties	Anesthesiology; Neurology; Psychiatry	2	4	6
Pediatrics	Pediatrics; Child and adolescent psychiatry	0	3	3
General medicine	General medicine	5	2	7

Demographic data were assessed at the beginning of each interview for each participant *via* questionnaire. For one participant, the information regarding specialty was not available. This participant was included in the qualitative data analysis only when this information was not relevant.

Table 2 Ingredients of the "ideal medical history taking": Identified themes

		Percent	*n* = 33
Positive associations			
Knowledge		72.73	24
Relationship building: +		66.67	22
	Trust: +	39.40	13
Structure		60.61	20
Precision		60.61	20
Attitude	Personality	57.58	19
	Empathy	45.45	15
Negative associations			
Language barrier		33.33	11
Relationship building: -		48.48	16
	Trust: -	15.15	5
Incomplete information gathering		27.27	9
Time pressure		30.30	10
Interruptions		18.18	6

Qualitative data analysis was carried out as explained in the method section (step model of inductive category development). Themes were extracted from the audiotaped interviews. The table shows the number and percentage of interviews a theme was identified within.

specific difference: 61.53% of questioned female attending physicians made quotes relating to "attitude" as an important tool in history taking as opposed to 55% of their male colleagues.

With respect to mentioning "empathy", we were able to identify a robust gender-specific frequency in favor of female attending physicians: 61.54% of questioned female attending physicians mentioned "empathy" in the context of a favorable influence on history taking, whereas only 35% of male colleagues made similar quotes.

The opposite was true for "precision", identified in 20 interviews (25 quotes). "Precision" was mostly mentioned by male physicians (70%). However, "precision" was, above all, found to be especially important to surgeons, with a higher percentage of males in this subgroup (66.67%).

Desirable student skills

When remembering their students' overall performance and reflecting upon desirable characteristics in anamnesis taking, the importance of knowledge (69.70%, *n* = 23) and showing interest for the patient (63.64% *n* = 21), together with attitude (66.67%, *n* = 22), empathy (33.33%, *n* = 11), and structure (51.52%,

Table 3 Quotes on the importance of knowledge

	% quotes	*n* quotes	*n* specialists	*n* (q)/*n* (s)
Internal medicine	13.96	6	7	0.86
General medicine	27.90	12	7	1.71
Non-surgical subspecialties	20.93	9	6	1.50
Paediatrics	11.63	5	3	1.67
Surgical specialities	18.60	8	6	1.34
Surgical sub-specialities	6.98	3	3	1.00
Total	100	43	32	

The percentage and frequency of quotes about the importance of knowledge are shown for each specialist group. Multiple statements on each theme were possible for each participant. It is to be noted that considering the different number of specialists in each group, the number of quotes per group alone is not an accurate measure of the distribution of quotes in the groups. The quotient of the number of quotes in each group per number of specialists was highest for general medicine, pediatricians, and non-surgical subspecialties (1.71, 1.67, and 1.50 respectively).

Table 4 Quotes on the importance of relationship establishment

	% quotes	*n* quotes	*n* specialists	*n* (q)/*n* (s)
Internal medicine	7.55	4	7	0.57
General medicine	18.87	10	7	1.43
Non-surgical subspecialties	32.08	17	6	2.83
Paediatrics	11.32	6	3	2.00
Surgical specialities	26.42	14	6	2.33
Surgical sub-specialities	3.77	2	3	0.67
Total	100	53	32	

The percentage and frequency of quotes about the importance of relationship establishment are shown for each specialist group. Multiple statements on each theme were possible for each participant. It is to be noted that considering the different number of specialists in each group, the number of quotes per group alone is not an accurate measure of the distribution of quotes in the groups. The quotient of the number of quotes in each group per number of specialists was highest for non-surgical subspecialties, surgical specialties, and pediatricians (2.83, 2.33, and 2.00 respectively).

n = 17) were mentioned more often than experience (36.36%, n = 12).

Memories of observed skills

When asked to remember one concrete example of a student taking a medical history, health care professionals described empathic behavior and a positive attitude as much as they did the lack of it. Concerning the students' performance, attitude and showing empathy/empathic behavior were included in one coding.

Positive aspects: Observed students' interest, motivation, and engagement were remembered by 16 attending physicians (48.48%).

Eleven of the attending physicians mentioned their students' attitude in the context of having a positive impact on the quality of their respective history taking (34.38%). Three of the physicians mentioning attitude were female and eight were male (*i.e.* 23.08% of all questioned female physicians, and 35% of all interviewed male physicians). We identify this as a gender-specific difference. These observations were equally distributed among all represented specialties.

Negative aspects: When asked to remember observations perceived as unfavorable, poor precision or incompleteness (54.55%; n = 18), insufficient structure (due to inadequate knowledge 24.14% or failed clinical reasoning 15.15%) were often mentioned.

Attitude was observed to influence the medical history taking negatively by 11 (33.33%) of the attending physicians. No gender-specific effect was found.

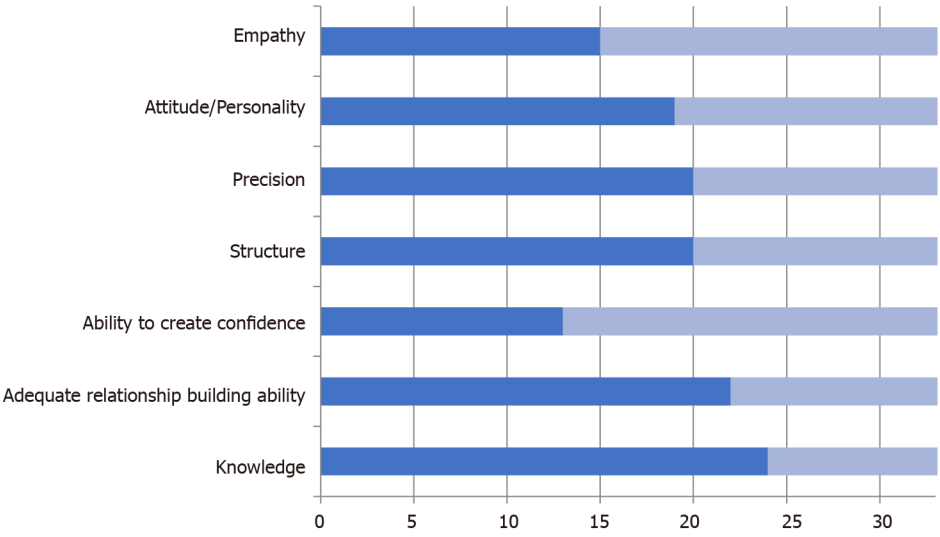

Figure 1 Theoretical conception: Ingredients of the ideal medical history taking. The figure shows theoretical conceptions about medical history taking only. The frequency with which a quote about a specific theme was identified in the qualitative analysis of the interviews is shown. Thus, multiple answers were possible for each participant.

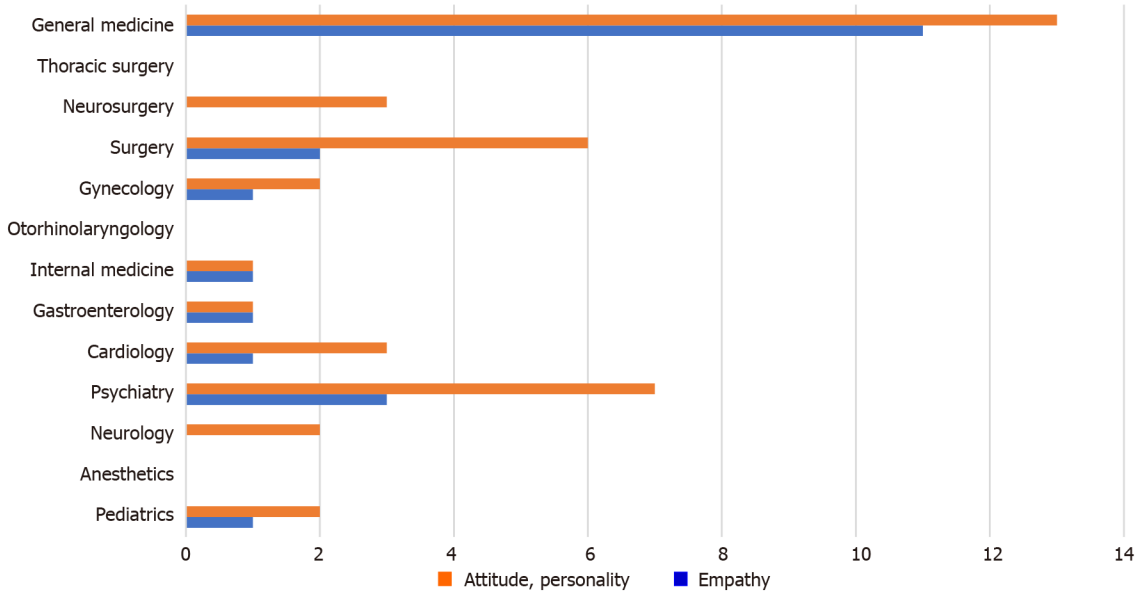

Figure 2 Quotes about empathy and attitude. Theoretical conceptualizations about necessary features required for a student's medical history taking were discussed in this part of the interview. The figure shows the frequency of quotes about empathy and attitude, identified per specialization as taken from the content analysis. Multiple quotes per participant and theme were possible. As mentioned in the results section, "attitude" was mentioned in 22 interviews (8 females, 14 male), while empathy was mentioned in 11 (6 females, 5 males).

DISCUSSION

Dimensions identified as being relevant to anamnesis-taking included "knowledge" (mentioned by 24 participants), soft skills ("empathy", "relationship building ability", "trust", "attitude"), methodical approach ("structuring", "timing", "precision", "completeness of information-gathering"), as well as environmental ones ("time pressure", "interruptions", "language barrier").

As the interview asked about memories of ideal anamnesis-taking, and two categories were already given through the structure of the questions (*i.e.* positive *vs* negative associations), we suggest that future research should explore the identified dimensions along a continuum ranging from "ideal" to "abysmal".

One of the observations made in the present investigation was that negative associations were at first in timing, or more readily made by most participants when freely associating about taking an anamnesis. Thus, experience might lead to insight into the pitfalls of human conversations. Another explanation for this could be implicit bias found in the effects of supervision and quality control.

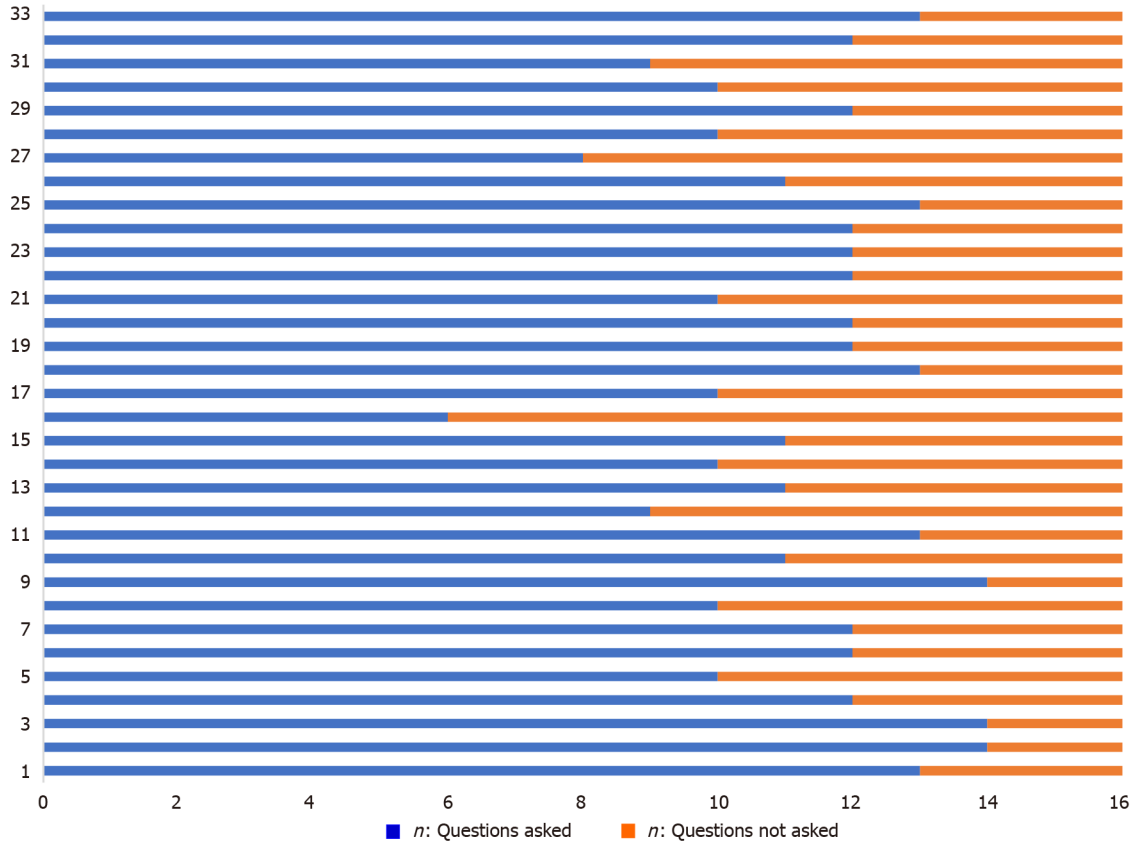

Figure 3 Questions asked per interview. This figure shows the number of questions asked per interview, as discussed in the limitation section. Blue: Number of questions asked in interview 1-33. Number of available questions: 16. Number of interviews: 33.

In assessing memories and observations, due to the known link between affective loading, accessibility, and storage of memory contents, the categories derived from this analysis are likely to be more accessible to clinicians in their actual clinical environment. An interview indirectly assesses the expert's ability to mentalize one's own and others' mental states. Overall, experts showed a reflected and integrated view, mentioning both positive and negative memories.

In the present qualitative analysis of interviews on memories regarding anamnesis, relationship-building was mentioned to be an important skill, as was empathy.

Although the frequency of quotes that emphasize the importance of knowledge, attitude, and empathy differed among the included specialty groups (*i.e.* *n* quotes about a specific theme/*n* participants of the group), this finding must be interpreted with caution. What does it really mean if a theme is mentioned more than once by a given participant in a semi-structured interview? One ability often mentioned in conjunction with "knowledge" by the participants in this actual study was the ability to structure a discourse. To discuss a matter in a structured way within a limited timeframe, it may be sufficient to mention the importance of a specific theme once and then proceed to the next. However, mentioning the importance of something multiple times could also be a way of addressing the importance of the subject. Thus, it might be the case that observed differences between specialties do exist (Table 3 and Table 4). The importance of knowledge was mentioned most often by general practitioners, pediatricians, and non-surgical specialties. The ability to establish a relationship was mentioned most often by non-surgical subspecialties, general surgeons, and pediatricians.

Integrating knowledge from different disciplines will become more challenging as scientific findings expand.

Interestingly, when asked to remember a concrete example of a student performing a good anamnesis, interest, motivation, and engagement were the main themes. Differing themes arose only when freely associating about theoretical history taking. Methodical issues prevailed when remembering a negative example (*i.e.* lacking precision, completeness, structure). Environmental aspects and explicitly pronounced relationship-building factors (besides engagement) were not mentioned in this context, either meaning that actual medical history taking does not usually lack these aspects, or that suppression impeded the memories of said aspects in contrast to when the task consisted predominantly of recall and theoretical conceptualization.

Interventions aiming to enhance students' communication skills often lack both effectiveness and comparative effectiveness analyses[55]; further research on this topic is needed.

Enhancing learning, especially the accessibility of learned memory contents when related to skills and applied knowledge (*i.e.* not to recall theoretical knowledge), has been extensively investigated. Accessibility of attitudes from memory seems to be a function of the manner of attitude formation. With regards to attitude, one can distinguish the process of attitude formation, attitude accessibility, and attitude-behavior consistency, such that one may begin to investigate how and which specific attitudes affect later behavior[56]. A meta-analysis assessing factors relevant to attitude-behavior relation found that direct behavioral experiences produce stronger object-evaluation associations and more accessible attitudes. Behavior is determined by attitudes that are accessible and stable over time, and that affirm effects of direct experience, attitude, and confidence based on one-sided information[57].

The role of affectivity in attitude formation and its role in knowledge and skill development is obvious. Emotion seems to guide attention in learning and determines the availability of memory contents[58]. The so-called "seeking system" initiates memory and learning, as well as generating positive emotions, hope, expectancy, and enthusiasm[59].

The relevance of embodied empathy for learning has also been suggested[60]. Observation and imitation in empathic social relationships lead to the acquisition of embodied skills. A synchronization of intentions and movements seems to occur in empathic relationships with skilled practitioners, shaping the student's perception[58]. Describing embodied knowledge is difficult, as it is not mediated through words alone, but rather learned through lived and shared experiences that established meaning.

Empathy has been classified as a basic relationship skill involving resonance and communication, and is especially relevant when aiming at patient-centered care[20,48,61]. An intrinsic disposition for empathy has been claimed and has been shown to be trainable[14-16,62-64].

Empathy levels in practitioners and therapists are quite variable. Health care professionals with high levels of empathy seem to be more vulnerable to stress-related mental conditions (*e.g.*, burn out/exhaustion and compassion fatigue)[65-67] with a protective role of compassion satisfaction, and sensory processing sensitivity as a risk factor[68].

Studies assessing empathy in students often rely on self-assessment. Self-perceived empathy declines during medical school[18,24,36,69-72] and seems to depend on specialty choice[33,34,72], with higher perceived empathy in patient-oriented specialties. The decrease in empathy can be attributed to increased negative emotions such as stress and anxiety, which are highly dependent on context (*e.g.*, workload, exposure to suffering and death, work hours, sleep deprivation) and impede empathy[18,35,70,73,74]. With the increase of negative affects during medical formation, remembering negative contents is more likely to influence accessible attitude.

How physicians spend their time during their workday has been analyzed for different specialties with very different profiles of work tasks and emphasis on communication skills, work-related stress, and job satisfaction[75-77].

Analysis of empathy profiles of psychotherapists shows a four-way dependence on competence in perspective taking, their tendency to experience personal distress, their fantasy (*i.e.* their ability to identify with fictional characters), and their empathic concern (*i.e.* the ability to feel compassion towards a person in distress)[78]. The profiles distinguish between types that may be characterized as "average", "insecure-self-absorbed", therapists showing "empathic immersion", and those who are "rational empathic". With experience, the "rational empathy" becomes more prevalent.

A given clinician's empathic range and flexibility seem to be modifiable independent of context; however, circumstances can influence them. Emergency settings, for example, have been shown to produce a high level of burnout frequency[79,80], which reduces predisposition for empathic behavior.

Especially interesting is the observation of students' positive attitude and empathic behavior and their positive impact on the quality of history taking as perceived across all specialties, instead of merely mentioning attitude and empathy as important tools on a theoretical level. Physicians mentioning attitude and empathy in the theoretical context of ideal history taking represent predominantly general medicine and psychiatry, and are mainly female. The observation of the positive impact of attitude and empathy on actual student history taking is described mainly by male health care professionals, without showing any predominance of specialty. Again, accessibility of memory contents depends on the content's affective links and its links to real experience[59,81,82]. Cognitive processes are influenced by emotions[83]: "Substantial evidence has established that emotional events are remembered more clearly, accurately, and for longer periods than are neutral events"[59]. Thus, contents normally less accessible are easier to remember when an actual experience is associated. The fact that more women mention attitude and empathy even when theorizing, whereas men only do so when remembering an actual observation, could indicate a difference in perceived value and importance of the theme, perhaps due to different socialization, among other things.

Observations of healthcare professionals are supported by extensive data describing the practitioners' positive impact on patient health, shortening the diagnostic process[23-26].

When dealing with embodied knowledge, there may be a gap between recalled themes and the actual performance of practitioners, particularly as evidence shows that empathic therapists show this (socially desirable) behavior rather automatically, independent from their conscious intention or personality. However, it is to be noted that even if attitude (including empathy) is described by fully one-third of the questioned attending physicians as having been observed among students (with positive impact on

their history taking), a similar proportion of them recognize deficits in this area. Interventions promoting empathy and improving attitudes, including underlying processes of self-reflection and mentalization, could enhance the acquisition of this skill[84-88].

Attitude is particularly influenced by those more senior than us[89]. Therefore, change cannot only be implemented at the undergraduate-level but must also impact the postgraduate system.

Whether perspective representation or simply a sensitivity to the perspective of others is necessary for successful communication has been questioned; however, the importance of perspective-taking for systematic success is well known[90]. Forming representations of the mental and affective states of others determines attachment and mind-reading abilities[82]. Memory and attention processes have an important role in enabling communication[91,92]. Becoming sensitive to one another's perspective can happen due to contextual effects, like when information is made available from priming and automatic recall, together with attention cueing[90]. When trying to mentalize, retrieval of memory traces that include or overlap with all kinds of information that is shared occurs[91]. Cues about what a person might already know about what she/he can see or hear (*e.g.*, conversational common ground, knowledge, local routines, *etc.*) might be accessible. How a person perceives reality, however, might be a less straightforward guess to make. A modulating role for such memories in mentalizing abilities has been suggested. When mentalizing, whole events (real or imagined), as well as episodic memories linked to the target person, are remembered and become (mentally) ingrained. Thus, the content and quality of imagination might play a central role in more or less adequate attributions of mental states [82].

However, using one's own theories of mind to infer others' intentions requires motivation and effort [90,93]. Experiments by Lin *et al*[93] showed that attention-demanding secondary tasks reduce people's ability to mentalize. Lower working memory capacity predicted less effective use of the theory of mind.

Thus, the everyday routine in clinical settings, what with the necessity of shiftwork, multi-tasking, as well as frequent interruptions, might negatively influence performance[94], learning, and accessibility of memory (including attitudes). Moreover, other skills not considered essential by financing bodies of healthcare providers may also fall by the wayside. Contemporary health finance policies might increase pressure to focus on higher-paying tasks, potentially incentivizing unfavorable behaviors. However, evidence for empathy and attitude in learning and for outcomes in healthcare already exists.

Future research into social cognition in health care should focus on the conditions that increase the likelihood that other perspectives are represented during conversations, counterbalance an egocentric perspective, and enhance behavior.

Experience-based training programs could address the gap between theoretical conceptions of the importance of empathy for self- and patient care, as well as improve mentalizing and emotional regulation, which is necessary for letting empathy guide social behavior. These interventions implement specific feedback mechanisms that are easy to establish in clinical contexts, such as peer-supervision, once the basic concept is taught[18]. Remembering, collecting, and using the information to predict what others think, feel, or might do depends on an individual's cognitive abilities, context, and disposition. Research into the mechanism of change revealed that change most likely happens when intense and enduring negative affect accumulates; thus, motivation to modify views first arises, followed by a systemic reorganization.

Limitation

As the interviews were conducted in a semi-structured way, and open-ended questions were predominant, the number of questions varied between the interviews due to time constraints. Also, after 17 interviews, one additional question was added to the initial catalog of 15 questions. No question was asked in every interview. For the percentage of questions asked, see Figure 3. The number of questions asked ranged from 6 to 14 (mean = 11.30, SD = 1.79), with an average of 4.70 questions not asked. However, questions overlapped in terms of their subject, as the questionnaire aimed to investigate the topic in depth from different viewpoints.

Inductive category development as a way of qualitative content analysis has been questioned, because derived definitions do not appear to be functionally justified, and practical relevance has been doubted[95,96]. Alternative frameworks for category formation have been recommended, suggesting that coding decisions should be made in accordance with the individual study at hand. However, regarding the current investigation (explorative design), inductive category formation was adequate in minimizing the possible influence of preexisting assumptions.

One should also account for possible bias arising from all interviewers being female.

Finally, our sample size was somewhat small (n = 33), as the approach was a hypothesis-generating one. Nevertheless, our sample might be quite representative, as the number of participants per sub-specialty was selected according to the distribution of medical sub-specialties in Austria. However, depending on circumstances (*e.g.*, clinical department differences) and socialization, conceptions of the importance of empathy and communication might vary.

CONCLUSION

Our findings show that dimensions identified as being relevant to anamnesis-taking included expert knowledge-related skills, as well as soft skills, methodical, and environmental ones.

The analysis of interviews adds to the ongoing theoretical discussion of competency-based education in medicine.

ARTICLE HIGHLIGHTS

Research background

If a change should be facilitated - either in individual patients for a better health status, or society at large for overcoming difficult circumstances - understanding of minds, reflection and empathy is needed. These change processes with the mentioned ingredients should be assessed further for the long run.

Research motivation

Knowing one's own mind to transform oneself is essential. Empathy is needed in the context of patient-centered care.

Research objectives

To assess how medical students perform in their ability to provide an empathic medical history taking.

Research methods

Interviews with experienced physicians/mentors.

Research results

Differences between medical specialties are shown, but in general all physicians claim for a strengthening of empathy.

Research conclusions

Concise structure and an empathic attitude are necessary for the understanding of minds in order to get the needed information for adequate clinical reasoning and clinical decision making.

Research perspectives

Understanding of minds and mentality can be facilitated, trained and strengthened.

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FOOTNOTES

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Medical University of Vienna (EK-Nr. 1381/2015).

Informed consent statement: Participants were required to give informed consent to the study. No patients were enrolled in the study. Furthermore, the analysis used anonymous data that were obtained after each participant had agreed to the assessment by written consent.

Conflict-of-interest statement: We have no conflict of interest and no financial relationships to disclose.

Data sharing statement: Data is available on request.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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ORIGINAL ARTICLE

Observational Study

Cross-sectional study of traumatic stress disorder in frontline nurses 6 mo after the outbreak of the COVID-19 in Wuhan

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Abstract

BACKGROUND

Frontline nurses in Wuhan directly fighting severe acute respiratory syndrome coronavirus-2 diseases are at a high risk of infection and are extremely susceptible to psychological stress, especially due to the global coronavirus disease 2019 (COVID-19) pandemic. The psychological after-effects of this public health emergency on frontline nurses will last for years.

AIM

To assess factors influencing post-traumatic stress disorder (PTSD) among

frontline nurses in Wuhan 6 mo after the COVID-19 pandemic began.

METHODS

A total of 757 frontline nurses from five hospitals in Wuhan, China, participated in an online survey from July 27 to August 13, 2020. This cross-sectional online study used a demographic information questionnaire, the PTSD Checklist for the Diagnostic and Statistical Manual of Mental Disorders, the Connor-Davidson Resilience Scale, and the Patient Health Questionnaire-4. The chi-square test and logistic regression were used to analyze the association of demographics, COVID-19-related variables, and PTSD. Logistic regression was also conducted to investigate which variables were associated with PTSD outcomes.

RESULTS

A total of 13.5%, 24.3%, and 21.4% of the frontline nurses showed symptoms of PTSD, depression, and anxiety, respectively. The multivariate logistic regression analysis showed that the following factors were strongly associated with PTSD: Having a relative, friend, or colleague who died of COVID-19; experiencing stigma; or having psychological assistance needs, depressive symptoms or anxiety. Showing resilience and receiving praise after the COVID-19 outbreak were protective factors.

CONCLUSION

Frontline nurses still experienced PTSD (13.5%) six months after the COVID-19 outbreak began. Peer support, social support, official recognition, reward mechanisms, exercise, better sleep, and timely provision of information (such as vaccine research progress) by the government *via* social media, and adequate protective supplies could mitigate the level of PTSD among nurses responding to COVID-19. Stigmatization, depression, and anxiety might be associated with a greater risk of PTSD among nurses.

Key Words: Post-traumatic stress disorder; Frontline nurses; COVID-19; Mental health; Pandemic

Core Tip: The mental health of frontline nurses in Wuhan has been significantly affected by the coronavirus disease (COVID-19). This study aims to evaluate the influencing factors of post-traumatic stress disorder (PTSD) among frontline nurses in Wuhan six months after the COVID-19 pandemic began and implement a mental health plan. The prevalence rates of PTSD, depression and anxiety among frontline nurses were 13.5%, 24.3%, and 21.4%, respectively. The risk factors for nurses to develop PTSD are the death of a relative, friend, or colleague from COVID-19, stigma, depression, and anxiety. Resilience and reward mechanisms are protective factors to prevent PTSD.

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INTRODUCTION

A novel coronavirus disease (COVID-19) was first reported in December 2019 in Wuhan, China. The World Health Organization (WHO) Director-General announced that the COVID-19 outbreak was a public health emergency of international concern on 30 January 2020[1]. As of 14 August 2020, 20439814 confirmed cases and 744385 confirmed deaths had been reported by the WHO, and the disease eventually spread to more than 216 countries, areas, or territories[2]. Increasing demand for the care of COVID-19 patients and high morbidity and mortality continue to challenge the global health system.

Wuhan was considered a high-risk area for COVID-19. According to the daily report on COVID-19 statistics released by the National Health Commission of China, as of 24:00 on February 24, 2020, Wuhan had a total of 47071 confirmed cases and a total of 2043 deaths[3]. To efficiently stop the spread of COVID-19, medical staff fought the disease. However, there were a total of 3387 cases of COVID-19 infection among medical staff in mainland China. More than 90% of medical staff infections occurred in Hubei Province, mainly in Wuhan[4]. While rescuing lives, frontline medical staff witnessed the clinical

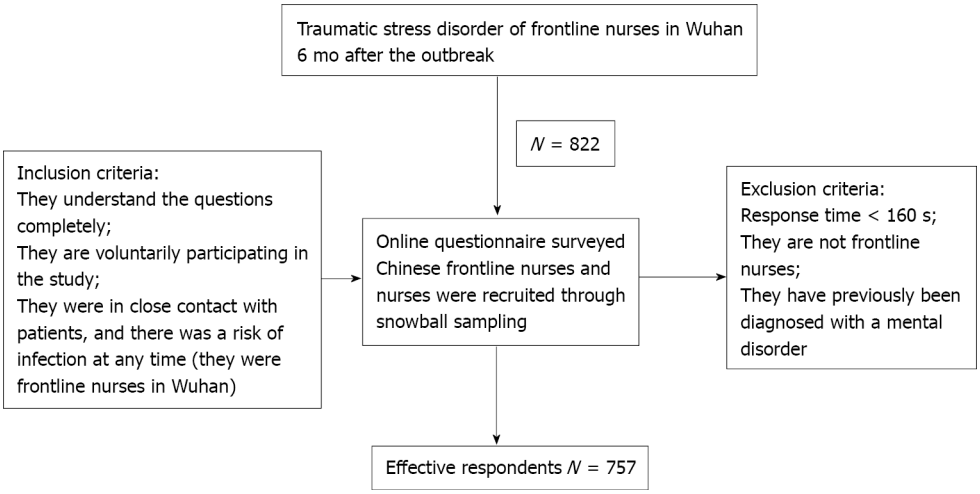

Figure 1 The inclusion and exclusion criteria of the online questionnaire.

reactions and deaths of numerous patients with severe cases of COVID-19.

An overwhelming workload, shortage of medical supplies, insufficient rest, high risk of infection, stigma, and fear of infection of family members or friends increase the risk of post-traumatic stress disorder (PTSD) among frontline nurses. PTSD[5,6] is a mental disorder characterized by intrusive thoughts, avoidance, cognitive and mood disturbances, and arousal symptoms that may be experienced after traumatic life events, such as threats of severe injury, death, war, sexual offenses, and terrible catastrophes.

Due to the COVID-19 pandemic, frontline nurses were considered susceptible to PTSD. Studies on the COVID-19 outbreak in China[7], Spain[8], Italy[9], Jordan[10], and the United States[11] have discussed how the battle against COVID-19 caused anxiety, depression, and PTSD symptoms among frontline nurses.

Studies on the impact of severe acute respiratory syndrome (SARS)[12], Middle East respiratory syndrome[13], and influenza A[14] found that one to two years after a disease outbreak, frontline nurses endured symptoms of anxiety, depression, and PTSD. However, there is little information available on the long-term impact of PTSD on frontline nurses who treated SARS patients during the COVID-19 outbreak.

This study aims to investigate the influencing factors of PTSD six months after the COVID-19 outbreak among frontline nurses who were exposed to COVID-19. It is imperative to provide mental health support for frontline nurses, and facilitate their psychological recovery from PTSD related to the COVID-19 pandemic.

MATERIALS AND METHODS

Ethical considerations

The study was reviewed and approved by the Ethics Committee of the Union Hospital affiliated to Tongji Medical College, Huazhong University of Science and Technology (Approval number 2020-0189). This study was conducted according to the principles of the Declaration of Helsinki.

Design

The research team assessed the traumatic stress disorder of frontline nurses who worked in Wuhan during the outbreak through a cross-sectional survey using social media (such as WeChat and QQ) six months after the outbreak, from July 27 to August 13, 2020. Before starting the investigation, all participants had to give their informed consent, and the purpose of the study was explained. The participants could exit the survey at any time.

Participants

The study recruited 822 first-line medical staff from six tertiary general hospitals. After those who met the exclusion criteria were removed, 92.1% (757 out of 822) of the staff were included in the statistical analyses. A total of 274 participants (36.2%) were from Zhongnan Hospital of Wuhan University, 149 (19.7%) were from Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 39 (5.2%) were from Wuhan Central Hospital, 150 (19.8%) were from Wuhan Jin Yin Tan Hospital (Wuhan Medical Treatment Center), 104 (13.7%) were from Wuhan Third Hospital, and 41 (5.4%) were from Renmin Hospital of Wuhan University. The participants worked in Wuhan during the

height of the pandemic from January to February 2020. The inclusion and exclusion criteria are presented in Figure 1. The demographics of the study participants are presented in Table 1.

Demographic questionnaire

This questionnaire collected information on the participants' general characteristics, including age, sex, and job-related information, and COVID-related information.

Post-traumatic stress disorder

The PTSD Checklist for the Diagnostic and Statistical Manual of Mental Disorders[15] was used to measure the post-traumatic stress disorder of frontline nurses in Wuhan six months after the outbreak. This scale has been widely and commonly used in previous studies[16]. The scale consists of 20 items scored on a Likert-type scale ranging from 0 = "not at all" to 4 = "extremely". The total scores range from 0 to 80, with higher scores indicating more severe symptoms (cutoff score ≥ 33). These statements are classified into four distinct domains: Re-experiencing (5 items, score 0 to 20); avoidance (2 items, score 0 to 8); negative alteration in cognition and mood (6 items, score 0 to 24) and arousal (7 items, 0 to 28).

Resilience

The psychometric properties of the Connor-Davidson Resilience Scale (CD-RISC 10) are well documented. The CD-RISC 10[17], in its Chinese version[18], was used to assess psychological resilience, especially the ability to cope with adversity. The 10 self-report items are scored on a Likert-type scale from 0 = "not true at all" to 4 = "true nearly all the time". The total score ranges from 0 to 40, and higher scores indicate better resilience (cutoff score ≥ 30).

Anxiety and depression

The Patient Health Questionnaire-4 (PHQ-4)[19], including the PHQ-2 and Generalized Anxiety Disorder-2 (GAD-2), were used to assess both depression and anxiety disorders, respectively. The Chinese versions[20] have been validated and widely used. The PHQ-2 and GAD-2 use two core criteria to assess the levels of major depressive disorder and anxiety, respectively. Each item is scored on a 4-point Likert-type scale from 0 = "not at all" to 3 = "nearly every day". The total score ranges from 0 to 6, and higher scores indicate greater levels of depression and anxiety (cutoff score ≥ 3).

Statistical analysis

Data were analyzed using IBM SPSS version 21.0 (Chicago, IL, United States). Frequencies and percentages were calculated for the categorical data. The chi-square test was used to verify differences in the categorical variables between groups. Binary logistic regression analyses were used to explore the factors impacting post-traumatic stress, such as demographics, anxiety, depression, and resilience. The test level was $P = 0.05$; that is, a P-value of less than 0.05 was considered statistically significant.

RESULTS

Demographic characteristics

A total of 757 participants were included in this investigation. The mean age was 32.60 years (SD = 7.64). The mean working time was 10.16 years (SD = 8.28). The study sample consisted of 688 women (86.4%) and 69 men (13.6%). The demographics of the participants are presented in Table 1.

Levels of PTSD, anxiety, and depression

The mean PTSD, resilience, depression, and anxiety scores were 17.74 ± 11.87, 25.29 ± 6.95, 1.75 ± 1.43, and 1.70 ± 1.43, respectively. A total of 13.5% of the sample met the symptom criteria for PTSD. The prevalence of depression was 24.3%, and 21.4% of the participants had anxiety symptoms. The proportion of frontline nurses in Wuhan enrolled in this survey who scored above the established cutoff for resilience was 28.7%.

Factors associated with PTSD

Six items found significant differences between nurses with post-traumatic stress disorder, including having a relative, friend, or colleague who died of COVID-19, experiencing stigma, receiving praise, showing resilience, having depression symptoms, and having anxiety symptoms. No differences were observed between groups in sex, age, education, marital status, working years, or previous anti-epidemic experience (all $P < 0.05$) (Table 1).

Six items were significantly associated with PTSD among nurses, including having a relative, friend, or colleague who died of COVID-19, experiencing stigma, receiving praise, showing resilience, having depression symptoms, and having anxiety symptoms ($P < 0.05$). No differences were observed between groups in gender, age, marital status, education, working years, or previous anti-epidemic experience (P

> 0.05) (Table 1).

Regression analyses of PTSD

As shown in Table 2, several variables were found to be associated with a higher risk of PTSD, such as having a relative, friend, or colleague who died of COVID-19 [odds ratio (OR): 2.226, $P < 0.01$], experiencing stigma (OR: 3.038, $P < 0.01$), not receiving praise (OR: 0.442, $P < 0.01$), lacking resilience (OR: 0.190, $P < 0.01$), having depressive symptoms (OR: 3.625, $P < 0.01$), and having anxiety symptoms (OR: 3.849, $P < 0.01$).

DISCUSSION

Key findings

This study found that six months after the COVID-19 outbreak began in Wuhan, China, the prevalence of PTSD, depression, and anxiety among frontline nurses were 13.5%, 24.3%, and 21.4%, respectively. The following factors were associated with a greater likelihood of having PTSD: Having a relative, friend, or colleague who died of COVID-19; experiencing stigma; having depression symptoms; and having anxiety symptoms. Showing resilience and receiving praise after the COVID-19 outbreak were helpful in prevent PTSD.

The prevalence of PTSD

The incidence of PTSD among frontline nurses was lower at the time of the survey than at the initial stage of the COVID-19 outbreak (16.83%-71.5%)[21-25]. A possible reason might be that the nurses may have been under less psychological stress six months after the outbreak than they were during the initial period, which was also found in Cai *et al*[7]'s research.

Factors influencing PTSD

It is important to note that the participants who had a relative, friend, or colleague who died of COVID-19 were more likely to report high levels of PTSD. In contrast, no differences in the history of personal infection were observed between those who did not have PTSD. This study highlights that exposure to high-risk work environments (such as directly caring for infected patients) was not the main determinant of adverse psychological outcomes. This result was also found 13 to 26 mo after the SARS outbreak[26] among medical staff at Toronto hospitals that treated SARS patients. A previous study showed[27] that during the SARS outbreak, the death of colleagues created a stressful atmosphere in the hospital. It is also possible that the death of a relative, friend, or colleague places a heavy psychological burden on nurses[28]. These trends may be explained by peer support promoting adaptive coping.

Stigmatization was found to be predictive of a high level of PTSD. Frontline nurses at hospitals are vulnerable to stigmatization, loneliness, and exclusion due to working in areas with the highest incidence of COVID-19. COVID-19-related fear may have led the nurses to be isolated from other individuals, which may also have had different effects on their social support. Experience of stigma can have long-term adverse effects on nurses' mental health. Such effects were examined by Liu *et al*[29], Zandifar *et al*[30], and Röhr *et al*[31].

The logistic regression analysis showed that the nurses who had received praise from government agencies were less likely to report high levels of PTSD. Frontline nurses who are officially recognized, which is common in Chinese society, have a strong sense of being protected and supported by organizations. Such recognition may play an important role in experiencing satisfaction through continued working in these settings. Previous studies[32,33] reported that people with severe PTSD symptoms performed better than those without PTSD symptoms in reward trials. In response to the ongoing psychological effects among nurses after the COVID-19 outbreak, official recognition and reward mechanisms appear to be needed.

Psychological resilience was a significant protective factor for PTSD among the frontline nurses six months after the COVID-19 outbreak. Lutha and Cicchetti[34] refers to an individual's ability to positively adjust after trauma and respond to adverse experiences. Psychological resilience research[35] during the COVID-19 epidemic showed that more frequent exposure to the outdoors and sunlight, more exercise, greater perceived social support, better sleep, and more frequent prayer may contribute to greater psychological resilience.

Personal depression and anxiety contributed to adverse outcomes

One study[36] conducted in China during the COVID-19 outbreak showed that increased distress, decreased sleep quality and increased self-efficacy could cause anxiety among medical staff, which could affect their mental health. Making difficult ethical decisions regarding the distribution of medical supplies, the lack of personal equipment, and progress in COVID-19 vaccine research made medical staff particularly vulnerable to mental health problems. Therefore, reasonable rest time and shifts, a safe work environment, the satisfaction of basic needs, and the availability of information on vaccine

Table 1 Socio-demographic characteristics and its subscales among study participants (*n* = 757)

Variables	Characteristics	Total *n* (%)	PTSD *n* (%)		χ^2	*P* value
			No	Yes		
Sex	Male	69 (9.1)	64 (8.5)	5 (0.7)	2.526	0.112
	Female	688 (90.9)	591 (78.1)	97 (12.8)		
Age	< 25	132 (17.4)	116 (15.3)	16 (2.1)	3.859	0.452
	26-30	232 (30.6)	205 (27.1)	27 (3.6)		
	31-35	183 (24.2)	156 (20.6)	27 (3.6)		
	36-40	88 (11.6)	71 (9.4)	17 (2.2)		
	> 40	122 (16.1)	107 (14.1)	15 (2.0)		
Marital status	Married	492 (65.0)	422 (55.7)	70 (9.2)	0.684	0.408
	Single/Divorced/Other	265 (35.0)	233 (30.8)	32 (42.2)		
Education	Secondary education	98 (12.9)	82 (10.8)	16 (2.1)	0.842	0.656
	Bachelor's degree	585 (77.3)	508 (67.1)	77 (10.2)		
	Postgraduate/Doctoral degree	74 (9.8)	65 (8.6)	9 (1.2)		
Working years	0-2	114 (15.1)	101 (13.3)	13 (1.7)	1.289	0.863
	3-5	148 (19.6)	128 (16.9)	20 (2.6)		
	6-10	219 (28.9)	191 (25.2)	28 (3.7)		
	11-20	178 (23.5)	150 (19.8)	28 (3.7)		
	≥ 20	98 (12.9)	85 (11.2)	13 (1.7)		
Previous anti-epidemic experience	No	694 (97.1)	600 (79.3)	94 (12.4)	0.035	0.851
	Yes	63 (8.3)	55 (7.3)	8 (1.1)		
Nurse infected by COVID-19	No	732	634	98	0.141	0.707
	Yes	25	21	4		
A relative, friend or colleague died of COVID-19	No	611 (80.7)	542 (71.6)	69 (9.1)	12.929	0.000[b]
	Yes	146 (19.3)	113 (14.9)	33 (4.4)		
Experienced stigma	No	596 (78.7)	536 (70.8)	60 (7.9)	27.902	0.000[b]
	Yes	161 (21.3)	119 (15.7)	42 (5.5)		
Received praise	No	504 (66.6)	425 (56.1)	79 (10.4)	6.262	0.012[a]
	Yes	253 (33.4)	230 (30.4)	23 (3.0)		
Resilience (CD-RISC-10)	< 30	540 (71.3)	442 (58.4)	98 (12.9)	35.297	0.000[b]
	≥ 30	217 (28.7)	213 (28.1)	4 (0.5)		
Depression (PHQ-2)	< 3	573 (75.7)	541 (71.5)	32 (4.2)	125.861	0.000[b]
	≥ 3	184 (24.3)	114 (15.1)	70 (9.2)		
Anxiety (GAD-2)	< 3	595 (78.6)	558 (73.7)	37 (4.9)	125.549	0.000[b]
	≥ 3	162 (21.4)	97 (12.8)	65 (8.6)		

[a]*P* < 0.05.

[b]*P* < 0.01. PTSD: Posttraumatic stress disorder; COVID-19: Coronavirus disease 2019; CD-RISC-10: Connor-Davidson Resilience Scale; PHQ-2: Patient Health Questionnaire-2; GAD-2: Generalized Anxiety Disorder-2.

research progress may help reduce stress among nurses. Previous studies[37-39] also found that anxiety could lead to PTSD, exacerbated by the effects of a higher frequency of social media exposure. Notably, having up-to-date authoritative and true information about COVID-19 on social media may reduce the rate of PTSD.

Table 2 Logistic regression analyses for posttraumatic stress disorder (*N* = 757)

	B	SE	Wald	Sig	Exp (B)	95% Confidence interval	
						Lower bound	Upper bound
A relative, friend or colleague died of COVID-19 (No)	0.800	0.283	7.969	0.005	2.226	1.277	3.879
Experienced stigma (No)	1.111	0.270	16.974	0.000	3.038	1.791	5.154
Received praised (No)	-0.816	0.288	8.042	0.005	0.442	0.252	0.777
Resilience < 30	-1.662	0.540	9.475	0.002	0.190	0.066	0.547
Depression < 3	1.288	0.322	15.962	0.000	3.625	1.927	6.818
Anxiety < 3	1.348	0.321	17.678	0.000	3.849	2.053	7.214
Constant	-5.010	0.999	25.134	0.000	0.007		

COVID-19: Coronavirus disease 2019.

Limitations

Several limitations of this survey must be mentioned. First, since the COVID-19 pandemic has had a long-term negative psychological impact on nurses, longitudinal research should be conducted in the future. Second, the research may have been biased because the participants were not recruited randomly. Third, due to the endpoint of the study, the challenges and opportunities of vaccination remain unknown.

CONCLUSION

Six months after the COVID-19 outbreak began, frontline nurses were still experiencing pandemic-related distress, which could lead to long-term PTSD. Our findings indicated that peer support, social support, exercise, better sleep, official recognition, and reward mechanisms should be prioritized to alleviate the negative psychological responses of nurses dealing with the pandemic. Our study further shows that the timely provision of information (such as vaccine research progress) by the government on social media and adequate protective supplies might mitigate the level of PTSD among nurses responding to COVID-19. Stigmatization, depression, and anxiety might be associated with a greater risk of PTSD among nurses.

ARTICLE HIGHLIGHTS

Research background

The worldwide spread of coronavirus disease 2019 (COVID-19) is an international public health emergency posing challenges for health care systems. The mental health of nurses was significantly affected by this crisis, and nurses played a crucial role in successfully fighting the COVID-19 pandemic.

Research motivation

Few studies have focused on the risk of post-traumatic stress disorder (PTSD) among frontline nurses six months after the COVID-19 outbreak. Our research group aimed to investigate the prevalence of PTSD among nurses and the implementation of mental health programs.

Research objectives

This study aimed to evaluate the factors associated with PTSD, determine what psychosocial support nurses need, and identify ways to reduce the level of PTSD among nurses responding to the COVID-19 pandemic in Wuhan, China.

Research methods

A total of 757 frontline nurses from six tertiary general hospitals in Wuhan, China, were recruited. The structured questionnaire included a demographic information section, the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders, the Connor-Davidson Resilience Scale, the Patient Health Questionnaire-4, and COVID-19-related items. The cross-sectional survey was conducted from July 27 to August 13, 2020, *via* social media.

Research results

This study found that six months after the COVID-19 outbreak in Wuhan, China, the prevalence of PTSD, depression, and anxiety among frontline nurses was 13.5%, 24.3%, and 21.4%, respectively. The following factors were associated with a greater likelihood of having PTSD: Having a relative, friend, or colleague who died of COVID-19; experiencing stigma; having depressive symptoms, and having anxiety symptoms. Showing resilience and receiving praise after the COVID-19 outbreak were helpful in preventing PTSD.

Research conclusions

Frontline nurses still experienced long-term pandemic-related distress six months after the COVID-19 outbreak. Peer support, social support, official recognition, reward mechanisms, better sleep, exercise, and the timely provision of information (such as vaccine research progress) by the government on social media, and adequate protective supplies could mitigate the level of PTSD among nurses responding to COVID-19. Stigmatization, depression, and anxiety might be associated with a greater risk of PTSD among nurses.

Research perspectives

Considering the long-term adverse effects of PTSD on frontline nurses, longitudinal studies should be conducted in the future. Additional research is needed to better understand whether the vaccine could mitigate the negative impact on the mental health of nurses and other populations.

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FOOTNOTES

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SYSTEMATIC REVIEWS

Catatonia in older adults: A systematic review

Walter Jaimes-Albornoz, Angel Ruiz de Pellon-Santamaria, Ayar Nizama-Vía, Marco Isetta, Ines Albajar, Jordi Serra-Mestres

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Abstract

BACKGROUND

Catatonia is a complex psychomotor syndrome that often goes unrecognized and untreated, even though its classification has evolved in recent years. Prompt and correct identification of catatonia allows for highly effective treatment and prevention of possible complications. The underrecognition of catatonia in older patients is also frequent, and research in this population is scarce.

AIM

To conduct a systematic review of the literature on catatonia in older people to ascertain its clinical characteristics across settings.

METHODS

Following the PRISMA guidelines, MEDLINE, EMBASE, and PsycINFO databases were searched from inception to December 2021, with a strategy aimed at identifying all articles published on catatonia in older adults. Titles and abstracts were scanned and selected independently by two authors. Papers investigating issues related to catatonia and/or catatonic symptoms in older people, with English abstracts available, were included. References of selected articles were

revised to identify other relevant studies.

RESULTS

In total, 1355 articles were retrieved. After removing duplicates, 879 remained. Of the 879 identified abstracts, 669 were excluded because they did not meet the inclusion criteria. A total of 210 articles underwent full text review, and 51 were eliminated for various reasons. Fourteen more articles were selected from the references. Overall, 173 articles were reviewed: 108 case reports, 35 case series, 11 prospective cohort studies, 6 case-control studies, 3 retrospective cohort studies and 10 reviews. We found several particular aspects of catatonia in this population. Catatonia in older patients is highly prevalent and tends to have a multifactorial etiology. Older patients, compared to younger patients, have a higher risk of developing catatonia with benzodiazepine (BZD) withdrawal, in bipolar disorder, and in the general hospital. Age, together with other risk factors, was significantly associated with the incidence of deep venous thrombosis, neuroleptic malignant syndrome poor outcome, other complications and mortality. Treatment with BZDs and electroconvulsive therapy is safe and effective. Prompt treatment of its cause is essential to ensure a good prognosis.

CONCLUSION

Catatonia in older patients is highly prevalent and tends to have a multifactorial etiology. The risk of developing catatonia in some settings and conditions, as well as of developing complications, is high in this population. Symptomatic treatment is safe and effective, and timely etiologic treatment is fundamental.

Key Words: Catatonia; Older adults; Etiology; Phenomenology; Prevalence; Treatment

Core Tip: Catatonia in older people is underrecognized and undertreated, as demonstrated by the scarce bibliography published in this age group, in which the prevalence is high and the etiology usually multifactorial. Catatonia can frequently present together with delirium. General medical conditions and neurological disorders have a very important role in its etiology. Older people could have a higher risk of developing catatonia in bipolar disorder, the general hospital and with benzodiazepine (BZD) withdrawal. Also, they have a higher risk of developing complications secondary to this condition. BZDs and electroconvulsive therapy have been proven to be safe and effective symptomatic treatments, but the correct identification and treatment of the etiology are crucial for a full recovery.

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INTRODUCTION

Catatonia is a psychomotor syndrome caused by physical illnesses, such as infections; endocrine, metabolic, and neurologic disorders; psychiatric conditions, mainly affective and psychotic; and medications and other substances[1]. The contemporary concept of catatonia has evolved significantly. The Diagnostic and Statistical Manual - Fifth Edition (DSM-5) classifies catatonia either as a specifier of all mental disorders, as secondary to a general medical condition (GMC), and as catatonia not otherwise specified for when the syndrome is identified but not yet their etiology[2]. Based on a review of the available evidence published in recent decades and considering their clinical utility and global applicability, the International Classification of Diseases - 11th Edition classifies catatonia as a new diagnostic group at the same hierarchical level as the other included disorders. This edition, approved in May 2019, considers that catatonia can be caused by mental disorders, psychoactive substances (including medications), and medical conditions. In the former, catatonia is valued with the symptom specifier within the category "psychomotor symptoms" and, in the other two cases, as a secondary presentation form[3]. In patients older than 18 years, catatonia is mostly associated with affective disorders[1]. Its early recognition is important, as it is a potentially deadly syndrome. However, it is highly treatable, usually responding to treatment of the cause and to short courses of benzodiazepines (BZDs) or electroconvulsive therapy (ECT)[4-7].

Catatonia is also underrecognized in older adults, something that in this population may lead to delayed treatment, misdiagnosis, adverse events, and even death[8,9]. Despite the increasing amount of research on catatonia, there have been few specific studies on older patients. This review aims to summarize the published literature on catatonia in older adults to provide up-to-date knowledge about this entity for clinicians working with this population.

MATERIALS AND METHODS

This systematic review was conducted using the PRISMA method[10]. The MEDLINE, EMBASE, and PsycINFO databases were searched from inception through December 2021. The search strategy was as follows: CATATONIA/or catatoni*.af. and aged/or "aged, 80 and over"/or frail elderly/or (elder* or "old people" or geriatr* or senior* or aged or "over 65" or "over 80" or "65 year*" or "85 year*").ti,ab. Articles identified were imported into a standard reference manager, EndNote X7, and duplicate manuscripts were removed. Papers that investigated issues related to catatonia and/or catatonic symptoms in older people, with an English abstract available, were included. Titles and abstracts were scanned for relevance. Papers were selected according to the inclusion criteria by two authors independently (Jaimes-Albornoz W and Serra-Mestres J). Full texts were ordered in case of uncertainty to maximize sensitivity. References of selected articles were cross-checked to identify other potentially eligible studies. Case reports, case series, controlled studies, or review articles were eligible for inclusion in this review. The full texts of studies that passed the initial screening were reviewed and potentially excluded based on the same criteria. From this selection we only included Abstracts/Conference proceedings and letters to the editor that describe cases of catatonia whose clinical correlates have not been previously described. The literature search strategy is summarized in the flow chart presented in Figure 1. We also present all the clinical correlates of our catatonic patients in a psychogeriatric unit (Tables 1, 2 and 3). Information on patients diagnosed with dementia in this series has been published previously[11].

RESULTS

In total, 173 articles were considered: 108 case reports, 35 case series (12 also carried out a systematic review of the literature), 11 prospective cohort studies, 6 case control studies, 3 retrospective cohort studies, and 10 reviews. All articles were reviewed and are summarized below.

Epidemiological aspects

The prevalence of catatonia is largely dependent on its recognition, diagnostic criteria used, and setting. Although the general prevalence of catatonia is not fully known, it is considered to be between 5% and 20% among acute psychiatric patients; however, it varies according to the underlying or comorbid conditions[12]. A prevalence of 14%-71% has been described in mood disorders, 4%-67% in schizophrenia spectrum disorders, and between 4%-46% in GMCs[13]. A recent meta-analysis including 74 studies and 107304 individuals showed an overall pooled mean prevalence of catatonia of 9.2% among subjects diagnosed with a variety of psychiatric and medical conditions[13].

In the older population, the prevalence of catatonia also seems to vary depending on the setting and diagnostic criteria used. In liaison psychiatry services using the Bush Francis Catatonia Rating Scale (BFCRS) criteria, the prevalence of catatonia was 5.5%[14] and 8.9%[8]. Another study conducted in older patients in an acute inpatient general psychiatry ward reported a prevalence of 11.2% using the BFCRS and 6.1% using the DSM-5 criteria[15]. The prevalence was noted to be higher in acute psychogeriatric units in the United Kingdom (Table 1) and Spain[16], where the prevalence was 27% and 39.6% and 24.3% and 20.8%, respectively, using the BFCRS and DSM-5 criteria.

Pathophysiology

The specific brain mechanisms underlying catatonia are still poorly understood. The model developed by Northoff *et al*[17,18], who hypothesized that catatonic symptoms are mainly associated with orbitofrontal-prefrontal/parietal cortical dysfunction ('top-down' model of catatonia), abnormal 'horizontal' cortical-cortical modulation, and basal ganglia-cortical dysfunction (a 'bottom-up' mechanism), is criticized because the results are inconsistent and have generally been limited to schizophrenic patients with catatonia[19]. Studies with structural and functional brain imaging[20], clinical observations made after lobotomies and frontal lobe lesions, and experiments carried out in animals[21] have described incompatible results with Northoff's theory[17,18]'s theory. We are still far from having an integrative pathophysiological model of catatonia resulting from clinical, structural, and functional abnormalities of such a different nature. In this regard, only two articles were found about older people with catatonia that used brain imaging. The first was in patients with bipolar disorder (BD) and major depressive disorder (MDD), employing functional near-infrared spectroscopy[22], and the other used SPECT in

Table 1 Catatonia in a United Kingdom acute psychogeriatric ward

Abstract	
Aims	To determine the frequency and characteristics of catatonia in older people in a psychogeriatric ward
Methods	All patients admitted were screened for catatonia with the Bush-Francis Catatonia Screening Instrument over a period of 6 mo. Data was collected on sociodemographics, past medical/psychiatric/drug history, clinical findings, treatment, complications/outcome, and investigations. Treatment with lorazepam orally or intramuscularly was initiated in patients who fulfilled diagnostic criteria for catatonia
Results	37 patients were admitted. Prevalence of catatonia was 27%, 10 out of 37 (Bush-Francis criteria) and 24.3%, 9 out of 37 (DSM-5 criteria). The 10 catatonic patients have a mean age of 75.8 years; range: 67-87; and 8 were female. 90% of these patients had a cardiovascular risk factors. The etiology was multifactorial in 50% of the cases. 6 patients had dementia. In 3 of them catatonia was associated with the use of neuroleptics, in 1 with neuroleptics and a urinary infection (she also had delirium), in another with major depression and in only one dementia was a possible etiology. 40% of the cases developed catatonia secondary to affective disorders and 10% to schizophrenia spectrum disorder. In the total sample there were 14 patients with dementia. The catatonia rate in these patients was 42.8% (6 of 14). 9 patients received treatment for catatonia with lorazepam, all of which achieved complete remission, 1 of the these was also treated with clonazepam. 1 patient was treated with sodium valproate and achieved a partial response. 3 patients developed complications secondary to catatonia. One had an elevated creatine kinase of 1083 IU/L, another a deep venous thrombosis, and the last one, hypokalemia
Conclusions	Catatonia is a very prevalent entity in the psychogeriatric ward. The etiology is usually multifactorial. This condition occurred frequently in patients admitted with dementia. Treatment with lorazepam is highly effective and safe

DSM-5: Diagnostic and Statistical Manual - Fifth Edition.

Table 2 History, antipsychotic exposure and current diagnoses in patients with catatonia in United Kingdom acute psychogeriatric ward

Age/sex	Medical history	Psychiatric history	Current acute medical diagnosis/antipsychotic exposure	Current acute psychiatric diagnosis
67/F	Bowel obstruction resulting in perforation	Bipolar disorder	None	Bipolar disorder, current episode depressive severe without psychotic symptoms
87/M	Hypertension; Hyperlipidemia; Lip carcinoma	Alzheimer's disease	None/(risperidone, quetiapine)	Late onset Alzheimer's disease
76/F	Hypertension; DM2; Hyperlipidemia	Vascular dementia	None/quetiapine	Vascular dementia
75/F	Ischemic heart disease; Irritable bowel syndrome; Hypothyroidism; Pulmonary fibrosis; Diveticulitis	RDD; Health anxiety; Dementia	None	Late onset Alzheimer's disease; RDD, current episode severe without psychotic symptoms
71/F	Hyperlipidemia; Atrial fibrillation; Repeated urinary tract infections; Diverticulitis	RDD; Alcohol misuse; Alzheimer's disease	Urinary tract infection/(aripiprazole, olanzapine)	Young onset Alzheimer's disease; Delirium superimposed on dementia
70/F	Hypertension; Osteoarthritis	RDD	None	RDD, current episode severe with psychotic symptoms
74/F	Parkinson's disease; Glaucoma; Obesity	Schizoaffective disorder	None	Schizoaffective disorder not otherwise specified
68/F	Hyperlipidemia	Young onset Alzheimer's disease	None/none	Young onset Alzheimer's disease
85/M	Hypertension; DM2; Jaw osteomyelitis; Isquemic heart disease; Pacemaker	Mixed dementia	None/risperidone	Mixed dementia
85/F	Hypertension; Atrial fibrillation; Breast cancer	Depression	None	Severe depressive episode without psychotic symptoms

RDD: Recurrent depressive disorder; DM2: Type 2 diabetes mellitus.

older patients who developed catatonia as a result of late-onset schizophrenia[23]. Their conclusions were similar to those previously reported in adult patients.

It has also been suggested that catatonia could be a manifestation of intense anxiety and/or fear, resembling tonic immobility in animals, an evolutionary adaptive defense strategy to survive contact with predators attacking moving prey[24]. In humans, fear could also be caused by internal events and psychopathological experiences, such as hallucinations and delusions or anxiety/fear. This freezing would correspond to the immobility, stupor, catalepsy, and mutism observed in catatonia. Alternatively, catatonic excitement would be analogous to the 'fight-flight' response mediated by the

Table 3 Catatonia signs frequency using Bush Francis Catatonia Rating Scale in older people

Catatonia signs	Country, clinical setting, (*n*: Patients)					Total (*n* = 79)	%
	Spain[5] CLS, (*n*: 10)	Australia[10] CLS, (*n*: 6)	United Kingdom[7] PW, (*n*: 10)	Hungary[11] APW, (*n*: 11)	Spain[12] PW, (*n*: 42)		
Inmobility/stupor	10	5	7	7	24	53	67.1
Staring	10	3	7	7	22	49	62.0
Mutism	8	2	7	4	18	39	49.5
Negativism	7	3	4	0	25	39	49.5
Withdrawal	8	3	4	3	18	36	45.6
Rigidity	9	4	6	2	15	36	45.6
Excitement	0	0	3	3	27	33	41.8
Posturing	7	4	5	6	8	30	37.9
Verbigeration	1	1	2	0	26	30	37.9
Perseveration	1	0	3	2	20	20	33.0
Stereotipies	4	1	4	2	15	26	33.0
Autonomic abnormalities	1	1	3	1	16	16	27.8
Impulsivity	1	0	2	1	15	19	24.0
Automatic obedience	1	1	3	1	16	22	21.5
Combativeness	2	0	4	0	14	20	20.4
Ecophenomena	6	1	2	0	5	14	17.7
Ambitendency	0	1	2	2	8	13	16.5
Grasp reflex	0	1	1	2	9	13	16.5
Grimacing	3	1	0	0	8	12	15.3
Mitgehen	3	0	0	5	1	9	11.4
Gegenhalten	3	0	3	2	0	8	10.2
Waxi flexibility	2	0	4	0	0	6	7.6
Mannerism	0	0	0	0	4	4	5.1

APW: Acute psychiatric ward; CLS: Consultation-Liaison service; PW: Psychogeriatric ward.

sympathetic nervous system. A recent study in older patients with MDD found that those with catatonia and with agitation had increased hair cortisol concentrations[25], a hormone associated with stress. Nevertheless, it has also been postulated that it is possible to differentiate between emotive and nonemotive subtypes of catatonia, suggesting that not all catatonia patients experience emotional distress[26]. This theory seems to be supported by the findings that catatonia in older adults is not always related to intense anxiety[27].

Phenomenology, clinical signs, and diagnosis of catatonia

The clinical presentation of catatonia in older adults (frequency of catatonic signs and clinical types) is generally similar to that of younger patients. Table 3 shows the frequency of signs of catatonia evaluated with the BFCRS in the 5 prospective observational studies carried out in older people[8,11,14-16]. Two clinical types of catatonia have been consistently reported in both populations[1,28]. A hypokinetic variant (retarded-stuporous) is characterized by reduced movement or immobility, mutism, and withdrawal. This is most frequently observed in depressive disorders and GMCs. A hyperkinetic or excited variant, presenting with increased aimless motor activity (qualitatively different from the overactivity of pure mania, which is purposeful), confusion, and frequent autonomic dysfunction, is mostly observed during manic episodes and in delirious mania. It is noteworthy that both forms of catatonia can coexist in the same patient, occurring in quick succession[1].

A forgotten subtype of catatonia, also described in older people[29], is periodic catatonia. It is characterized by rapid onset, brief and recurrent episodes of catatonia with a longitudinal course. Prognosis is

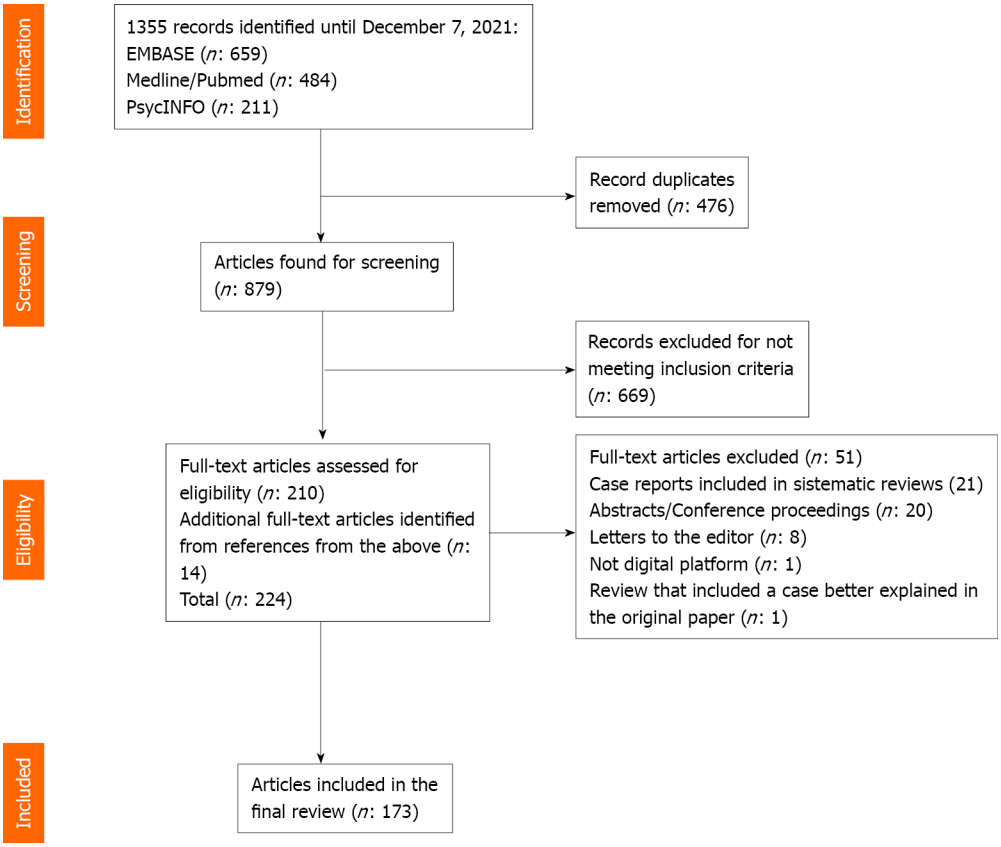

Figure 1 PRISMA flow diagram.

typically better than systematic catatonia, which is insidious and progressive. If it is properly identified can respond extremely well to ECT[29].

The assessment of catatonia requires careful observation during the clinical interview and the elicitation of specific signs during the neurological examination[28]. The routine use of validated rating scales is recommended to facilitate the identification of catatonic signs and the diagnosis of catatonia [30]. In adult patients, seven catatonia rating scales are available. The BFCRS is the most commonly used in research and clinical settings, including older people, because of its validity and reliability and its ease of administration[28,30]. It is also very sensitive, requiring only 2 out of 14 signs of the screening instrument to diagnose this condition[30]. The DMS-5 states that a diagnosis of catatonia can be made if there are at least three symptoms out of 12 presents at the time of assessment: Stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerisms, stereotypy, agitation, grimacing, echolalia and echopraxia[2].

The association of catatonia and delirium has been increasingly described[31,32]. Delirium is considered the most salient factor to predict a medical cause of catatonia[33]. Both share clinical features, lack specific laboratory findings and biomarkers and are diagnosed in similar clinical settings [32]. Delirium is a prominent clinical manifestation of malignant catatonia[34], delirious mania[35] , and neuroleptic malignant syndrome (NMS)[34,36]. Coexisting delirium was found in 30%[8] and 50%[14] of cases of older adults with catatonia in acute medical settings, in which the clinical presentation was generally in the retarded-stuporous form. This high prevalence decreases significantly in acute psychogeriatric wards, where delirium was described in 4.8%[16] and 10%[11] of catatonic cases. The differential diagnosis between catatonia and delirium is challenging, as both cause prominent psychomotor abnormalities. Delirium's classification predominantly relates to its motor aspects and is thus divided into hyperactive, hypoactive, and mixed forms[31]. There are also hypoactive and hyperactive forms of catatonia. Catatonia can be misdiagnosed as delirium and managed as such, and while delirium appears in the list of differential diagnoses of catatonia, the latter rarely figures into that of delirium[32]. Furthermore, unlike delirium, approximately 80% of catatonia cases of medical etiology are due to neurological disorders[33]. However, there are differences in their pharmacological management. The treatment of choice in catatonia, lorazepam, is rarely the treatment of choice in delirium, except when caused by BZD withdrawal. The most widely used symptomatic treatment of choice in delirium, antipsychotics, is generally to be avoided in the management of catatonia. Therefore, the ability of clinicians to ascertain a catatonic dimension in cases of delirium will facilitate selection of the appropriate treatment[31,32].

Course and prognosis of catatonia

Catatonia in older people often presents acutely, but it can also have an insidious presentation. The duration can be transient or chronic, lasting for weeks, months or even years[37,38]. The total duration of illness could be significantly lower if the etiology is a GMC when compared with affective or psychotic disorders[38,39]. Acute catatonia has a good prognosis if it is diagnosed early, its symptoms and etiology are treated in a timely fashion, and the necessary measures are taken to prevent complications. If complications are already present, they are treated aggressively[28]. In organic catatonia, structural brain lesions may have a worse prognosis than metabolic causes[8,40]. Older patients in general hospitals with a longer duration of untreated catatonia may have a worse outcome in terms of rates of complications (40%) and even death (20%)[8].

Catatonia may develop a chronic or continuous course in some patients, mainly with chronic psychoses. In a study in chronically hospitalized older schizophrenic patients, catatonic symptoms were less common and less severe than in acute hospital patients, but the clinical pattern was similar[37]. According to the authors of the study, these findings suggest that catatonic phenomena may persist for years, a course described by Kahlbaum in several cases where catatonia persisted, in some patients, until their death[37].

Etiology-catatonia due to GMCs

Neurological disorders: Dementia: Catatonia has been described in all dementia types, with reports in patients with Alzheimer's disease (AD)[41-43]; frontotemporal dementia (FTD)[44-49]; dementia with Lewy bodies (DLB)[50-55]; and other cases with mixed, vascular, or nonspecified dementia[56,57]. Two prospective studies in psychogeriatric units reported a high prevalence of catatonia in patients with dementia using DSM-5 criteria, at 35.3%[16] and 42.8%[11]. This prevalence was found to be lower in another study in a general psychiatric ward, which report a prevalence of 4.7% using the same criteria [15]. In this last series, almost three-quarters of the patients with catatonia had dementia; 28% of patients had associated depressive disorder, and 36% had a GMC[15], an association also present in most of the published dementia case reports.

Encephalitis: Encephalitis occurs more frequently in younger people; however, a few case reports in older patients have been found[58-62]. Among the patients with anti- N-methyl-D-aspartate (NMDA) receptor encephalitis[59-62], one also tested positive for herpes simplex virus[59]. In this population, in this type of encephalitis, until 17.4% patients could present with catatonia[63]. The remaining case reports of catatonia in older patients involved a patient with paraneoplastic encephalitis[58] and a patient with anti-Hu encephalitis[61]. Prior to catatonia onset, most cases presented with an array of psychopathologies, such as delusions[58-60], auditory hallucinations[60], visuotactile hallucinations [59], and mania[61]. The only exception was a case report of a patient with a history of anxiety who presented with parkinsonism[62].

Epilepsy: In this review, 12 older patients with catatonia in the context of epileptic activity were found. Most had nonconvulsive status epilepticus (NCSE)[61,64,65], one case had complex partial seizures secondary to viral encephalitis in a patient with BD[61], one case of frontal lobe epilepsy in a patient with dementia[66], and a patient with schizophrenia who developed clonic seizures[64]. Among NCSE patients, 4 cases were associated with the use of antidepressants (bupropion 75 mg/d[64], paroxetine 20 mg/d[67], sertraline 50 mg/d[67], mirtazapine 30 mg/d and sertraline 50 mg/d[67]) and 1 with paroxetine 7.5 mg/d and gabapentine 900 mg/d withdrawal[64]. Five had delirium[64,68], 1 had acute kidney injury[65], 4 had acute depressive symptoms[64], 3 had acute psychotic symptoms[64,68], 1 had mania and anti-Hu meningoencephalitis[61].

Cerebrovascular disease: There were articles reporting older patients who developed catatonia secondary to acute strokes[8,69-72] and past or chronic vascular changes[73,74]. No relation was found between lesion location and emergence of catatonia. Some of these cases had longstanding depression as well[71]. As to newer onset psychopathology, there were 1 case with delirium[69], and 2 patients with psychosis[70,71].

Parkinson's disease: Two papers found that catatonia could be differentiated by parallel ratings of parkinsonian symptoms and catatonia scales in older adult patients with schizophrenia[37] or depression[75]. In the Starkstein's study[75], apomorphine improved Parkinson's symptoms without affecting catatonic symptoms, thus supporting a biological basis for a distinction between the two conditions. Our review found 6 older patients with catatonia and Parkinson's disease[76-81]. The cases presented with diverse psychiatric conditions. For instance, one case had depression[81] and another case had depression and posttraumatic stress disorder[76]. All these patients developed symptoms, such as depression[78,79] and psychosis[76-80], prior to catatonia onset.

Other neurological disorders: Other neurological entities found in older patients with catatonia were epidural empyema[7], progressive supranuclear palsy[82], frontotemporal lobes atrophy[83], cerebral Whipple's disease[84], Creutzfeld-Jakob disease[85] and cerebral anoxia after a cardiac arrest[86].

Metabolic, infectious, endocrine, nutritional and neoplastic disorders: Some metabolic derangements can cause catatonia in older people. These include acute renal failure[15,52,87], heart failure[8,15], liver failure[15], post liver transplantation[88], dehydration[15], hypernatremia[87,89] and hyponatremia[90-93]. Infectious disorders associated with catatonia are acute[94-96] and chronic recurrent urinary tract

infection[97]; pneumonia[8,15,98] and coronavirus disease 2019[99-101]. Associated endocrine disorders are hyperparathyroidism[102,103], hypothyroidism[93,95], subclinical Cushing's syndrome[104], and hyperthyroidism due to Grave's disease[105]. Finally, pertaining to nutritional and neoplastic etiologies, only one case of cyanocobalamin deficiency[106] and another of a colon tumor have been described[15]. Most of these patients had a psychiatric history and developed catatonia secondary to a GMC or in association with drug withdrawal. None of these cases presented with acute psychopathology, with the exception of 4 cases that showed affective and/or psychotic symptoms secondary to the primary metabolic[93] and endocrine disorders[103,105,106].

Etiology-drugs and toxic substances

Antipsychotics: Many cases of catatonia related to antipsychotic use in older patients have been published. Of these, there were patients that developed NMS associated with aripiprazole[107] haloperidol[108-113] and loxapine[114]. In addition, there are reports of catatonia induced by pipothiazine[115], quetiapine[11,116], and droperidol[117] and cases secondary to exposure to more than one antipsychotic: Haloperidol and trifluperazine[109], risperidone and quetiapine[11], aripiprazole and olanzapine[11], and risperidone, haloperidol and tiapride[8].

Other drugs and toxic substances: In total, eleven case reports were found of patients who developed catatonia after exposure to normal doses of a wide variety of drugs, such as phenelzine[118], allopurinol [119], prednisone[95] rivastigmine[41], donepezil[120], azithromycin[121], cefepime[122], amiodarone [123], methotrexate[124], tacro-limus[125] and imiquimod[126]. Eight out of 11 patients were female, one case had a stable BD prior to the index episode[125], another case had DLB[120] and another had AD[41]. None of them had current affective or psychotic psychopathology before exposure to the drug. One case presented with hyponatremia[126] and another with acute interstitial nephritis[122]. The others developed psychotic or depressive symptoms prior to, or simultaneously with, catatonia. There was also a catatonia case secondary to neurotoxicity reported by manganese[96] and another after deep brain stimulation successfully treated with lorazepam and right unilateral ECT[127].

Catatonia secondary to drug withdrawal: Descriptions of catatonia after the rapid tapering or abrupt discontinuation of BZDs after prolonged use have been published. These cases were related to nitrazepam[128], diazepam and alprazolam[128] , oxaze-pam and temazepam[128], clonazepam[128, 129], alprazolam[128], temazepam[128], diazepam[128], chlordiazepoxide[128] and lorazepam[130]. The doses of BZDs vary widely, but they are usually in the therapeutic range. The onset of withdrawal catatonia is 3-7 d after discontinuation, and the duration is 3-10 d. Also, it appears to present without electroencephalography abnormalities, such as diffuse slowing[128]. Moreover, there are sporadic reports of withdrawal catatonia secondary to antipsychotics and other psychotropics, such as clozapine [131], olanzapine[94], risperidone and olanzapine and chlorpromazine[56], haloperidol and cyamemazine[132], bromperidol and levomepromazine[133], amantadine[79], gabapentin[64,134], and lithium[94].

Etiology-catatonia secondary to psychiatric conditions

Affective disorders: Studies in psychogeriatric units found a prevalence of affective disorders in catatonia of 40% (Table 1) and 42.8%[16]. In a psychiatric general inpatient service, catatonia was most prevalent among older patients with severe depression[75]. These patients had more severe cognitive impairment and more severe deficits in activities of daily living than depressed noncatatonic patients [75]. In a similar setting in Hungary, 28% of catatonic patients suffered from dementia associated with depressive disorder[15]. This relationship between the development of catatonia and organic conditions in patients with affective disorders has been replicated in most of the case reports or case series published[61,64,68,135].

Most case reports of catatonia in affective disorders have been published emphasizing the unusualness of the presentation (patient that can masquerade as Creutzfeld-Jakob disease[136]), the associated psychopathology (cases with nihilistic delusions suggestive of Cotard's syndrome[137,138]), or the comorbid conditions present (the affective cases described in the sections on catatonia secondary to GMCs or drug use/withdrawal).

Schizophrenia spectrum disorders: Reports of older patients with catatonia in psychotic disorders are sporadic. Cases of catatonia have been described in association with schizophrenia[139], psychotic disorder not otherwise specified[16], brief psychotic disorder[135] and schizoaffective disorder[11,15, 16]. In a study conducted in older adults with schizophrenia, a catatonia prevalence of 69% using BFCRS criteria was found[37]. In acute inpatient wards, schizophrenia spectrum disorders (SSD) is the third most frequent condition in catatonic older patients following affective disorders and those secondary to GMCs[11,16].

Other disorders: Catatonia has been reported in adjustment disorder[16,140], substance use disorder [16], conversion disorder[140,141], and posttraumatic stress disorder[142]. In one case report, there was a background of melancholia and a recent withdrawal of thioridazine; in another case report, the

adjustment disorder was diagnosed with depressed mood. In the remaining reports, psychiatric or organic comorbidities were not detailed. Table 4 shows all the etiologies associated with catatonia described above.

Treatment

BZDs: BZDs are an effective treatment for catatonia in older adults in whom a full resolution is described within hours/days of treatment initiation[6]. Lorazepam is recommended as the first-line medication, and it is extensively reported to be highly effective, irrespective of the underlying cause[5,6,143,144]. Other BZDs, such as diazepam[128,145], midazolam[146,147], alprazolam[148], oxazepam [128], flunitrazepam[139], temazepam[128] and clorazepate[108], have also been described as useful in older people. This treatment should be maintained until the catatonia etiology is identified and appropriately treated[1,28]. In this review, the initial doses of lorazepam found ranged from 0.25 to 4 mg daily, with most patients receiving 1-2 mg. If catatonic symptoms respond partially to low doses of BZDs, titration to higher doses is recommended to achieve full symptom resolution[5,6]. During catatonic states, in this and in the other age groups, high BZD doses are typically well tolerated[6]. In older people, the associated risks are oversedation, respiratory depression, cognitive impairment, and falls[149]; therefore, monitoring is necessary. In the reviewed cases, doses ranged from 3-20 mg lorazepam/d. Lower response rates to BZDs have been described in patients with structural brain damage or with schizophrenia when compared with mood disorders or acute medical etiologies[5,6].

ECT: ECT should be a first-line treatment in patients with nonresponse or contraindication to BZDs, those who need a rapid response because of life-threatening conditions, or when malignant catatonia features are present[5,6,150]. Better response rates to treatment were found in catatonia related to mood disorders than in catatonia related to nonaffective psychosis[5,6,68]. Even so, ECT is one of the best treatments for catatonic schizophrenia, and this was also described in older patients by Suzuki *et al* [139], with excellent response rates in this group.

Among the older catatonic patients successfully treated with ECT, the etiology in most of them were mood disorders, followed by those secondary to non-affective psychosis. Less frequently the etiology was related to a GMC.

The number of sessions ranged from 2 to 25, but only 3 patients needed more than 15 sessions to respond. The mean number of sessions among all catatonic episodes was 10.33 sessions/episode. Exceptionally high initial seizure threshold in catatonic older patients treated with ECT has been reported[151].

The most common application frequencies during acute course ECT were 2 or 3 times a week. Most cases were treated with bifrontotemporal electrode placement and also, there has been reports of patients that received right unilateral ECT with a resolution of catatonia[152,153]. Furthermore, there is a report of a patient with catatonic schizophrenia who was treated by successful seizure induction by means of ECT, with electrodes applied bilaterally to the parietotemporal region after bifrontotemporal ECT failed to induce adequate seizures[154]. On the other hand, 3 articles described only a partial response to ECT in 3 older patients during a catatonic state after receiving 7-8 ECT sessions[8,78,155]. All these cases were associated with GMCs (cognitive impairment, Parkinson's disease, and manganese poisoning).

Two cases of catatonia refractory to ECT treatment have been reported. One on them was associated with encephalitis secondary to ovarian teratoma[58] and another one in a patient with depression and autistic spectrum disorder[151]. Continuation or maintenance ECT is recommended when relapse occurs despite pharmacological treatment and in patients with recurrence of catatonic symptoms when ECT is suspended[139]. Three cases were described with periodic relapses, but each new catatonic episode responded again to a course of ECT. Although there are no absolute contraindications for the use of ECT in older patients and it is considered a safe and well-tolerated treatment, medical risks must be evaluated individually[143,150]. There are case reports of catatonic patients with unstable or potentially unstable clinical conditions, such as a 95-year-old pacemaker user[156], full anticoagulation after pulmonary embolism[157], a 100-year-old patient with severe aortic stenosis[158], deep venous thrombosis[159]; that illustrates how, with the proper precautions, the benefits of ECT in such conditions might outweigh its risks.

ECT requires general anesthesia. Serious adverse effects related to ECT are extremely infrequent but include arrhythmia, seizures, or even death, although these have not been specifically reported in this population. Other mild adverse effects are considered transient, but they can be relevant in the older population, such as cognitive impairment, delirium, hypertension, increased risk of falls, or hypomania [150]. Cognitive impairment related to ECT is reported as transient, even in older patients, but limited cases of prolonged amnesia have also been described[160].

Etiological treatment: Early identification and treatment of etiological causes of catatonia are crucial, especially in this population[8,11,14]. Even in those patients with a previous history of psychiatric disorder, medical etiologies should always be considered because of the frequent simultaneous occurrence of both conditions[8,14,15,143]. Organic, toxic, and pharmacological conditions are common causes of catatonia and are overrepresented in the older population. In most cases of catatonia in this

Table 4 Catatonia etiology in older people

Psychiatric disorders	General medical conditions	Drugs and toxic substances
Schizophrenia spectrum disorders: Schizophrenia; Schizoaffective disorder; Brief psychotic disorder; Psychosis not otherwise specified. Affective disorders: Major depressive disorder; Bipolar disorder. Others psychiatric disorders: Post-traumatic stress disorder; Conversive disorder; Adjustment disorder; Substance use disorder	Neurologic: Dementia: Alzheimer´s dementia; Frontotemporal dementia; Lewy bodies dementia; Mixed dementia; Organic dementia; Dementia not otherwise specified. Epilepsy. Cerebrovascular disease; Parkinson´s disease. Others: Cerebral anoxia; Creutzfeldt-Jakob's disease; Epidural empyema; Frontotemporal lobes atrophy; Cerebral Whipple's disease; Progressive supranuclear palsy. Metabolic: Acute renal failure; Heart failure; Liver failure; Post liver transplantation; Dehydration; Hyponatremia; Hypernatremia. Infectious: Urinary tract infection; Pneumonia; COVID-19. Endocrine: Hyperparathyroidism; Hypothyroidism; Hyperthyroidism. Others: Cyanocobalamin deficiency; Colon tumor	Drugs: Regular use: Antipsychotics: Haloperidol; Droperidol; Loxapine; Pipotiazine; Trifluoperazine; Tiapride; Aripiprazole; Risperidone; Quetiapine. Other drugs: Phenelzine; Allopurinol; Prednisone; Rivastigmine; Donepezil; Azithromycin; Cefepime; Amiodarone; Tacrolimus; Methotrexate; Imiquimod. Withdrawal: Benzodiazepines: Nitrazepam, diazepam, alprazolam, oxazepam, temazepam, clonazepam, chlordiazepoxide and lorazepam. Antipsychotics: Clozapine, olanzapine, risperidone, chlorpromazine, levomepromazine, bromperidol, haloperidol and cyamemazine. Others: Amantadine, lithium, gabapentine. Toxic substances: Manganese

COVID-19: Coronavirus disease 2019.

literature search, remission occurred after specific catatonia symptomatic treatment was administered as well as treatment for the underlying medical condition[8,11,64,94]. Some reports noted remission of catatonia only when treating the underlying medical condition, without symptomatic treatment for catatonia[8,69,102,161]. Recent medication changes should be considered relevant because they highly suggest drug-induced catatonia. Suspension of the causal drug should be considered as part of the treatment, as in some patients, resolution of the catatonic state was only achieved with discontinuation of the drug[8,92,95], while others also needed con-comitant symptomatic catatonia treatment[8,95,109,162].

Other treatments: Zolpidem was broadly reported as an effective treatment for catatonia but with transient efficacy. In general, it was used as a diagnostic test because of its very short half-life when catatonia was suspected[108]. Other reports described the successful treatment of catatonic older patients with zolpidem alone or in combination with other treatments; thus, it could be considered an alternative treatment[45,49,58,104]. The NMDA receptor antagonists memantine and amantadine have also been reported as useful symptomatic treatments for catatonia, even in treatment-resistant patients [163]. Memantine doses ranged from 5-10 mg daily[163]. Amantadine was described as effective (doses ranging from 100-200 mg daily)[78,163]; however, nonresponsiveness was also reported[42,45,164,165]. Anticonvulsant drugs have been used as a catatonia treatment option in this population alone or in combination with partial or complete response. There are reports of valproate at doses ranging from 400-1250 mg daily[11,91,135,163], carbamazepine (100 mg/daily)[78], and topiramate[166]. Additionally, there are articles that described no response to valproate[91,163] or carbamazepine 600 mg/daily[167]. Dopaminergic drugs have also been postulated as potential treatments for catatonia due to the hypothesis that the dopaminergic system is involved in its pathophysiology. There are isolated reports of treatment with bromocriptine[112] and dopamine, the latter being used to treat hypotension during a catatonic state with full recovery[168]. The patient received bupropion as continuation treatment without relapse of catatonia. Also, there have been published a NMS cases which were treated satisfactorily with 25 ECT sessions and bupropion 300 mg/d[164] and with 11 ECT sessions and bromocriptine 15 mg/d[112]. Another article reported a case of successful treatment with methylphenidate in an older depressed patient with catatonic stupor who did not respond to lorazepam[169]. There are articles reporting anecdotal evidence of successful treatment of catatonia with propofol[170] , biperiden[171,172], olanzapine[162,173] and lithium[174]. Another article reported the on efficacy of tramadol in several consecutive catatonic episodes in an older patient with a diagnosis of schizoaffective disorder[132]. Finally, neuromodulation treatments, such as repetitive transcranial magnetic stimulation [111] and transcranial direct current stimulation[175], were also described as effective. The catatonia treatments used in older people are summarized in Table 5.

Prevention and treatment of adverse events

Catatonic states can induce complications in relation to immobility, dehydration or inability to have oral intake, which are especially relevant in older patients. Some of these complications include deep vein thrombosis (DVT), pulmonary embolism, pressure ulcers, infections, acute renal injury, rhabdomyolysis, electrolyte distur-bances, pulmonary aspiration and secondary pneumonitis and/or pneumonia, or muscular contractures[143,165,176].

In a retrospective chart review, Ishida *et al*[176] concluded that age and the presence of risk factors for dynamic vascular patterns were significantly associated with the incidence of DVT. Patients older than 65 years had an odd ratio (OR) of 3.23, and younger patients had an OR of 1[176].

Table 5 Catatonia treatments used in older people

1º line	2º line	3º line
Benzodiazepines: Lorazepam; Diazepam; Midazolam; Alprazolam; Oxazepam; Flunitrazepam; Temazepam	Electroconvulsive therapy: Bifrontotemporal ECT; Right unilateral ECT; Acute ECT; Continuation ECT; Maintenance ECT	Drugs: Amantadine; Biperiden; Bupropion (as continuation treatment); Bromocriptine; Carbamazepine; Dopamine; Lithium; Memantine; Methylphenidate; Olanzapine; Propofol; Topiramate; Tramadol; Valproate; Zolpidem. Neuromodulation treatments: Repetitive Transcranial Magnetic Stimulation; Transcranial Direct Current Stimulation

ECT: Electroconvulsive therapy.

Early identification and treatment of catatonia and its underlying cause are crucial to rapidly improve stupor and prevent all these complications[5,6,144]. Specific preventative measures include frequent vital sign checks, anticoagulation, postural changes, intravenous fluids, nasogastric feeding, and urinary catheterization[165]. Additionally, the progression to malignant catatonia with autonomic instability and hyperthermia is a life-threatening condition that should be watched.

DISCUSSION

Catatonia in older people is an underrecognized entity and is consequently undertreated, as evidenced by the scarce literature found after a systematic search. The majority of articles are case reports or case series, with few prospective studies. However, a very interesting fact is evident: Most case descriptions show similar medical and psychiatry histories, clinical manifestations, etiologies, comorbidities and responses to treatment; clinical correlates that are very similar to those cases reported by prospective studies.

Catatonia in this population is highly prevalent, and the prevalence increases when the clinical setting studied is more specific (general hospital: 5.5%[14] and 8.9%[8]; general psychiatry unit: 11.2%[15]; psychogeriatric units: 27% (Table 1) and 39.6%[16]. Catatonia prevalence in younger patients in similar settings is lower: 1.6%[177], 1.8%[108] and 2.4%[8] in liaison services and approximately 10% in acute inpatient wards[13]. This suggests that older people may have a higher risk of developing catatonia than those under 65 years of age, as shown in Navarra's liaison psychiatry study, where their patients over 65 years were 3.95 times more likely to develop catatonia than their younger counterparts [8].

There is some evidence that supports the possibility that somatic and cognitive impairment have a significant role in the development of catatonia[16]. This could be related to the highest prevalence of dementia and medical disorders, such as cardiovascular risk factors (hypertension, type 2 diabetes mellitus, and dyslipidemia), in this population[178], which were present in most case reports described in the United Kingdom psychogeriatric ward (Table 1) and in all patients of the psychiatry liaison consultation studies[8,14] (the other 2 prospective studies did not specify these data). It has been considered whether dementia is a specific risk factor for developing catatonia. Takács *et al*[15], in a study in a general psychiatry ward, concluded that it was not a risk factor, as the prevalence of catatonia was not very different in their patients with dementia (4.7%) compared to the total study sample (6.1%). However, in studies on psychogeriatric wards, the prevalence was higher in patients with dementia (35.3%[16] and 42.8%[11]) than in the total number of patients [20.8%[16] and 24.3% (Table 1)]. This nonconcordance could be caused by differences in the clinical settings and leaves open the role of dementia as a risk factor for catatonia.

The clinical presentation of catatonia is quite similar to that of adults under 65 years of age. In general, the most frequent signs are the same (immobility, staring, mutism, negativism, withdrawal, rigidity and posturing)[5,12,38]. Unlike what happens in patients under 65 years of age, excitement (41.8%), verbigeration (37.9%), perseveration (33%) and autonomic abnormalities (27.8%) seem to also be very frequent. In older people, the high prevalence of dementia and cardiovascular risk factors could also explain this different profile. In all catatonia prospective studies, the assessment was undertaken in a systematic way using the BFCRS; notably, the low frequency of the catatonic signs considered DSM-5 diagnostic criteria [ecophenomena (17,7%), grimacing (15,3%), waxy flexibility (7,6%) and mannerism (5,1%)] and the high frequency of other catatonic signs included in the BFCRS and not the DSM-5 criteria [staring (62%), withdrawal (45,6%) rigidity (45,6%) and autonomic abnormalities (27,8%)] (Table 3). These results could suggest the need to review the very strict current diagnostic criteria and to take into account what was reported by Stuivenga *et al*[12], that giving a dimensional approach to catatonic signs could help improve diagnostic sensitivity. In older people, it may be better to use, in an initial assessment, the Bush Francis Catatonia Screening Instrument, which includes the above catatonic signs, to identify more patients susceptible to receiving potentially very effective treatment.

Catatonia and delirium co-occur relatively frequently in older people. Management could be a challenge for clinicians; however, if we follow a therapeutic and care algorithm, the chances of better

results are greater[32]. A systematic review on the issue recommended identifying and treating the etiology of both conditions, initially trying a challenge test with lorazepam; avoiding the use of high-potency neuroleptics; taking the necessary measures to prevent and treat complications; and if there is no response with lorazepam, considering the use of amantadine, memantine or topiramate. ECT is indicated in refractory or life-threatening cases[32].

The probability that catatonia in acute medical settings has a medical etiology or is related to drug use/withdrawal is greater than 50%. The prevalence of catatonia was strongly associated with age in the setting of critical illness[179]. This probability increases in critically ill elderly patients by up to 80%-100%[33]. These high rates of catatonia in clinical settings should lead us to consider that the etiology of catatonia is medical until proven otherwise, especially in older adults[33]. It has been frequently reported that the possible organic etiology of patients with catatonia tends to be overlooked, even more so if they have a psychiatric history because of a belief that the psychiatric disorder is the cause of catatonia[143,180].

In almost all dementia cases traced, these disorders were not the cause of catatonia; rather, they emerged as a consequence of the acute onset of psychopathology, GMCs, and/or due to the use of drugs, mainly neuroleptics. This occurred in 29 of 31 (93.5%) patients with dementia reported in observational prospective studies[8,11,14-16]. This does not appear to occur in FTD patients. Catatonia and FTD share a common pathophysiology, frontal lobe dysfunction, and similar symptoms (mutism, stupor, stereotypy, mannerisms, perseveration, negativism, echophenomena, and others[44], which are a central part of their diagnostic criteria[2,181]. This could cause catatonia to be even more underdiagnosed and therefore not adequately treated in this specific type of dementia. In FTD, catatonia should be suspected when the patient has a sudden and sustained increase in previous psychomotor symptoms or when the appearance of new catatonic symptoms is observed. In the rest of the reports of catatonia secondary to neurological disorders, GMCs and the use of drugs, something similar takes place. Catatonia occurs frequently when GMCs cause psychotic or depressive symptoms or when the latter appear as drug adverse effects and/or in patients with a psychiatric history of disorders of both spectra. In future studies, the systematic evaluation of the presence or absence of depressive or psychotic psychopathology in these patients will reveal their roles in the development of catatonia.

In general, in this population, antipsychotics can also increase the risk of NMS and can contribute to the development or worsening of catatonic symptoms[182,183]. Moreover, the NMS risk of poor outcome and mortality is associated with older age[184]. Some authors have recommended antipsychotic discontinuation during the acute phase of catatonia and to reinitiate treatment once catatonia is in remission[5,185]. Due to the risks concerning the safety of antipsychotics, their use in acute catatonia is generally not recommended in this population[185]. Caution should be the rule on prescribing, and the risk assessment should be individualized to each patient[6]. Catatonia can also appear after withdrawal from different types of drugs, mainly BZDs. The predominant subtype was stuporous catatonia with sporadic reports of catatonic excitement. Given that BZD withdrawal is more frequently associated with motor hyperactivity, excited catatonia may not be reported as such[128]. A significant number of these reports described a series of concurrent psychiatric and GMCs that could have played a role in the development of catatonia, mainly depression[128], dementia[57], pneumonia, and infectious exacerbation of chronic obstructive pulmonary disease[128]. Rosebush and Mazurek[186] suggest the possibility that older individuals may be more vulnerable to developing catatonia upon BZD withdrawal, particularly if the drug is rapidly tapered or abruptly discontinued in patients who have taken them for a long time.

In relation to catatonia secondary to psychiatric conditions, this syndrome is more frequently associated with mood disorders than with SSD, as occurs in patients between 18 and 65 years of age. In this population, mood disorders were associated with a 2.7-fold higher risk of developing catatonia compared to psychotic conditions[16]. Again, in patients with affective disorders, age could be a risk factor for developing catatonia. A naturalistic cohort study in BD patients showed that it could present more frequently in older people with catatonic features compared with younger people[187]. As in affective conditions, most of the reports of catatonia in SSD patients have acute psychotic and/or depressive psychopathology and various organic disorders. Although catatonia has been described in practically all the mental conditions of our classification systems, in older adults, cases published outside of affective and SSD disorders are anecdotal and probably due to lack of recognition.

General treatment recommendations on catatonia are derived from case reports or observational studies due to the lack of randomized controlled trials[188]. Despite a possible publication bias, usual treatments, such as BZDs and ECT, show excellent response rates and are considered effective in older adults[5,6,143,144]. Lorazepam is the most extensively used BZD, but other options (Table 5) were tested with good responses. ECT is considered the most successful treatment for catatonia. It is also a safe and effective option for treating catatonia in older patients, regardless of the etiology[5,6]. Some studies have suggested that ECT may be more effective in older patients than in other age groups[139]. It remains controversial whether ECT should be considered a first-line treatment in older patients when catatonia symptoms appear in the context of a MDD[150]. Faster and higher remission rates have been described with ECT in comparison with antidepressant medications. Therefore, it seems reasonable to consider ECT as a priority option if catatonia is present and the underlying condition is also responsive to ECT [150]. There are interesting descriptions of the response to catatonia treatment with other drugs;

however, we can consider these options as a third-line treatment because of the limited literature available on the matter (Table 5).

Our review has important limitations, the main one being that all the conclusions are based on the results of mostly case reports and few prospective studies. Publication bias may be present, and the heterogeneity of the prospective studies does not allow for qualitative analysis. The hypotheses presented here will have to be confirmed in prospective studies designed specifically for that purpose. However, the clinical correlates of all these cases significantly coincide with the results of prospective studies, regardless of the year or place of publication or etiology of catatonia. The most important strength is the summarizing of all the bibliographies on catatonia in older adults published since inception in the main medical databases until December 2021, using articles obtained through a systematic search following the PRISMA recommendations.

CONCLUSION

Catatonia in older people is highly prevalent and is associated with affective disorders, GMCs, and SSDs in that order of frequency, although its etiology is frequently multifactorial. GMCs, mainly dementia and other neurologic disorders, have a significant role in the etiology, and this is sometimes overlooked. Older patients, compared to younger patients, have a higher risk of developing catatonia in BD, in psychiatric liaison services, and they may be more vulnerable to developing catatonia with BZD withdrawal. Age, together with other risk factors, was significantly associated with the incidence of DVT, NMS poor outcome, other complications and mortality. The response to symptomatic treatment with BZDs and ECT is very good and safe, and other effective options are also available. The simultaneous treatment of the etiology of catatonia is also fundamental. Specifically, designed prospective studies are needed to more accurately identify the clinical correlates of catatonia in older people.

ARTICLE HIGHLIGHTS

Research background

Catatonia in older people is an underrecognized and undertreated systemic medical syndrome despite having specific treatment that has shown great effectiveness. These patients are at increased susceptibility of developing potentially life-threatening complications.

Research motivation

Systematic reviews on this topic have not been conducted. Similar previous reviews were not systematic, and since their publication, the number of papers in this regard has practically doubled. We considered that an update was necessary.

Research objectives

This review aimed to synthesize all the published literature related to catatonia in older patients. This summary will provide up-to-date knowledge about this condition.

Research methods

A comprehensive systematic review was conducted according to PRISMA recom-mendations. An extensive search strategy was developed, and the MEDLINE, EMBASE, and PsycINFO databases were searched. Screening was completed in duplicate. Papers that investigated issues related to catatonia and/or catatonic symptoms in older people with an English abstract available were included. Additionally, we provided all the clinical correlates of our series of catatonia in a psychogeriatric ward.

Research results

In total, 173 articles were considered in this systematic review. Most of them were case reports and case series (143), and only 11 were prospective cohort studies. Catatonia in older people is highly prevalent, and in most cases, its etiology is multifactorial. Neurological disorders could play a very important role in catatonia development; in part, cardiovascular risk factors could explain this association. BZDs and ECT are very effective and well tolerated treatments.

Research conclusions

This systematic review provides a comprehensive summary of catatonia in older people. These patients have a higher risk of developing catatonia than younger patients with BD in the general hospital and secondary to BZD withdrawal. Age is related, within other risk factors, to poor NMS prognosis and the development of complications.

Research perspectives

The current review revealed that the number and quality of studies on this issue are scarce. Given the high morbidity of catatonia in older people, prompt identification and treatment are essential. Thus, further prospective research is warranted to more accurately identify all the clinical aspects of catatonia in older people.

FOOTNOTES

Author contributions: Jaimes-Albornoz W and Serra-Mestres J designed this study and completed article screening, data extraction, analysis and interpretation as well as manuscript preparation; Isetta M prepared and wrote the methods section, acquired data and performed initial screening; Ruiz de Pellon-Santamaria A, Nizama-Vía A and Albajar I completed additional data extraction, analysis and interpretation and prepared and wrote manuscript subsections; all authors read and approved the final manuscript.

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SCIENTOMETRICS

Burnout amongst radiologists: A bibliometric study from 1993 to 2020

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Abstract

BACKGROUND

Burnout amongst radiologists is common in many different institutions and is increasing day by day. To battle burnout, we have to address the root causes already recognized in published literature. Therefore, it is crucial to examine and discern important publications.

AIM

To provide evidence-based data and trends related to burnout in radiologists so that researchers can work on it further and develop preventive strategies to overcome this problem.

METHODS

Bibliometric analysis conducted by two independent reviewers separately used Scopus Library for data extraction by using medical subject heading and International Classification of Diseases keywords. Forty-nine articles were selected for analysis after an extensive scrutiny. Statistical Package for the Social Sciences version 20 was used for analysis. Pearson correlation coefficient, Kruskal Wallis test, and Mann-Whitney U test were applied.

RESULTS

The most productive period with regards to the number of publications was between 2017 and 2019. A total of 160 authors contributed to the topic burnout among radiologists, with an average of 3.26 authors *per* paper. About 41.68% of the authors were female, whilst 35% of them were first authors. The co-citation analysis by author involved 188 cited authors, 13 of whom were cited at least 70 times. Only six out of forty-nine studies were funded by various government

institutions and non-governmental organizations.

CONCLUSION
Current analysis casts a spotlight on important trends being witnessed in regard to the mental health of radiologists, including lack of funding for mental health research, narrowing of female *vs* male citation gap, as well as authorship and citation trends.

Key Words: Bibliometric; Analysis; Burnout; Radiologist; Stress; Scientometrics

Core Tip: Our analysis casts a spotlight on important trends being witnessed in regard to the mental health of radiologists. These include lack of funding for mental health research, narrowing of female *vs* male citation gap, as well as authorship and citation trends. By studying these patterns, we can understand key areas lacking in the current bulk of radiological research and subsequently address them to improve the long-term yield, variety, and impact of radiological studies.

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INTRODUCTION

Burnout is a syndrome described in International Classification of Diseases 11th edition as a result of chronic workplace stress that has not been successfully managed. It is characterized by feelings of exhaustion, negativism, and reduced professional efficacy[1,2]. Burnout is a major problem that is affecting multiple specialties[3]. The Medscape National Physician Burnout and Depression Report of 2018 conducted a survey that involved 15000 physicians from different specialties. It revealed that 42% of physicians were burned out, 12% were feeling depressed, and 3% were clinically depressed[4]. According to National Physician Burnout and Suicide Report 2020, radiologists rank among the top five specialties most burned out. Diagnostic radiologists have a higher rate of burnout than the average for all physicians[5]. Several studies have shown burnout in both radiology physicians and radiology trainees[6,7].

Burnout amongst radiologists is common in many different institutions and is increasing day by day. Shanafelt *et al*[8] stated the prevalence of burnout among radiologists in the United States to be 61.4% (n = 261) in 2014; a statistically significant increase from 47.7% (n = 216) in 2011[8]. Burnout in radiologists is also common in Canada because of increased workload and employment constraints[9]. A study conducted in Saudi Arabia concluded that one-fourth of radiology residents have high burnout rates [10]. These high rates of burnout not only affect the physicians' well-being but also their patients and the healthcare system as a whole. It is associated with medical errors, lapses in patient safety, disruptive workplace behaviors, depression, and substance abuse[11]. People suffering from burnout are also at an increased risk of cardiovascular-related events, metabolic syndrome, systemic inflammation, and impaired immunity[12].

Essentially, bibliometric is the application of quantitative analysis and statistics to publications such as journal articles and their accompanying citation counts[13]. Analysis of the citation counts can reveal the most productive authors, countries, institutions, and journals within a particular research area[14]. The procedure is transparent, and results can be reproduced using the same method and are scalable. It serves the purpose of guiding limited resources to important research areas[14]. This research will provide evidence based data and trends related to burnout in radiologists so that researchers can work on it further and develop preventive strategies to overcome this problem.

MATERIALS AND METHODS

Data extraction software

Scopus Library was selected as the preferred library for data extraction because of its extensive coverage of articles from all over the globe, it is faster and operator friendly, and citation analysis is faster as compared with Web of Science, Google Scholar, and PubMed[15].

Article selection

Only original articles were included in research to maintain authenticity of the paper. Reviews, editorials, reports, guidelines, and commentary were excluded. Articles written in English language were only included in the study. Only articles related to consultant radiologist and radiology trainees/postgraduates were selected for analysis. Articles related to radiology nurses, radiology technicians, and other helping staff were excluded in order to get an authentic estimation of burnout among radiology doctors. There was no limitation on the basis of time of publication of article.

Keywords selection

The International Classification of Diseases 11th edition, medical subject heading, and review articles from various sources were used to form a final list of keywords. They were searched in abstract, article title, and keywords section of articles. Keywords include "burnout", "burnout syndrome", "stress", "mental stress", "strain", "mental strain", "overload", "exhaustion", "mental distress", "depersonalization", "companion fatigue", "emotional wellbeing", "job satisfaction", "radiologist", "radiology resident", "radiology trainee", "radiology postgraduate", "radiology post-graduate", "consultant radiologist", "radiology department", and "radiology fellow".

Data extraction

Data were extracted in the month of March 2020 by two authors (MFHQ and MHA) separately and a final list of articles was prepared. A difference of 7.4% was identified between both the lists, which was resolved by consulting a third reviewer (DM). The final list of articles was composed by extensive vetting of articles through complete text reading of articles and determining its characters based on inclusion criteria. Forty-nine articles were selected for analysis. Data were extracted to Microsoft Excel from Scopus consisting of name of article, year of publication, number of citations, digital object identifier, affiliation of authors, country of origin of authors, journals, H-factor, and funding of study. Gender of authors was determined by searching for their profiles on official institutions sites. Impact factor was determined by Journal Citation Report 2019.

Statistical analysis

Statistical Package for the Social Sciences (SPSS), version 20 (Armonk, NY, United States) was used for analysis. In order to determine association between impact factor of journals and citations, the Pearson correlation coefficient test was used. In order to determine impact of funding and citations, Kruskal Wallis test was applied. For association of gender with citations, Mann-Whitney U test was applied. $P < 0.05$ was considered as significant. Co-citation analysis was performed using Vos Viewer version 1.6.14.

RESULTS

All the articles on burnout among radiologists with their total citation and digital object identifier are given Table 1 in descending order in reference to their year of publication. The mean number of citations for the article in Table 1 was 27, while the median was 10 (interquartile range = 18). When citations of all the articles were summed up, the sum was found to be 1328, of which 5.9% ($n = 76$) were self-citation. The number of citations *per* year ranged from one to 12 (Table 1).

Figure 1 shows the total number of citations *per* year, with the graph increasing rapidly after 2016. The most productive time period with regards to number of publications was between 2017 and 2019, in which 16 articles were published out of 49, as shown in Figure 2, while the least productive time period was before 1993, during which not a single article was published on burnout among radiologists.

Top rated journals and institutions

All 49 articles were published in 29 journals belonging to different parts of the world; journals were ranked according to the greatest number of publications, which are shown in Table 2, along with their citations and impact factors. Impact factors of journals ranged from 0.32-15. Statistically significant association was found between number of publications and journal impact factor, with P value of < 0.01, while journal impact factor and number of citations was also significant, with P value of 0.02.

Harvard Medical School and Università Cattolica Del Sacro Cuore, Rome were the leading institutions, with more than five publications, respectively, followed by University of Washington, Seattle (four publications) and University of Texas MD Anderson Cancer Centre (three publications) (Supplementary Table 1).

Top authors and their countries of origin

A total of 160 authors contributed to the topic burnout among radiologists, with an average of 3.26 authors *per* paper. Author *per* article ranged from 1 to 12. Nineteen out of 160 worked on more than one article, as shown in Table 3 along with their H-index and gender. In total, 41.68% of the authors were female, while 35% of them were first authors. Statistically significant association was found between

Table 1 Articles with digital object identifier and number of citations

No	Article title	DOI	Number of citations
1	Burnout among Interventional Radiologists	10.1016/j.jvir.2019.06.002	1
2	Burnout in Canadian Radiology Residency: A National Assessment of Prevalence and Underlying Contributory Factors	10.1177/0846537119885672	1
3	Burnout in Academic Radiologists in the United States	10.1016/j.acra.2019.12.029	1
4	Radiologist Burnout According to Surveyed Radiology Practice Leaders	10.1016/j.jacr.2019.07.008	5
5	Burnout in Chairs of Academic Radiology Departments in the United States	10.1016/j.acra.2018.12.006	3
6	Association of Racial Bias with Burnout among Resident Physicians	10.1001/jamanetworkopen.2019.7457	6
7	Stressors contributing to burnout amongst paediatric radiologists: Results from a survey of the Society for Paediatric Radiology	10.1007/s00247-019-04370-z	3
8	Prevalence of Burnout Among Paediatric Radiologists	10.1016/j.jacr.2018.08.016	10
9	Impact of work hours and sleep on well-being and burnout for physicians-in-training: The Resident Activity Tracker Evaluation Study	10.1111/medu.13757	4
10	Using Wellness Days to Mitigate Resident Burnout	10.1016/j.jacr.2018.09.005	1
11	Burnout Phenomenon and Its Predictors in Radiology Residents	10.1016/j.acra.2019.09.024	0
12	Non-radiation occupational hazards and health issues faced by radiologists-A cross-sectional study of Indian radiologists	10.4103/ijri.IJRI_403_18	1
13	Prevalence of Burnout Among Canadian Radiologists and Radiology Trainees	10.1016/j.carj.2018.05.005	5
14	Burnout: Job Resources and Job Demands Associated with Low Personal Accomplishment in United States Radiology Residents	10.1016/j.acra.2017.12.002	14
15	Burnout: Prevalence and associated factors among radiology residents in New England with comparison against United States resident physicians in other specialties	10.2214/AJR.16.17541	30
16	Emotional Wellness of Current Musculoskeletal Radiology Fellows	10.1016/j.acra.2016.12.024	8
17	Occupational burnout among radiographers, sonographers and radiologists in Australia and New Zealand: Findings from a national survey	10.1111/1754-9485.12547	6
18	Reading efficiency can be improved by minor modification of assigned duties; a pilot study on a small team of general radiologists	10.1007/s11604-017-0629-8	4
19	Prevalence of burnout among musculoskeletal radiologists	10.1007/s00256-017-2578-9	22
20	Burnout, stress and satisfaction among Australian and New Zealand radiation oncology trainees	10.1111/1754-9485.12541	14
21	'You can't be a person and a doctor': The work-life balance of doctors in training – A qualitative study	10.1136/bmjopen-2016-013897	26
22	Factors associated with burnout among residents in a developing country	10.1016/j.amsu.2016.01.090	17
23	Evaluation of the effect of a 1-day interventional workshop on recovery from job stress for radiation therapists and oncology nurses: A randomised trial	10.1111/1754-9485.12322	15
24	Quality care, public perception and quick-fix service management: A Delphi study on stressors of hospital doctors in Ireland	10.1136/bmjopen-2015-009564	8
25	A study on the relationship between stress and fatigue and the musculoskeletal symptoms experienced by Korean radiation workers	10.1589/jpts.27.427	4
26	Stress, satisfaction and burnout amongst Australian and New Zealand radiation oncologists	10.1111/1754-9485.12217	35
27	Work-related stress, musculoskeletal disorder complaints, and stress symptoms among radiographers in the northern part of Jordan	10.1016/j.jmir.2014.04.002	0
28	Audit of the job satisfaction levels of the UK radiography and physics workforce in UK radiotherapy centres 2012	10.1259/bjr.20130742	12
29	Association of work-related stress with depression and anxiety in radiologists	10.1007/s11547-013-0355-y	12
30	Work stress and metabolic syndrome in radiologists: First evidence	10.1007/s11547-013-0329-0	23
31	Results of a Canadian study examining the prevalence and potential for developing compassion fatigue and burnout in radiation therapists	10.1017/S1460396914000144	5

32	Is there a gender gap in Italian radiology? A cross-sectional study	10.1016/j.ejrad.2013.04.007	11
33	The emotional wellness of radiology trainees: Prevalence and predictors of burnout	10.1016/j.acra.2012.12.018	29
34	The incidence of burnout or compassion fatigue in medical dosimetrists as a function of various stress and psychologic factors	10.1016/j.meddos.2012.07.006	4
35	Burnout in therapy radiographers in the UK	10.1259/bjr/16840236	25
36	Anxiety and depression in doctors undergoing postgraduate training courses at Armed Forces Postgraduate Medical Institute Rawalpindi	Not Available	0
37	The relevance of psychological support to medical resident and specializing in radiology and imaging diagnosis	10.1590/S0100-39842011000200006	1
38	An investigation into work related stressors on diagnostic radiographers in a local district hospital	10.1016/j.radi.2009.09.005	11
39	Satisfaction at work among radiologists	10.1007/s11547-009-0461-z	14
40	Work stress, satisfaction and burnout in New Zealand radiologists: Comparison of public hospital and private practice in New Zealand: Radiology-Original article	10.1111/j.1754-9485.2009.02063.x	19
41	Job stress and job satisfaction of physicians, radiographers, nurses and physicists working in radiotherapy: A multi-centre analysis by the DEGRO Quality of Life Work Group	10.1186/1748-717X-4-6	71
42	Occupational stress and its predictors in radiographers	10.1016/j.radi.2006.09.008	14
43	Work stress in radiologists. A pilot study	10.1007/s11547-008-0259-4	35
44	Repetitive Stress Symptoms in Radiology: Prevalence and Response to Ergonomic Interventions	10.1016/j.jacr.2008.01.014	31
45	The informational roles and psychological health of members of 10 oncology multidisciplinary teams in the UK	10.1038/sj.bjc.6602816	66
46	Satisfaction and stress factors in the radiologist's profession	Not Available	5
47	Job stress and satisfaction among clinical radiologists	10.1053/crad.1999.0379	62
48	Mental health of hospital consultants: The effects of stress and satisfaction at work	10.1016/S0140-6736(96)90077-X	628
49	Job satisfaction in the medical imaging profession: alleviating the shortage of personnel	Not Available	6

DOI: Digital object identifier; UK United Kingdom.

Table 2 Top rated journals with number of publications, citations, and impact factor

No.	Journals	No of document	Citation	Impact factor
1	*Academic Radiology*	6	55	2.0
2	*Journal of Medical imaging and Radiation Oncology*	5	89	1.2
3	*Journal of the American College of Radiology*	4	47	1.6
4	*Radiologia Medica*	4	84	1.8
5	*BMJ Open*	2	34	2.6
6	*British Journal of Radiology*	2	37	2.1
7	*Canadian Association of Radiologist Journal*	2	06	0.9
8	*Radiography*	2	25	0.7

female as first author and number of citations, with a *P* value of 0.03.

Authors belonged to 20 different countries of the world (Supplementary Table 2). United States was the leading country, with the greatest number of researchers, followed by United Kingdom, Italy, Australia, Canada and South Korea as shown in Table 4.

Co-citation analysis

Co-citation analysis is important to understand if there is a subject similarity between two documents. Co-citation analysis by author shows the intellectual structure of scientific disciplines. When two authors are cited together in a third document, they are said to be co-cited. If two authors are cited together in more papers, the stronger the relationship, hence greater the co-citation strength and therefore, higher will be their probability to be logistically related in terms of substance and linguistics.

Table 3 Top rated authors with number of articles and H-index

Author	Gender	Number of articles	H-index
Magnavita N	Female	5	25
Fileni A	Male	4	13
Mulcahy MJ	Male	4	6
Chew FS	Male	3	26
Ahmed FS	Male	2	10
Ayyala RS	Female	2	04
Bergamaschi A	Male	2	31
Ganeshan D	Male	2	16
Graham J	Female	2	12
Guenette JP	Male	2	7
Leung J	Male	2	8
Probst H	Female	2	8
Ramirez AJ	Female	2	45
Relyea-Chew A	Female	2	13
Richards MA	Male	2	64
Rioseco P	Female	2	4
Ruzal-Shapiro C	Female	2	20
Smith SE	Female	2	14
Taylor GA	Male	2	48

Table 4 Leading countries on the basis of origin of authors

Country/Territory	Number of author
United States	18
United Kingdom	8
Italy	5
Australia	4
Canada	4
South Korea	2

The co-citation analysis by author involved 188 cited authors, 13 of whom were cited at least 70 times. The authors that were most cited included Schulze W, followed by Schlen S and Dormin C. Supplementary Figures 1 and 2 depict the network; the names of authors are shown by a circle. The importance of an author is indicated by the size of the circle, the distance between the labels signifies the relevance, the connection represents collaboration, and the same color indicates belonging to the same cluster.

Funding and its relationship with citations

Only six out of forty-nine studies were funded by various government institutions and non-governmental organizations. Five of them yielded a positive result as compared to hypothesis. There was no significant relationship between funding and number of citations (P = 0.69). Funding organization is shown in Table 5.

Table 5 Funding organization for research

Funding organization	Frequency
National Institutes of Health	2
Mayo Clinic	1
National Cancer Institute	1
National Heart, Lung, and Blood Institute	1
University of Texas MD Anderson Cancer Centre	1

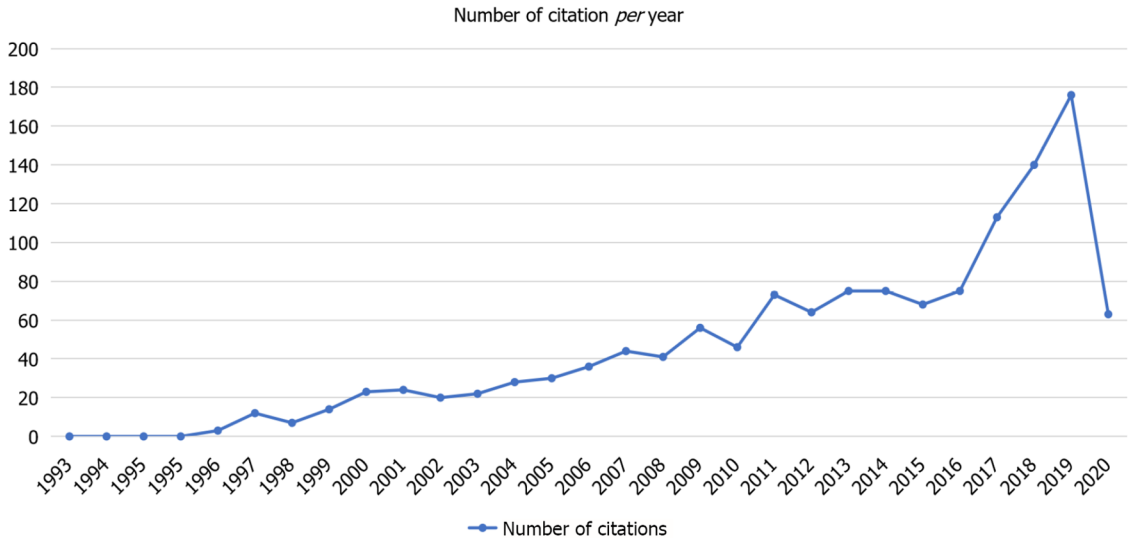

Figure 1 Number of citations *per* year.

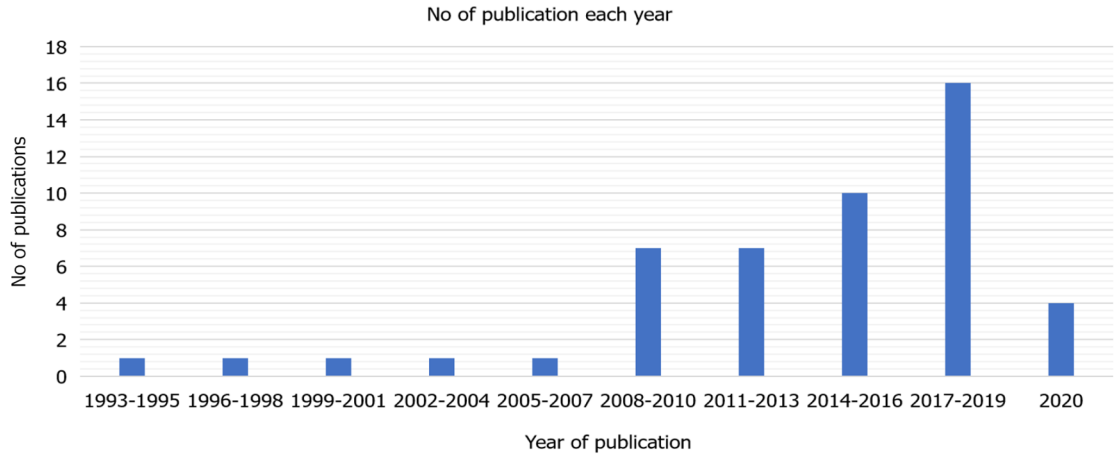

Figure 2 Number of publications *per* year.

DISCUSSION

Year of publications of articles and citations

Articles for most notable work burnout towards the field of radiology are listed in Table 1. The top cited source 'Mental health of hospital consultants: The effects of stress and satisfaction at work' was cited in 1996. The second most cited source 'Job stress and job satisfaction of physicians, radiographers, nurses and physicists working in radiotherapy: A multi-centre analysis by the DEGRO Quality of Life Work Group' was cited in 2009. The third most cited source was 'The informational roles and psychological health of members of 10 oncology multidisciplinary teams in the UK' was cited in 2005. This shows that there does not seem to be a particular trend amongst the most cited sources. They range from 1996-2009.

However, what can be noted is that the top cited sources show a more general picture in the trend of burnout. In other words, the top cited sources involve multiple disciplines and healthcare workers such as consultants in different fields and different health care workers in the field of radiology. This allows the articles to be cited by multiple authors in different fields. If radiology-specific studies are seen then the trend shows that the top cited articles, which include 'Stress, satisfaction and burnout amongst Australian and New Zealand radiation oncologists' and 'Burnout: Prevalence and associated factors among radiology residents in New England with comparison against United States resident physicians in other specialties', are sited in the year 2017.

As far as the trend, in the field of radiology, most of the citations in radiology peaked after 1979[16]. Furthermore, the trend of psychiatric disorders and neuroimaging increased after 1989, with most neuroimaging studies produced in 2007[17]. However, there are no particular bibliometric analyses produced for depression and burnout amongst healthcare workers. The trend in this particular research shows that studies on burnout started in 1993, but the bulk of studies involving burnout in radiologists were seen between 2017-2019.

Top authors and their countries of origin

Table 2 shows that the top number of citations, which were (n = 89) and (n = 84), were seen in the journals the *Journal of Medical imaging* and *Radiation Oncology and Radiologia Medica*. These journals have lower impact factors compared to other journals such as *BMJ Open*. This refutes Bradford's law that states that most authors prefer publishing in core journals because straying from main articles reduces the impact of an article[18]. In other words, journals with more citations do not correlate with journals that have higher impact factors, specifically for the topic of burnout.

The impact of each author and their work is shown in Table 3. An observation to be made is that the number of articles does not correlate with an increased H-index. In fact, the authors with the highest H-index only have two articles published, whereas the author with five articles has a lower H-index than the top authors. The highest H-index was seen by author, Richard MA, with an H-index of 64. He has only published two articles. The author, Magnavita N has five articles published but has an H-index of 25. This is supported by an article that states that H-index is loosely related to the number of articles [19]. Rather, H-index is more closely associated with academic rank in certain fields[20]. Therefore, more articles do not correlate with high H-indexes in the topic of burnout in radiology.

The study shows that the majority of papers were published in the United States with a number of 18 authors. This trend seems to be the basic trend in many current and older studies in multiple fields[21]. A study by Tran *et al*[22] about depression and artificial intelligence showed the same trend that more papers were produced from the United States[22]. This trend happens because, according to an article on reviewer analysis, it seems that papers from the United States are reviewed and considered more highly than other papers from different countries[23].

Overall, 58.3% of the authors were males and 41.7% were female, and the proportion of female first authors (84.0%) was larger than the proportion of male first authors (82.3%). The differences in total authors could be attributed to the fact that, according to the World Health Organization, the number of male physicians on average worldwide generally outweighs their female counterparts[24]. However, the slightly higher proportion of female first authors indicates women are better at collaborating with their peers for research purposes. This could be due to their more egalitarian nature[25] and hence a more collaborative approach in the workforce. Our analysis found a significant association (P = 0.03) between female first authors and number of citations, indicating that female first authors tended to be cited more than their male counterparts. This is in contrast to a prior study that reported low citations in primary female authors[26], which could indicate a possible narrowing of prior lack of female representation.

Co-citation analysis

All of the articles in our top-cited list focused on the prevalence, causes, and prevention aspect of burnout. This was also demonstrated by the co-citation analysis by author. Co-citation creates clusters of research for the articles that are cited together. These clusters reveal which researchers all over the world are working on burnout among radiologists, and this research will have a substantial effect on the betterment of working environment and preventive strategies. Interestingly, the conclusions of these studies were consistent and help the reader to determine the burden of disease and its importance.

Funding and its relationship with citations

Only 6 out of 49 studies were funded by various government institutions and non-governmental organizations. Five of them yielded a positive result as compared to the hypothesis. Our analysis shows that most research was privately funded/funded by non-government agencies, hence raising the ethical concerns about a possible conflict of interest in regards to reporting of results[27]. Moreover, we found no significant relationship between funding and the number of citations (P = 0.69), which is in contrast to prior research that claimed grant sponsored articles to receive generally more citations and be published in higher quality journals[28].

It could also be concluded that government emphasis and subsequent funding on mental health research regarding radiologists remain small-scale despite adequate data showing significant burnout being noted in one-fourth of all radiologists[29], while another study noting only 19% of radiologists having mechanisms to address burnout[30].

Limitations

Inherent limitations of bibliometric analysis should be considered, the first being technical problems: Spelling and name changes, progressive changes in the database, language biases, and problems with journal impact factor[31]. These limitations apply to our study as well; nevertheless we tried to alleviate their impact by choosing articles only from the Scopus database to ensure some degree of uniformity in method and use of citations. However, using solely Scopus predisposes us to the exclusion of influential studies present in other databases and the exclusion of any studies before 1996 due to the lack of complete citation information in the database before that year[32,33].

CONCLUSION

Our analysis casts a spotlight on important trends being witnessed in regards to the mental health of radiologists. These include lack of funding for mental health research, narrowing of female *vs* male citation gap, as well as authorship and citation trends. By studying these patterns, we can understand key areas lacking in the current bulk of radiological research and subsequently address them to improve the long-term yield, variety, and impact of radiological studies.

ARTICLE HIGHLIGHTS

Research background

Burnout is an important topic in today's era, with many articles trying to figure out the causes and stressors in the medical field. As a health community, we need to collect all the data for burnout to first understand the prevalence in each area and then the causes for each area. Burnout among radiologists is common in many different institutions and is increasing.

Research motivation

To battle burnout, we have to address the root causes already recognized in published literature. It is crucial to examine and discern important publications. This analysis will allow us to see which areas have collected data on the prevalence and causes of burnout. This analysis will also allow us to determine the missing areas from where we need data.

Research objectives

The current study will provide evidence-based data and trends related to burnout in radiologists so that researchers can work on it further and develop preventive strategies to overcome this problem.

Research methods

Bibliometric analysis was conducted using Scopus Library for data extraction by using Medical subject heading and International Classification of Diseases keywords. Forty-nine articles were selected for analysis after extensive scrutiny. Statistical Package for the Social Sciences, version 20 was used for analysis. Pearson correlation coefficient, Kruskal Wallis test, and Mann-Whitney U test were applied.

Research results

The most productive time period with regards to the number of publications was between 2017 and 2019. A total of 160 authors contributed to the topic burnout among radiologists, with an average of 3.26 authors *per* paper. About 41.68% of the authors were female, while 35% of them were first authors. The co-citation analysis by the author involved 188 cited authors, 13 of whom were cited at least 70-times. Only six out of 49 studies were funded by government institutions and non-governmental organizations.

Research conclusions

The current analysis casts a spotlight on important trends being witnessed in regards to the mental health of radiologists, including lack of funding for mental health research, narrowing of female *vs* male citation gap, as well as authorship and citation trends.

Research perspectives

This analysis provides high yield information that will allow for the identification of additional areas of interest that need to be addressed and what information has high value. This information can be used in the long run to produce higher-quality papers.

FOOTNOTES

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