ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2017 June 22; 7(2): 77-132

Published by Baishideng Publishing Group Inc

WJP World Journal of Psychiatry

A peer-reviewed, online, open-access journal of psychiatry

Editorial Board

2016-2019

The *World Journal of Psychiatry* Editorial Board consists of 398 members, representing a team of worldwide experts in psychiatry. They are from 43 countries, including Australia (15), Austria (5), Azerbaijan (1), Belgium (1), Brazil (6), Canada (22), China (18), Colombia (2), Croatia (2), Czech Republic (1), Denmark (1), Egypt (2), Finland (5), France (9), Germany (20), Greece (6), Hungary (10), India (7), Iran (4), Ireland (3), Israel (12), Italy (31), Japan (16), Mexico (3), Netherlands (12), New Zealand (2), Norway (5), Poland (3), Portugal (1), Russia (1), Singapore (2), Slovenia (1), South Africa (1), South Korea (4), Spain (20), Swaziland (1), Sweden (7), Switzerland (6), Tunisia (1), Turkey (9), United Arab Emirates (1), United Kingdom (28), and United States (91).

Nela Pivac, *Zagreb*

Czech Republic

Ladislav Hosak, *Hradec Kralove*

Denmark

Betina Elfving, *Risskov*

Egypt

Yasser Mohamed Amr, *Tanta*
Sherifa A Hamed, *Assiut*

Finland

Jyrki Jaakko Antero, *Turku*
Liisa Keltikangas Jarvinen, *Helsinki*
Seppo Kahkonen, *Helsinki*
Jouko Miettunen, *Oulu*
Simo Saarijarvi, *Turku*

France

Jean-Michel Azorin, *Marseille*
Michel S Bourin, *Nantes*
Jean-Christophe Cassel, *Strasbourg*
Emmanuelle Corruble, *Le Kremlin Bicêtre*
Marion Feldman, *Paris*
Antoine Guedeney, *Paris*
Yannick Marchalant, *Marseille*
Lejoyeux Michel, *Paris*
Hervé Perron, *Lyon*

Germany

Michael Deuschle, *Mannheim*
Manfred M Fichter, *München*
Eberhard Fuchs, *Göttingen*
Peter J Gebicke-Haerter, *Mannheim*
Heinz Häfner, *Mannheim*
Florian Lang, *Tuebingen*
Undine Emmi Lang, *Berlin*
Adrian Loerbroks, *Mannheim*
Wolfgang Maier, *Bonn*
Matthias J Müller, *Giessen*
Ulrich W Preuss, *Halle*
Ralf Pukrop, *Cologne*
Matthias W Riepe, *Ulm*
Marcus Christian Rosenhagen-Lapoirie, *Berlin*
Frank Schneider, *Aachen*
Ulrich Schweiger, *Lübeck*
Thomas Straube, *Jena*
Philipp Arthur Thomann, *Heidelberg*
Ursula Voss, *Bonn*
Hans-Ulrich Wittchen, *Dresden*

Greece

Panagiotis P Ferentinos, *Athens*
Sifis Micheloyannis, *Crete*
Charalampos I Mitsonis, *Athens*
George Panagis, *Rethymno*
Snorri Bjorn Rafnsson, *Athens*
Petros Skapinakis, *Ioannina*

Hungary

Balazs Antus, *Budapest*
Judit Balazs, *Budapest*
Csaba Barta, *Budapest*
Sandor Fekete, *Pecs*
Gábor Gazdag, *Budapest*
Szabolcs Keri, *Szeged*
Bertalan Petho, *Budapest*
Andrea Szekely, *Budapest*
Zsolt Szabolcs Unoka, *Budapest*
Viktor Voros, *Pecs*

India

Subho Chakrabarti, *Chandigarh*
BN Gangadhar, *Bangalore*
Sandeep Grover, *Chandigarh*
Samir Kumar Praharaj, *Karnataka*
Saddichha Sahoo, *Bangalore*
Jitendra Kumar Trivedi, *Lucknow*
Ganesan Venkatasubramanian, *Bangalore*

Iran

Shahin Akhondzadeh, *Tehran*
Ahmad R Dehpour, *Tehran*
Hamidreza Roohafza, *Isfahan*
Vandad Sharifi, *Tehran*

Ireland

Timothy G Dinan, *Cork*
Thomas Frodl, *Dublin*
David James Meagher, *Limerick*

Israel

Alan Apter, *Petach Tikva*
Pinhas N Dannon, *Beer Yaakov*
Uriel Heresco-Levy, *Jerusalem*
Vladimir Lerner, *Be'er Sheva*
Chanoch Miodownik, *Be'er Sheva*
Julia Mirsky, *Beer Sheva*
Alexander Michael Ponizovsky, *Jerusalem*
Shifra Sagy, *Beer-sheva*
Gal Shoval, *Petah Tiqva*
Zahava Haelion Solomon, *Ramat Aviv*
Perla Werner, *Haifa*
Abraham Zangen, *Rehovot*

Italy

A Carlo Altamura, *Milano*
Niki Antypa, *Bologna*
Alessandro Bertolino, *Bari*
Paolo Brambilla, *Milan*
Carlo Faravelli, *Florence*
Athanasios Koukopoulos, *Roma*
Carlo Lai, *Rome*
Giovanni Laviola, *Roma*
Laura Mandelli, *Bologna*
Roberto Maniglio, *Lecce*
Giovanni Martinotti, *Rome*
Andrea Martinuzzi, *Conegliano*
Marianna Mazza, *Roma*
Patrizia Mecocci, *Perugia*
Graziano Onder, *Roma*
Marco Orsetti, *Novara*
Francesco Panza, *Foggia*
Alberto Parabiaghi, *Milan*
Lucilla Parnetti, *Perugia*
Massimo Pasquini, *Rome*
Maurizio Pompili, *Rome*
Alberto Priori, *Milano*
Emilio Sacchetti, *Brescia*
Virginio Salvi, *Turin*
Marco Sarchiapone, *Campobasso*
Gianluca Serafini, *Rome*
Domenico Servello, *Trieste*
Gianfranco Spalletta, *Rome*
Giovanni Stanghellini, *Florence*
Antonio Tundo, *Roma*
Antonio Vita, *Brescia*

Japan

Toshiaki A Furukawa, *Kyoto*
Kenji Hashimoto, *Chiba*
Ryota Hashimoto, *Osaka*
Hideo Honda, *Yamanashi*
Yasuhiro Kaneda, *Tokushima*
Yoshiaki Kikuchi, *Tokyo*
Toru Kobayashi, *Yufu-City Oita*
Hiroshi Kunugi, *Tokyo*
Katsumasa Muneoka, *Tokyo*
Jude Uzoma Ohaeri, *Kuwait*
Motohiro Ozone, *Tokyo*
Shunichiro Shinagawa, *Tokyo*
Akihito Suzuki, *Yamagata*
Takeshi Terao, *Yufu-City Oita*
Rei Wake, *Izumo*
Norio Yasui-Furukori, *Hirosaki*

Mexico

Carlos M Contreras, *Veracruz*
Rogelio Apiquian Guitart, *Mexico City*
Ana Fresán Orellana, *Mexico City*

Netherlands

Anton van Balkom, *Amsterdam*
Inti A Brazil, *Nijmegen*
Eliyahu Dremencov, *Groningen*
SG Geuze, *Utrecht*
Judith Regina Homberg, *Nijmegen*
Remko Van Lutterveld, *Utrecht*
Henriette Nieman, *Amsterdam*
Liesbeth Reneman, *Amsterdam*
Jan Spijker, *Utrecht*
Joris C Verster, *Utrecht*
Wilma Vollebergh, *Utrecht*
Richard Christiaan Oude Voshaar, *Groningen*

New Zealand

Juan J Canales, *Christchurch*

Susanna Every-Palmer, *Wellington*

Norway

Trond Heir, *Oslo*
Stein Opjordsmoen Ilner, *Oslo*
Jorg Richter, *Oslo*
Bjørn Rishovd Rund, *Oslo*
Lars Tanum, *Oslo*

Poland

Andrzej Kiejna, *Wroclaw*
Andrzej Kokoszka, *Warszawa*
Janusz K Rybakowski, *Poznan*

Portugal

Vasco Videira Dias, *Lisbon*

Russia

Yuri B Yurov, *Moscow*

Singapore

Anqi Qiu, *Singapore*
Philip Yap, *Singapore*

Slovenia

Matej Kravos, *Maribor*

South Africa

Jonathan Kenneth Burns, *Durban*

South Korea

Won-Myong Bahk, *Seoul*
Sook-Haeng Joe, *Seoul*
Myung-Sun Kim, *Seoul*
Yong-Ku Kim, *Ansan*

Spain

Lorenzo Livianos Aldana, *Valencia*
Francisco J Acosta Artiles, *Las Palmas de Gran Canaria*
Miquel Bernardo, *Barcelona*
Angel LM Gonzalez, *Salamanca*
César Gonzalez-Blanch, *Santander*
Susana Ochoa Guerre, *Barcelona*
Gonzalo Haro, *Castellon de la Plana*
Juan Jose Lopez-ibor, *Madrid*
Peter J McKenna, *Barcelona*
Juan D Molina, *Madrid*
Manuel Munoz, *Madrid*
Jose M Olivares, *Vigo*
Joaquin Valero Oyarzabal, *Reus*
Rafael Penades, *Barcelona*
Victor Peralta, *Pamplona*
Migdyrai Martin Reyes, *Navarre*
Gregorio Rodríguez-Boto, *Madrid*
Pilar A Saiz, *Oviedo*
Julio Sanjuan, *Valencia*
Judith Usall, *Barcelona*

Swaziland

Uwe Herwig, *Zürich*

Sweden

Lena Flyckt, *Stockholm*
Hans Liljenstrom, *Uppsala*
Aleksander A Mathe, *Stockholm*
Jorg Melzer, *Zurich*
Ellenor Mittendorfer Rutz, *Stockholm*
Åke Wahlin, *Stockholm*
Henrik Zetterberg, *Molndal*

Switzerland

Heinz Boeker, *Zurich*
Stefan J Borgwardt, *Basel*
Serge Brand, *Basel*
Eich Dominique, *Zurich*
Yasser Nassib Khazaal, *Geneva*
Wulf Rössler, *Zurich*

Tunisia

Anwar Mechri, *Monastir*

Turkey

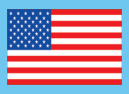
Feryal Cam Celikel, *Tokat*
Ali Saffet Gonul, *Izmir*
Mustafa Gulec, *Erzurum*
Ahmet Turan Isik, *Istanbul*
Ilker Ozyildirim, *Ordu*
Vedat Sar, *Istanbul*
Haluk A Savas, *Gaziantep*
Ozcan Uzun, *Ankara*
Burcu Balam Yavuz, *Ankara*

United Arab Emirates

Man Cheung Chung, *Abu Dhabi*

United Kingdom

MJ Arranz, *London*
Muhammad Ayub, *Durham*
Jim Barnes, *Oxford*
Philip Benson, *Aberdeen*
Andrea E Cavanna, *Birmingham*
Goultchira Chakirova, *Edinburgh*
Imran Bashir Chaudhry, *Accrington*
Ruoling Chen, *London*
Robert E Drake, *Hanover*
Jacki Gordon, *Glasgow*
Richard Gray, *Norwich*
Susham Gupta, *London*
Ellen Harley, *East Sussex*
Veena Kumari, *London*
Keith R Laws, *Hatfield*
Kwang-Hyuk Lee, *Sheffield*
Keith Lloyd, *Swansea*
Isaac Marks, *London*
Kevin Morgan, *London*
Joaquim Radua, *London*
Peter Anthony Sargent, *Oxford*
Viren Swami, *London*
Tim Thornton, *Lancashire*
Timothea Toulopoulou, *London*
Joe John Vattakatuchery, *Warrington*
Panos Vostanis, *Leicester*
Nora S Vyas, *Surrey*
Daniel Fekadu Wolde-Giorgis, *London*



United States

Charles M Beasley, *Indianapolis*
AL Beautrais, *New Haven*
Myron Lowell Belfer, *Boston*
Francine Mary Benes, *Lincoln*
Silvia Bernardi, *New York*
Eric Bui, *Boston*
Xiang-Ning Chen, *Richmond*
Priscilla K Coleman, *Bowling Green*
Kyaien O Conner, *Pittsburgh*
Paul Eugene Croarkin, *Dallas*
Rachel E Dew, *Durham*
Gabriel S Dichter, *Durham*
Ronald S Duman, *New Haven*
Igor Elman, *Belmont*
Elizabeth Flanagan, *New Haven*
Avi L Friedlich, *Charlestown*
Mark A Frye, *Rochester*
Qiang Fu, *Saint Louis*
Thomas D Geracioti, *Cincinnati*
Linda A Gerdner, *Burlington*
Anthony A Grace, *Pittsburgh*
Marco A Grados, *Baltimore*
Temple Grandin, *Fort Collins*
Yue Hao, *La Jolla*
John Hart, *Dallas*
Scott E Hemby, *Winston-Salem*
S Horvath, *Nashville*
Robert H Howland, *Pittsburgh*
Steven K Huprich, *Wichita*
Dawn E Jaroszewski, *Phoenix*
Peter S Jensen, *Rochester*
Arie Kaffman, *New Haven*
Rakesh Karmacharya, *Belmont*
Robert E Kelly, *White Plains*
Aaron S Kemp, *Orange*
Matcheri S Keshavan, *Boston*
Arifulla Khan, *Seattle*
Firas H Kobeissy, *Gainesville*
Karestan C Koenen, *Boston*
Wayne Lack, *Edmond*
Brian Trung Lam, *Long Beach*
Yijun Liu, *Gainesville*
Hong Liu-Seifert, *Indianapolis*
Brett Lu, *Honolulu*
Deborah L Mangold, *San Antonio*
Theo C Manschreck, *Boston*
Bortolato,Marco, *Los Angeles*
Ram K Mishra, *Hamilton*
Serge A Mitelman, *New York*
Howard B Moss, *Maryland*
Orla T Muldoon, *Limerick*
Harald Murck, *Princeton*

World Journal of Psychiatry

Contents

Quarterly Volume 7 Number 2 June 22, 2017

Contents

World Journal of Psychiatry
Volume 7 Number 2 June 22, 2017

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Quarterly

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Psychiatry
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
June 22, 2017

World Journal of Psychiatry

Submit a Manuscript: http://www.f6publishing.com

World J Psychiatr 2017 June 22; 7(2): 77-88

DOI: 10.5498/wjp.v7.i2.77

ISSN 2220-3206 (online)

REVIEW

Understanding the pathophysiology of postpartum psychosis: Challenges and new approaches

William Davies

William Davies, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics and Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff CF24 4HQ, United Kingdom

William Davies, School of Psychology, Cardiff University, Cardiff CF10 3AT, United Kingdom

William Davies, Neuroscience and Mental Health Research Institute, Cardiff University, Cardiff CF24 4HQ, United Kingdom

Author contributions: William Davies is the sole contributor to the article.

Supported by Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, No. MR/L010305/1.

Conflict-of-interest statement: The author has no conflicts of interest to declare.

Manuscript source: Invited manuscript

Correspondence to: Dr. William Davies, School of Psychology, Cardiff University, Tower Building 70, Park Place, Cardiff CF10 3AT, United Kingdom. daviesw4@cardiff.ac.uk
Telephone: +44-29-20870152
Fax: +44-29-20874679

Received: November 7, 2016
Peer-review started: November 10, 2016
First decision: January 14, 2017
Revised: February 8, 2017
Accepted: April 18, 2017
Article in press: April 20, 2017

Published online: June 22, 2017

Abstract

Postpartum psychosis is a severe psychiatric condition which affects 1-2 of every 1000 mothers shortly after childbirth. Whilst there is convincing evidence that the condition is precipitated by a complex combination of biological and environmental factors, as yet the pathophysiological mechanisms remain extremely poorly defined. Here, I critically review approaches that have been, or are being, employed to identify and characterise such mechanisms; I also review a recent animal model approach, and describe a novel biological risk model that it suggests. Clarification of biological risk mechanisms underlying disorder risk should permit the identification of relevant predictive biomarkers which will ensure that "at risk" subjects receive prompt clinical intervention if required.

Key words: *CCN3*; Immune system; Steroid sulfatase; Nephroblastoma-overexpressed; Mouse; Animal model; Risk factor

Core tip: Postpartum psychosis is a severe psychiatric condition affecting a small proportion of women shortly after childbirth. The pathophysiological mechanisms underlying risk for the condition are extremely poorly-defined, but may include perturbed immune function, altered tryptophan metabolism and serotonergic dysfunction. Here, I critically review evidence underlying these assumptions, and discuss a novel model for postpartum psychosis risk, involving maternal deficiency for the enzyme steroid sulfatase, and overexpression of the *CCN* gene family, based upon emerging data from a recently-developed mouse animal model. Identifying

and characterising predictive biomarkers for postpartum psychosis risk will help to ensure prompt clinical intervention if required.

Davies W. Understanding the pathophysiology of postpartum psychosis: Challenges and new approaches. *World J Psychiatr* 2017; 7(2): 77-88 Available from: URL: http://www.wjgnet.com/2220-3206/full/v7/i2/77.htm DOI: http://dx.doi.org/10.5498/wjp.v7.i2.77

INTRODUCTION

What is postpartum psychosis?

Postpartum, or puerperal, psychosis (PP) is a severe psychiatric disorder which typically manifests within days of childbirth in a small proportion of women (1-2 in every 1000 new mothers)[1,2]. The main symptoms of PP include hallucinations and delusions, cognitive disorganisation and confusion, anxiety and sleep problems[1,2]; rarely, affected mothers may attempt to injure themselves or their child, with maternal suicide and infanticide observed in some cases. Pharmacological treatments are relatively efficacious if administered promptly and in combination with psychotherapy and psychoeducation[1,2]: These include a range of typical and atypical antipsychotic drugs and mood stabilisers (given that mood fluctuations, or bipolarity, may precede and/or be exacerbated by PP); prophylactic pharmacotherapy may also be used judiciously in women at high risk of PP[1,2].

Risk and protective factors

The single largest risk factor for PP is a personal, or family, history of bipolar disorder or related psychotic disorder (seen in about 40%-50% of PP cases[1,2]). Other risk factors that have been suggested as modulators of PP risk include: Primiparity, maternal age, stress levels in the puerperium, and maternal sleep problems[1-4]; in contrast to postpartum depression, adverse early-life events do not appear to significantly enhance risk of developing PP in women with bipolar disorder[5]. The condition is associated with obstetric complications, notably pre-eclampsia[6], a potentially-damaging increase in maternal blood pressure. In common with other psychotic spectrum conditions such as schizophrenia, psychosis-related phenotypes in the perinatal period seem to be higher in immigrant populations, possibly as a function of being exposed to new infections, or to high levels of stress[7]. A recent intriguing study has tentatively suggested that women who smoke exhibit reduced risk of developing PP[8], although the questions as to whether this association is genuine, whether cigarettes somehow confer biological protection, or whether the smoking and non-smoking groups differ on some other critical demographic, biological or psychological measure unrelated to smoking remain to be directly addressed.

A biological basis to risk?

The temporal proximity of PP onset to childbirth, its high relapse rate, and its relatively stable prevalence and nature across societies and cultures, indicates that risk for the condition may be substantially influenced by biological factors[1,2]. The maternal body undergoes extreme physiological changes in the postpartum period, notably a massive drop in circulating oestrogens upon expulsion of the placenta. It has been suggested that abnormal sensitivity to this endocrinological disturbance may confer vulnerability to PP in some women[1,2], an idea supported by the fact that oestrogen supplementation may be beneficial to some patients[9,10]. The fact that PP is often responsive to antipsychotic treatment indicates that abnormal serotonergic and/or dopaminergic function may play a role in its pathogenesis; there is a well-established link between oestrogen levels and serotonergic function[11]. An increasing body of literature has implicated immune system dysfunction in psychotic disorders in general[12] and in PP specifically[13], whilst thyroid system abnormalities[14] and other autoimmune conditions[15] have been reported in some cases of PP.

Although the epidemiology, risk/protective factors, and comorbid phenotypes associated with PP have been systematically investigated and several have been consistently replicated (albeit by a small number of research groups), the molecular, cellular and neural pathophysiology of the condition is currently very poorly understood. Below, I list some contemporary approaches aimed at addressing this issue and their successes and limitations. Understanding the biological factors that confer PP risk will be important for identifying and characterising novel drug targets for more efficacious, less toxic, pharmacotherapy; however, given the reasonable efficacy of currently available medications this is perhaps not the main goal. A more pressing aim once biological risk pathways have been identified will be to describe predictive biomarkers which may be used to classify individuals at risk of the condition early in their pregnancy, and to ensure that they are closely monitored and have prompt access to appropriate clinical expertise and facilities if required.

CURRENT APPROACHES TO UNDERSTANDING POSTPARTUM PSYCHOSIS AND THEIR LIMITATIONS

There are a number of diverse approaches that have been employed in trying to understand the pathophysiology of PP. These investigational methods, and their relative advantages and limitations are summarised in Table 1.

Clinical biochemistry

One conceptually-simple approach to understanding the biology of PP is to compare the biochemistry of patients diagnosed with PP with that of appropriate controls

Table 1 The advantages and limitations of methods for investigating biological risk factors in individuals with postpartum psychosis

Investigational method	Advantages of method	Limitations of method
Clinical biochemistry or gene expression analyses	Direct assessment in patient or "at risk" groups Possibility of identifying peripheral biomarkers for PP risk	Difficult to access central nervous system; peripheral changes may not reflect central functional abnormalities Potential issues with obtaining consent for samples Substantial fluctuation of markers with participant demographics, experiences and treatments Possible issues related to reverse causation, *i.e.,* are abnormalities a cause or consequence of the disorder?
Neuroimaging	Direct assessment of brain structure, function or chemistry in patient or "at risk" groups	Cannot easily be performed during psychotic episodes Substantial exclusion criteria for procedure Limited resolution; cannot provide information on most neurochemical, cellular or molecular abnormalities Substantial fluctuation of measures with participant demographics, experiences and treatments Possible issues related to reverse causation, *i.e.,* are abnormalities a cause or consequence of the disorder?
Genetics	DNA can be readily obtained from patient or "at risk" groups from peripheral tissues DNA sequence is stable and unaffected by variability in patient's circumstances Possibility of identifying biomarkers that can predict risk at an early stage Few issues with reverse causation	Low power of genome-wide studies as a consequence of low prevalence of the condition; possibility of false positives and negatives
Porcine infanticide model	Some degree of face validity Direct access to brain tissue for detailed examination and DNA for genetic studies	Questionable relevance of animal behavioural phenotypes to PP symptoms Difficult and expensive to breed and maintain Not readily amenable to pharmacological studies; predictive validity unclear Difficult to systematically assess all brain regions
STS-inhibition mouse model	Some degree of face and predictive validity Direct access to brain tissue for detailed examination Relatively cheap to breed and maintain Amenable to pharmacological and genomic studies	Questionable relevance of animal behavioural phenotypes to PP symptoms Face and predictive validity require further confirmation STS deficiency unconfirmed in PP cases, hence construct validity unsubstantiated

PP: Postpartum psychosis; STS: Steroid sulfatase.

(either postpartum mothers without psychosis, or non-postpartum females). Studies to date have focussed on levels of tryptophan and its metabolites (*i.e.,* precursors of serotonin)[16], and the immune[13] and thyroid[14] systems, the latter two systems being in considerable flux during pregnancy and in the perinatal period. The main findings of these studies may be summarised, respectively, as: (1) deficient tryptophan breakdown, and lower kynurenine production, is evident in women with postpartum mood disorders; (2) abnormally low T cell numbers, and over-activation of the monocyte/macrophage arm of the immune system is evident in the postpartum period in women diagnosed with PP; and (3) patients with PP have a higher prevalence of autoimmune thyroid disease than controls.

Whilst this type of study undoubtedly provides clinically-relevant knowledge about the abnormal biology associated with PP, it is limited in several key ways. First, it is difficult to obtain biological samples from psychotic patients, particularly where these patients lack capacity to consent to experimental procedures, and where they may be socially and geographically isolated from individuals who can give consent on their behalf. Second, the biological samples that can be obtained are peripheral (typically blood or serum); accessibility to more relevant tissue from patients [brain, or even cerebro-spinal fluid (CSF)] is very limited or impossible. Whilst this may not be a major concern with regard to developing predictive peripheral biomarkers, the relationship between any peripheral tissue changes and abnormal brain function underlying behavioural phenotypes is difficult to characterise. Finally, biochemical measures can fluctuate substantially as a function of demographic variables, physiological and general health status, psychosocial factors and drug regime; hence, identifying physiological measures which definitively and reliably differentiate individuals with PP from healthy individuals, and establishing exactly how these measures correlate with phenotype, is extremely challenging. Moreover, there is the potential issue of reverse causation whereby it is difficult to establish unambiguously whether specific biochemical differences between individuals with PP and healthy controls are a cause or a consequence of the condition and its treatment.

Neuroimaging

The biochemical studies above are limited by their ability to directly assay brain function. The development of elegant neuroimaging techniques, including functional magnetic resonance imaging (fMRI) and Diffusion Tensor Imaging over the past couple of decades, has opened up the possibility of identifying neural substrates associated

with PP vulnerability. Neuroimaging studies in this area are scarce, presumably due to issues with participant recruitment and testing. To date, no brain circuitry has consistently be shown to develop or function abnormally in cases of PP. A recent case-control study has suggested that individuals developing PP have a reduced anterior cingulate cortex (ACC) volume[17]. As the ACC plays an important role in cognitive and emotional processing, including in impulse control, decision-making and cognitive organisation, it represents an interesting neural candidate for further study. Rare cases with PP who have been imaged have reported altered ventricular morphology[18], abnormal orbitofrontal cortex reactivity[19] and structural abnormalities of the corpus callosum[20].

Imaging studies, like biochemical studies, are limited in several ways. First, for practical reasons, it is not possible to examine brain function during psychotic episodes, and this has to be assessed in "recovered", or "at risk" participants - hence, the relevance of findings from, *e.g.,* fMRI studies to psychotic experiences is questionable. Moreover, imaging measures, particularly "snapshot" studies, may be confounded by a patient's demography, life history and comorbid diagnoses, and current and previous medication regimes. Finally, whilst neuroimaging can identify brain regions and circuits that may be of potential interest, and sophisticated techniques like magnetic resonance spectroscopy might identify reasonably highly spatially-resolved changes in limited brain neurochemistry, such approaches cannot identify most changes in neurochemistry, nor altered cellular or molecular function.

Genetics

Psychiatric genomics has recently come of age, with genetic risk variants associated with psychosis risk now being reliably identified *via* genome screens in patients with psychotic and mood disorders such as schizophrenia and bipolar disorder[21]. Genetic studies offer two key advantages over the above approaches: First, genomic material (DNA) can be reliably obtained from accessible tissues (typically saliva or blood), and DNA sequence is essentially conserved between these peripheral tissues and the brain. Second, genetic sequence is stable throughout life, and unlike biochemical or brain function measures, is not affected by environmental, psychosocial or pharmacological influences.

The robust identification of common risk variants that increase risk of complex psychiatric disorders by a small amount, or of rare variants that confer greater risk, necessitates the use of large sample sizes (conceivably up to 100000 cases to detect a high proportion of risk variants). For relatively common psychiatric disorders such as schizophrenia and bipolar disorder obtaining this number of cases is feasible through collaborative enterprises such as the Psychiatric Genomics Consortium[22]. For rare disorders such as PP it is unlikely that such large numbers of participants can be recruited, even with extensive inter-institutional working. Based upon our existing knowledge, it seems likely that, in common with related mood and psychotic disorders, genetic risk for PP will be complex and polygenic; hence, genomic analyses in PP, even with several thousand cases, will be limited by relatively low power.

Genetic studies that have been performed in PP to date have employed small sample sizes (< 1000 cases), and hence their conclusions should be regarded with caution: Low power implies a high rate of both false positive and false negative findings. A seminal genetic (linkage) study in bipolar affective postpartum psychosis suggested evidence for significant and suggestive risk loci at 16p13 and 8q24 respectively[23]; the regions implicated contained multiple genes, many of which could theoretically have mediated PP risk. Efforts are currently underway to undertake a sufficiently-powered genome-wide association study (GWAS) in bipolar affective postpartum psychosis, but as yet these have not yielded significant findings. Candidate gene-led studies in PP have focussed upon serotonergic system genes given the therapeutic efficacy of antipsychotics; one study provided suggestive evidence for association within the serotonin transporter and serotonin 2A receptor genes[24]. However, candidate gene association studies, which focus upon genes of likely biological relevance to a condition, often have low replication rates and are inevitably biased by our very limited current knowledge base[25]. Other candidate gene association studies in PP have examined a number of genes important in serotonergic and oestrogenic signalling, and the immune response, but, as yet, these have yielded mixed findings with little consistent evidence for robust risk variants[1]. Genomic techniques such as exome, or even whole-genome, sequencing are feasible in the relatively small number of PP samples available, but here again, low power will make drawing any conclusions about the pathogenicity of any potentially-causal genetic variants difficult.

Besides looking at the DNA sequence *per se*, insights into PP pathogenesis may be obtained by comparing the epigenome or gene expression profiles in individuals with PP and controls. One such study focussed upon microRNAs known to regulate the immune response and demonstrated altered expression of miR-146a and miR-212 in patients with PP relative to healthy controls[26]. However, whether these changes were a cause or consequence of the disorder (and associated medications) is unclear. Moreover, like with candidate gene association studies, expression studies focussing on just a handful of pre-selected genes provide limited information on the specificity of the changes or on general risk pathways; for example, it could feasibly be the case that the expression of a large proportion of microRNAs is perturbed in PP.

The porcine infanticide model of PP

A further approach towards understanding the biological basis of PP risk is through the use of animal models. Animal models permit a degree of experimental control that cannot be achieved in clinical, or other human,

studies and allow procedures that would be ethically prohibited in humans to be conducted; however, there is some resistance to the use of animals, and particularly non-primate species, for modelling complex psychiatric phenotypes characterised by deficits in "uniquely-human" aspects of behaviour and cognition. The first published animal model for PP is the infanticidal sow pig, which exhibits several epidemiological, behavioural and endocrinological traits associated with the condition[27]. An early quantitative trait locus (QTL) study in this model identified four possible genomic loci of interest on chromosomes 2, 10 and X, corresponding to human chromosomal loci 5q14.3-15, 1q32, Xpter-Xp2.1, and Xq2.4-Xqter respectively[27]; an independent linkage study confirmed an association between X-linked loci and maternal aggression, and suggested regions of interest on chromosomes 2, 6, 14 and 15[28]. Examination of hypothalamic gene expression in the maternal infanticide model identified multiple genes, the expression of which was altered in pigs showing aberrant behaviour; several of these mapped to the previously-implicated QTL regions [of particular note were the *HTR2C* (serotonin receptor 2C), *DRD2* (dopamine receptor 2) and *PRL* (prolactin) genes, the first two encoding antipsychotic drug targets[29]]. A genome-wide association study in this model indicated candidate regions on porcine chromosomes 3, 4 and 15, syntenic with human chromosomal regions implicated in bipolar disorder and postpartum psychosis (including 16p13)[30], whilst a candidate gene association study suggested preliminary evidence for association with oestrogen receptor (*ESR1*), excitatory amino acid transporter 2 (*EAAT2*) and dopamine receptor 1 (*DRD1*) genes, but not *HTR2C*[31].

The fact that the pig model described above shows some superficial phenotypic similarities to patients with PP ("face validity"), and that it indicates genomic regions, and specific gene candidates, of possible functional relevance, suggests that it may represent a reasonable model for PP. However, it should be acknowledged that the model is compromised in a number of ways which may limit its utility. First, there is a relatively poor correlation between the clinical and animal behavioural profiles, in that the vast majority of women with PP are not aggressive, and even those who are aggressive will not attempt infanticide. Second, this large animal model is difficult and expensive to breed, maintain, and analyse experimentally. Of particular note, it is difficult to test whether the infanticide phenotype is sensitive to antipsychotic administration - hence it is difficult to determine the extent to which this phenotype is analogous to PP, and to assess whether or not the model has any degree of predictive validity. Another main issue is that, because the brain of the pig is relatively large, it is difficult to investigate all regions where abnormal activity may be observed; whilst previous work has understandably focused on the hypothalamus given its known role in maternal behaviour, there is, as yet, little convincing evidence for impaired hypothalamic function in PP cases.

PATHWAYS TO PROGRESS

Despite decades spent studying the illness, and the availability of cutting-edge experimental techniques and research hardware, we are still far from understanding the biological and psychological risk factors underpinning PP and hence how to identify women at greatest risk for the condition. Below, I briefly outline what I believe is required in order to make progress in this area over the next decade.

Perhaps the main factor hindering progress in PP research is sample size. It is now well recognised in psychiatry that groups from around the world must collaborate in order to generate an adequately-powered, consistently and deeply-phenotyped cohort of patients (and their affected and non-affected relatives) in which genetic, biochemical and neuroimaging analyses can be undertaken; such a large sample will permit factors such as drug treatment, demography and symptomatology to be covaried for, and hence for robust genotype-biology-phenotype correlations to be ascertained. There are ongoing collaborative efforts in the field of PP research involving centres of excellence across Europe and the United States, and these should soon begin to bear fruit. One research area that has been relatively neglected to date is deciphering the fundamental psychological processes that distinguish mothers who develop PP from: (1) those who have bipolar disorder and do not develop the condition; or (2) from healthy mothers. Specifying how "at risk" women differ from "protected" women on measures of behaviour and cognition, may feasibly permit the development of a simple screening test to be applied prior to childbirth, and may provide clues as to underlying neurobiology.

Even with larger numbers of cases available for genome-wide genetic analyses, there is a strong possibility that only a handful of polymorphisms or mutations associated with PP risk will be identified, and that many will not reach genome-wide levels of significance after the requisite stringent multiple testing corrections. Hence, there may still be a role for sensible candidate gene association studies comparing variant frequency in cases and controls, where higher levels of alpha (as a consequence of reduced multiple testing) are more likely to give rise to statistically significant findings. However, as discussed above, traditional candidate gene studies based upon theoretical causal or therapeutic mechanisms have frequently been shown to be irreproducible, or to give rise to findings of a much smaller magnitude than initially suspected[25,32]. Moreover, genome-wide association studies have repeatedly demonstrated that genetic variants robustly associated with disorder risk are often poorly-annotated and have unknown effects on biology, and hence would not have been prioritised in candidate-led approaches[32]. Bearing in mind these caveats, proposals for candidate *PP* genes should be supported by multiple converging lines of evidence, and should ideally exhibit both positional and functional relevance. In the following section, I describe a candidate gene backed by

such evidence.

There is also clearly a need for more experimentally-tractable animal and cellular models, in which molecular, cellular and circuit mechanisms that may influence PP risk can be characterised. In terms of animal models, ideally these should be available to be tested in large, well-defined batches, be neurobiologically-amenable, and exhibit some degree of face, construct and predictive validity (the latter in contrast to the porcine infanticide model). In terms of cellular models, the advent of induced pluripotent stem cell technology technology now means that "pathological" samples such as brain cell cultures can ultimately be generated from patient fibroblast, or other peripheral, cells[33]. Any data generated from *in vitro* studies in which derived-brain cells are examined in isolation, should be extrapolated cautiously given that PP risk, in common with the risk of related psychiatric conditions such as schizophrenia and depression, is likely to be modulated by complex ongoing interactions between a multitude of intra-brain and extra-brain (*e.g.,* hormonal, placental or immune system) factors[34].

A NEW CANDIDATE GENE

I have previously proposed, based upon numerous lines of clinical and basic scientific evidence, that maternal deficiency for the enzyme steroid sulfatase, encoded by the X-linked *STS* gene, may represent one candidate risk mechanism for PP[35]. The STS enzyme cleaves sulfate groups from a variety of steroid hormones, notably dehydroepiandrosterone sulfate (DHEAS), thus allowing them to be used as precursors for a variety of androgens and oestrogens; hence it is a key modulator of the steroid hormone axis. There are a number of criteria that candidate genes and pathways for PP may be expected to meet based upon our existing knowledge; the *STS* gene and the processes which it modulates meet many of these.

One might expect the candidate system to be in flux in the postpartum period, and to influence immune function at this time; in mice, and perhaps also in man, brain levels of STS are elevated specifically shortly after giving birth[36]. In healthy women, reduced levels of serum DHEA in the postpartum period are associated with activation of the immune system[37]; conceivably, in STS-deficient women, abnormally low levels of postpartum DHEA (as a consequence of impaired DHEAS desulfation) may result in hyperactivation of the immune system.

The steroid hormone axis has repeatedly been implicated in the pathogenesis of PP given the sudden drop in circulating oestrogen levels in the mother following birth, and the suspected protective effects of oestrogens against psychosis[38]; indeed, early candidate gene association studies focussed upon those regions of the genome thought to be regulated by oestrogens[39]. STS is a key player within this axis. STS is highly expressed in key reproductive tissues (testis, mammary gland, placenta, uterus, brain[40]) and hence its dysfunction may, a priori, be expected to impact upon normal reproductive physiology. Recently, placental mis-expression of the *STS* gene has been implicated in pre-eclampsia risk[41]. It is plausible that in STS-deficient mothers, where baseline oestrogen levels may already be low[42], expulsion of the oestrogenic placenta precipitates psychosis vulnerability. There is also some evidence that women who are carriers for *STS* mutations, and who are STS-deficient, are at increased risk of psychological abnormalities (unpublished results) and of delayed, or prolonged labour, and related obstetric complications[43]; such complications, and the accompanying psychological stress, may be one precipitant of postpartum psychiatric distress, although a specific link to PP remains unconfirmed[1,44].

In the developing and adult brain, *STS* is expressed in regions implicated in postpartum psychosis. Specifically, it is highly expressed in the thalamus (involved in the integration and usage of sensory information) and throughout the cortex (including the cingulate cortex)[45,46]; it is also highly expressed in the hypothalamus, and outside the brain in the thyroid gland[45,46]. Hence, its absence may feasibly give rise to abnormal hypothalamic-pituitary-adrenal or hypothalamic-pituitary-thyroid function, consistent with notions of an abnormal stress response, or thyroid pathology, in cases of PP.

Parallel clinical and animal model studies have demonstrated that STS deficiency (or genetic variation within *STS*) gives rise to behavioural phenotypes of relevance to PP including psychosis, cognitive disorganisation, anxiety, depression and, rarely, aggression (unpublished results and ref.[46-49]). Moreover, there is a positive correlation between serum levels of DHEAS and psychoticism (anxiety, paranoia, psychosis) in healthy women and women exhibiting postpartum psychiatric distress[50,51]. Data from genetic and pharmacological rodent models suggest that deficiency for STS may impact upon neurochemistry of relevance to psychosis vulnerability including altered levels of hippocampal serotonin (and Htr2c receptors) and acetylcholine[52,53].

Finally, *STS* was explicitly suggested as a candidate gene underlying significant X-linked QTLs in the porcine maternal infanticide model of PP[27].

INSIGHTS FROM A NEW MOUSE MODEL

The only existing animal model for PP, the porcine maternal infanticide model, is sub-optimal. We have recently attempted to develop a more experimentally-tractable mouse model for the condition, based upon the idea that maternal steroid sulfatase deficiency is a putative risk factor[54].

Briefly, we showed that pharmacological inhibition of the steroid sulfatase enzyme in new mouse mothers resulted in behavioural, endocrinological and genetic phenotypes partially mirroring those seen in PP ("face validity"). Whilst STS inhibition did not affect gross health, maternal behaviours or activity, it did have subtle effects on

exploration of the elevated plus maze (increased rearing and reduced latency to enter the exposed open arms) and the startle response (reduced with enzyme inhibition); a reduced startle response is a feature of patients with bipolar disorder[55]. These observations support the notion of STS as a modulator of postpartum maternal behaviour. STS inhibition did not seem to influence levels of the main stress hormone corticosterone in mice, consistent with data indicating that women with PP show normal cortisol levels[56].

Previous work had suggested that a small genomic region on mouse chromosome 15 harboured a QTL influencing rearing and open arm latency measures in the elevated plus maze[57]; excitingly, this region of chromosome 15 was syntenic with human chromosome 8q24, a region implicated in PP pathogenesis by linkage[23]. Expression screening of the small number of genes within the mouse chromosome 15 interval revealed just one, *Nov*/*Ccn3*, whose expression was significantly altered (upregulated) in STS-inhibited brain; the expression of two other genes from the Ccn family (*Ctgf/Ccn2* and *Wisp1/Ccn4*), as well as genes whose products may be co-regulated with *Nov/CCN3* (*Arhgdig*, *Adcy8* and *Ccl2*) was also increased in STS-inhibited brain tissue[54].

An advantage of the mouse model is that it is possible to test whether putative PP-relevant behavioural and molecular features are sensitive to antipsychotic administration, *i.e.,* to test whether it has potential predictive validity. We showed that administration of clinically-relevant doses of the atypical antipsychotic ziprasidone reverses the deficient startle response, and tempers the over-expression of *Nov/Ccn3* in the STS-inhibited mouse, indicating that these facets of the model may be relevant to psychotic pathophysiology[54].

Although the STS-inhibited mouse shows some degree of promise as a model for PP, its face validity needs to be defined more thoroughly. For example, does it show the abnormalities in the tryptophan-kynurenine pathways and immune system that have been reported in PP cases? One limitation of the current pharmacological model is that steroid sulfatase is solely inhibited in the postpartum period - if STS deficiency is truly a risk factor for PP, it would likely be genetic in origin, and operate throughout life (including pregnancy and the postpartum period). Hence, it would be useful to examine the behaviour and physiology of new mouse mothers that lack one (or both) functional *STS* alleles, and hence have reduced constitutive STS expression; such knockout mice have historically proved difficult to generate due to the complex genomic architecture around the *STS* locus, but this difficulty may potentially be overcome with new genetic engineering technologies such as CRISPR.

A NEW PATHWAY TO PATHOLOGY AND TREATMENT?

The new mouse model described above indicates, on the basis of analyses agnostic to gene function, that dysregulation of the *CCN* gene family arising downstream of dysfunction of the STS axis may be implicated in PP risk. Is this a reasonable concept? If so, can this evaluation suggest molecular, cellular and neural pathways that could be perturbed in PP and that could feasibly be targeted *via* re-purposing of existing drugs, or through developing new drugs?

The *CCN* gene family encodes a number of secreted extracellular matrix-associated proteins that are highly-expressed in the brain[58]; impaired function of the extracellular matrix, and the subsequent abnormal cell-cell interactions, have recently received attention as a possible pathophysiological mechanism in a number of mood disorders[59]. This gene family is also known to be important in female reproductive function[60], exhibits dynamic brain expression throughout pregnancy and the puerperium[61], and modulates Notch and Wnt signalling pathways[57] that are disrupted in bipolar disorder[62] and cases of postpartum psychiatric disturbance[63]. Interestingly, the expression of CCN family members may also be altered by the administration of substances that induce psychosis-like states[64,65], by social stress[66] and by small molecules including cytokines and serotonin[67] suggesting these members as possible mediators of analogues of psychosis.

CCN3 is of particular interest as a candidate modulator of PP risk given the location of the associated gene directly under the 8q24 linkage peak. There is also emerging evidence from a study in human female (cervical cancer) cells that STS and DHEA can directly influence the expression of the integrin β1 molecule[68], a known interactor with CCN3 in the brain and a putative mediator of CCN3-induced effects on cytokine secretion[69].

The CCN3 protein exhibits a variety of additional features that strengthen its candidacy. First, it regulates intracellular calcium signalling[70] a process that goes awry in both bipolar disorder[71] and PP[72]. Second, it is highly expressed in the brain's cortex and limbic system[58], and its expression is dampened by circulating oestrogens[73]. It is apparently a regulator of axonal outgrowth of callosal projection neurons[74], a finding of interest in light of possible corpus callosum abnormalities in cases of PP[20]. The fact that CCN3 modulates placental angiogenesis[60], that the associated gene is located 70kb from a GWAS hit for hypertension[75] and that it, and its family members, are regulated by thyroid hormone derivatives in the cortex of the brain[76], is consistent with the epidemiological studies showing overlap between PP, pre-eclampsia and thyroid abnormalities. Given the preliminary findings regarding a potential attenuation effect of smoking on PP risk, it is interesting to note that the *CCN3* gene lies close to a single nucleotide polymorphism nominally associated with smoking cessation[77], and that in female mouse tissues *Ccn3* expression is reduced upon exposure to cigarette smoke[78]. The protein DDR1 is a putative receptor mediating CCN3 signalling[79]; there is some evidence suggesting association of genetic variants within DDR1 with psychotic illness[80,81].

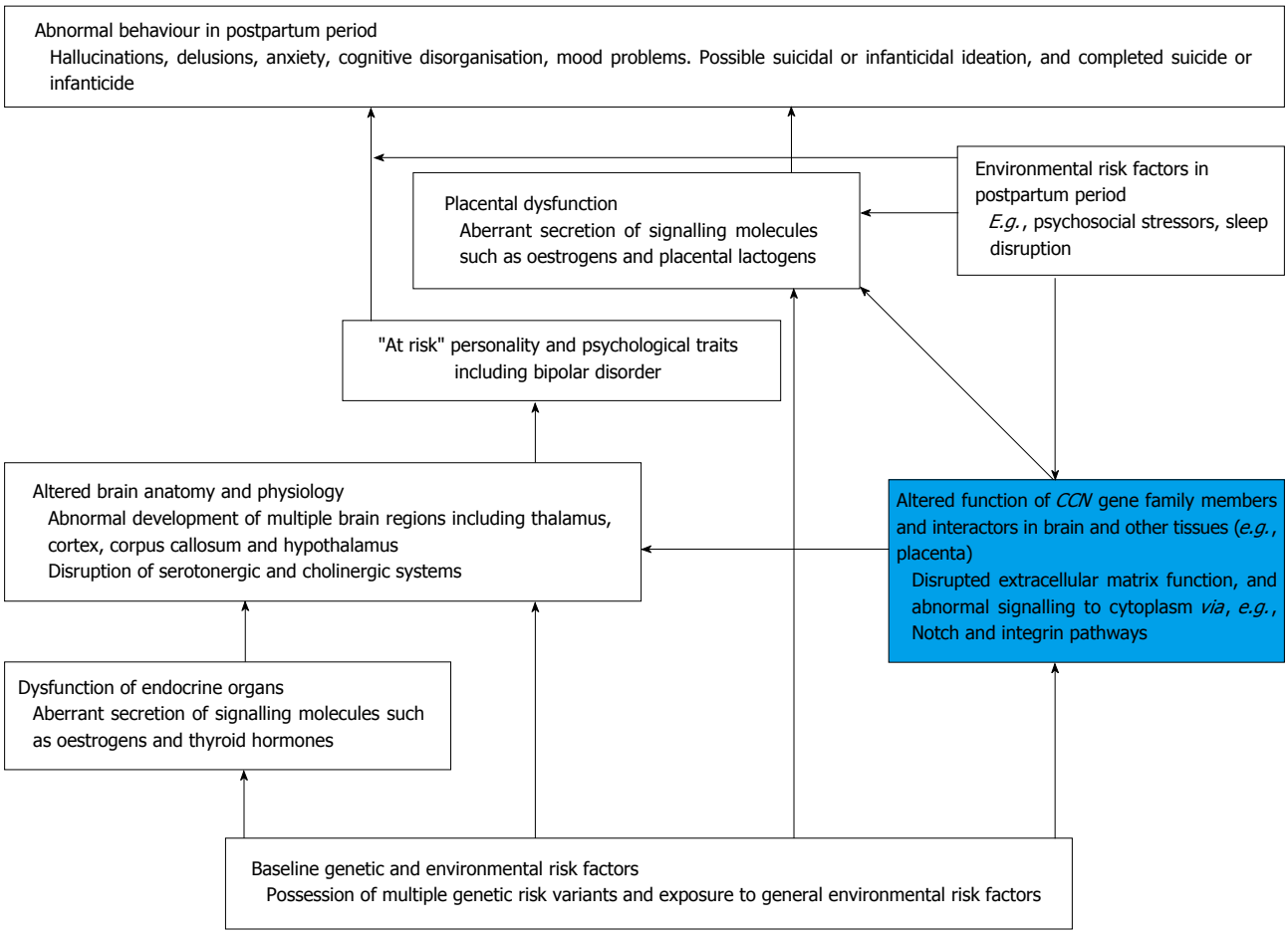


Figure 1 A revised model for postpartum psychosis risk. We suggest that multiple genetic risk variants (potentially influencing STS and CCN family member function), in combination with environmental risk factors, adversely affect the function of multiple endocrine organs (notably placenta and thyroid gland) and increase expression of CCN family members in brain and placenta, to elicit functional changes in brain architecture and neurochemistry which predispose to postpartum psychosis risk. This risk may be further exacerbated by acute environmental risk factors acting within the postpartum such as psychosocial stressors (plausibly also acting *via* CCN-mediated pathways). Putative and well-characterised protective factors such as smoking and antipsychotic administration respectively could potentially exert their effects *via* normalisation of CCN family member function.

Finally, converging evidence from a genetic mouse model is consistent with the notion that *Ccn3* over-expression is associated with abnormal maternal behaviour. Specifically, wildtype mouse mothers carrying pups with genetic modifications which affect placental (spongiotrophoblast) function exhibit abnormal maternal and anxiety-related behaviours in the postpartum period and significantly increased hippocampal *Nov/Ccn3* gene expression[54,82]; this finding is intriguing as it suggests the possibility that the secretion (or lack thereof) of one or more circulating factors from the placenta can indirectly affect brain expression of *Nov/Ccn3*, and subsequently maternal behaviour. The spongiotrophoblast is involved in the synthesis and secretion of multiple compounds which have been shown to influence maternal behaviour in rodent models and which may plausibly mediate this effect (*e.g.,* placental lactogens and pregnancy-specific glycoproteins[83]). Interestingly, in humans, placental lactogen is secreted by the syncytiotrophoblast of the placenta[84], a site of high STS expression[85].

An integrated model showing how PP risk may conceivably be influenced by STS deficiency, placental dysfunction, and disruption to CCN family members based upon current knowledge is presented in Figure 1. This model may be updated and refined as new data emerge from avenues including larger genomic screens, hypothesis-free gene expression screens in model systems, and physiological measurements in patients with PP. The model makes several readily-testable clinical predictions for PP cases relative to control subjects: (1) there will be an excess of genetic variants that reduce STS function and enhance CCN3 expression; (2) there will be an increased DHEAS:DHEA tissue ratio; and (3) there will be elevated levels of CCN3 in accessible fluids including serum, cerebrospinal fluid and urine[86]. In parallel to these clinical studies, we could potentially demonstrate whether or not CCN3 contributes significantly to abnormal maternal behavioural phenotypes in mice by administering an STS inhibitor to wildtype mice and readily-available *Ccn3* knockout mice[87], with the prediction being that wildtype mice would exhibit behavioural abnormalities whereas knockout mice would not.

Should CCN family member over-expression be confirmed as a PP risk factor by future clinical and basic

studies, it may be amenable to pharmacological amelioration by, amongst other approaches, antibody-targeting or knockdown strategies[88]; such interventions may have therapeutic benefits and offer an alternative to more conventional mood stabiliser and antipsychotic approaches.

CONCLUSION

Numerous features of postpartum psychosis (notably its low prevalence, its high degree of heterogeneity, its relative unpredictability and a lack of relevant animal and cellular models) make understanding its pathophysiology difficult. Whilst research to date has provided tantalising hints at pathways and systems that may be perturbed in the condition, the questions as to whether or not they are truly pathogenic remains to be addressed. Undoubtedly, there are many more risk pathways to be discovered.

To make meaningful progress in understanding the molecular, cellular, neural and psychological mechanisms underlying PP risk it will be necessary to adopt a converging experimental approach comprising large-scale genetic (association, copy number variations and sequencing), gene expression and genetic neuroimaging studies, clinical studies correlating behavioural phenotypes with physiological markers of immune, neurochemical and neuroendocrine dysfunction, and animal (pig and mouse) and cellular (*e.g.,* induced pluripotent stem cells) model studies, bearing in mind the many caveats raised above. Importantly, hypothesis-free approaches such as the genomic and animal/cellular model approaches may identify non-obvious risk pathways which can then be followed up in more focussed clinical analyses. The prioritisation of candidate pathways may be informed by work examining the physiology of related conditions and behaviours including bipolar disorder, other postpartum mood disorders, pre-eclampsia and smoking.

A main goal in PP research is to identify biomarkers within easily accessible tissues that can be sampled before, or during, pregnancy (*e.g.,* blood, saliva) that can accurately predict risk, a substantial challenge for such a rare condition; early identification of "at risk" individuals should facilitate rapid access to appropriate facilities and medical care (including close monitoring, administration of psychological or pharmacological treatments, and counselling). The experimental analyses proposed above are likely to result in the identification and characterisation of such biomarkers.

A recent study has shown that the expression of *Nov*/*Ccn3* in rat tissues is sensitive to the administration of the mood-stabilising drug lithium which has clinical efficacy in some cases of PP[89].

REFERENCES

1 **Jones I**, Chandra PS, Dazzan P, Howard LM. Bipolar disorder, affective psychosis, and schizophrenia in pregnancy and the postpartum period. *Lancet* 2014; **384**: 1789-1799 [PMID: 25455249 DOI: 10.1016/S0140-6736(14)61278-2]

2 **Sit D**, Rothschild AJ, Wisner KL. A review of postpartum psychosis. *J Womens Health* (Larchmt) 2006; **15**: 352-368 [PMID: 16724884 DOI: 10.1089/jwh.2006.15.352]

3 **Di Florio A**, Jones L, Forty L, Gordon-Smith K, Blackmore ER, Heron J, Craddock N, Jones I. Mood disorders and parity - a clue to the aetiology of the postpartum trigger. *J Affect Disord* 2014; **152-154**: 334-339 [PMID: 24446553 DOI: 10.1016/j.jad.2013.09.034]

4 **Lewis KJ**, Foster RG, Jones IR. Is sleep disruption a trigger for postpartum psychosis? *Br J Psychiatry* 2016; **208**: 409-411 [PMID: 27143002 DOI: 10.1192/bjp.bp.115.166314]

5 **Perry A**, Gordon-Smith K, Di Florio A, Forty L, Craddock N, Jones L, Jones I. Adverse childhood life events and postpartum psychosis in bipolar disorder. *J Affect Disord* 2016; **205**: 69-72 [PMID: 27420133 DOI: 10.1016/j.jad.2016.06.061]

6 **Bergink V**, Laursen TM, Johannsen BM, Kushner SA, Meltzer-Brody S, Munk-Olsen T. Pre-eclampsia and first-onset postpartum psychiatric episodes: a Danish population-based cohort study. *Psychol Med* 2015; **45**: 3481-3489 [PMID: 26243040 DOI: 10.1017/S0033291715001385]

7 **MacKinnon AL**, Naguib M, Barr HJ, Levinsson A, Robins S, Feeley N, Hayton B, Zelkowitz P, Gold I. Delusional ideation during the perinatal period in a community sample. *Schizophr Res* 2017; **179**: 17-22 [PMID: 27670238 DOI: 10.1016/j.schres.2016.09.027]

8 **Di Florio A**, Morgan H, Jones L, Forty L, Gordon-Smith K, Craddock N, Jones I. Smoking and postpartum psychosis. *Bipolar Disord* 2015; **17**: 572-573 [PMID: 26241192 DOI: 10.1111/bdi.12314]

9 **Balaraman Y**, Schmetzer AD. Hormonal replacement therapy in postpartum affective disorders. *Ann Clin Psychiatry* 2011; **23**: 71-72 [PMID: 21318198]

10 **Huang MC**, Wang YB, Chan CH. Estrogen-progesterone combination for treatment-refractory post-partum mania. *Psychiatry Clin Neurosci* 2008; **62**: 126 [PMID: 18289153 DOI: 10.1111/j.1440-1819.2007.01782.x]

11 **Barth C**, Villringer A, Sacher J. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. *Front Neurosci* 2015; **9**: 37 [PMID: 25750611 DOI: 10.3389/fnins.2015.00037]

12 **Leboyer M**, Oliveira J, Tamouza R, Groc L. Is it time for immunopsychiatry in psychotic disorders? *Psychopharmacology* (Berl) 2016; **233**: 1651-1660 [PMID: 26988846 DOI: 10.1007/s00213-016-4266-1]

13 **Bergink V**, Burgerhout KM, Weigelt K, Pop VJ, de Wit H, Drexhage RC, Kushner SA, Drexhage HA. Immune system dysregulation in first-onset postpartum psychosis. *Biol Psychiatry* 2013; **73**: 1000-1007 [PMID: 23270599 DOI: 10.1016/j.biopsych.2012.11.006]

14 **Bergink V**, Kushner SA, Pop V, Kuijpens H, Lambregtse-van den Berg MP, Drexhage RC, Wiersinga W, Nolen WA, Drexhage HA. Prevalence of autoimmune thyroid dysfunction in postpartum psychosis. *Br J Psychiatry* 2011; **198**: 264-268 [PMID: 21343331 DOI: 10.1192/bjp.bp.110.082990]

15 **Bergink V**, Armangue T, Titulaer MJ, Markx S, Dalmau J, Kushner SA. Autoimmune Encephalitis in Postpartum Psychosis. *Am J Psychiatry* 2015; **172**: 901-908 [PMID: 26183699 DOI: 10.1176/appi.ajp.2015.14101332]

16 **Veen C**, Myint AM, Burgerhout KM, Schwarz MJ, Schütze G, Kushner SA, Hoogendijk WJ, Drexhage HA, Bergink V. Tryptophan pathway alterations in the postpartum period and in acute postpartum psychosis and depression. *J Affect Disord* 2016; **189**: 298-305 [PMID: 26454336 DOI: 10.1016/j.jad.2015.09.064]

17 **Fuste M**, Pauls A, Reinders S, Mehta M, Simmons A, Williams S, Pariante C, Dazzan P. Anterior cingulate cortex abnormalities in postpartum psychosis: a structural MRI study. *Early Interv Psychiatry* 2014; **8** (Suppl 1): 35 [DOI: 10.1111/eip.12186]

18 **Lanczik M**, Fritze J, Hofmann E, Schiulz C, Knoche M, Becker T. Ventricular abnormality in patients with postpartum psychoses. *Arch Women Ment Health* 1998; **1**: 45-47 [DOI: 10.1007/s007370050005]

19 **Fahim C**, Stip E, Mancini-Marïe A, Potvin S, Malaspina D. Orbitofrontal dysfunction in a monozygotic twin discordant for

postpartum affective psychosis: a functional magnetic resonance imaging study. *Bipolar Disord* 2007; **9**: 541-545 [PMID: 17680927 DOI: 10.1111/j.1399-5618.2007.00404.x]
20 **Udaya SC**, Chauhan BN, Philip VJ. Bright splenium of a psychotic mind. *Ann Indian Acad Neurol* 2015; **18**: 80-83 [PMID: 25745318 DOI: 10.4103/0972-2327.145287]
21 **Neale BM**, Sklar P. Genetic analysis of schizophrenia and bipolar disorder reveals polygenicity but also suggests new directions for molecular interrogation. *Curr Opin Neurobiol* 2015; **30**: 131-138 [PMID: 25544106 DOI: 10.1016/j.conb.2014.12.001]
22 **Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium**. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat Neurosci* 2015; **18**: 199-209 [PMID: 25599223 DOI: 10.1038/nn.3922]
23 **Jones I**, Hamshere M, Nangle JM, Bennett P, Green E, Heron J, Segurado R, Lambert D, Holmans P, Corvin A, Owen M, Jones L, Gill M, Craddock N. Bipolar affective puerperal psychosis: genome-wide significant evidence for linkage to chromosome 16. *Am J Psychiatry* 2007; **164**: 1099-1104 [PMID: 17606662 DOI: 10.1176/ajp.2007.164.7.1099]
24 **Kumar HB**, Purushottam M, Kubendran S, Gayathri P, Mukherjee O, Murthy AR, Ghosh S, Chandra P, Reddy YC, Benegal V, Brahmachari SK, Jain S. Serotonergic candidate genes and puerperal psychosis: an association study. *Psychiatr Genet* 2007; **17**: 253-260 [PMID: 17728663 DOI: 10.1097/YPG.0b013e3280ae6cc3]
25 **Munafò MR**. Candidate gene studies in the 21st century: meta-analysis, mediation, moderation. *Genes Brain Behav* 2006; **5** Suppl 1: 3-8 [PMID: 16417611 DOI: 10.1111/j.1601-183X.2006.00188.x]
26 **Weigelt K**, Bergink V, Burgerhout KM, Pescatori M, Wijkhuijs A, Drexhage HA. Down-regulation of inflammation-protective microRNAs 146a and 212 in monocytes of patients with postpartum psychosis. *Brain Behav Immun* 2013; **29**: 147-155 [PMID: 23295264 DOI: 10.1016/j.bbi.2012.12.018]
27 **Quilter CR**, Blott SC, Wilson AE, Bagga MR, Sargent CA, Oliver GL, Southwood OI, Gilbert CL, Mileham A, Affara NA. Porcine maternal infanticide as a model for puerperal psychosis. *Am J Med Genet B Neuropsychiatr Genet* 2007; **144B**: 862-868 [PMID: 17503476 DOI: 10.1002/ajmg.b.30529]
28 **Chen C**, Guo Y, Yang G, Yang Z, Zhang Z, Yang B, Yan X, Perez-Enciso M, Ma J, Duan Y, Brenig B, Huang L. A genome wide detection of quantitative trait loci on pig maternal infanticide behavior in a large scale White Duroc x Erhualian resource population. *Behav Genet* 2009; **39**: 213-219 [PMID: 19130209 DOI: 10.1007/s10519-008-9252-x]
29 **Quilter CR**, Gilbert CL, Oliver GL, Jafer O, Furlong RA, Blott SC, Wilson AE, Sargent CA, Mileham A, Affara NA. Gene expression profiling in porcine maternal infanticide: a model for puerperal psychosis. *Am J Med Genet B Neuropsychiatr Genet* 2008; **147B**: 1126-1137 [PMID: 18361432 DOI: 10.1002/ajmg.b.30734]
30 **Quilter CR**, Sargent CA, Bauer J, Bagga MR, Reiter CP, Hutchinson EL, Southwood OI, Evans G, Mileham A, Griffin DK, Affara NA. An association and haplotype analysis of porcine maternal infanticide: a model for human puerperal psychosis? *Am J Med Genet B Neuropsychiatr Genet* 2012; **159B**: 908-927 [PMID: 22976950 DOI: 10.1002/ajmg.b.32097]
31 **Chen C**, Yang Z, Li Y, Wei N, Li P, Guo Y, Ren J, Ding N, Huang L. Association and haplotype analysis of candidate genes in five genomic regions linked to sow maternal infanticide in a white Duroc × Erhualian resource population. *BMC Genet* 2011; **12**: 24 [PMID: 21303561 DOI: 10.1186/1471-2156-12-24]
32 **Farrell MS**, Werge T, Sklar P, Owen MJ, Ophoff RA, O'Donovan MC, Corvin A, Cichon S, Sullivan PF. Evaluating historical candidate genes for schizophrenia. *Mol Psychiatry* 2015; **20**: 555-562 [PMID: 25754081 DOI: 10.1038/mp.2015.16]
33 **O'Shea KS**, McInnis MG. Neurodevelopmental origins of bipolar disorder: iPSC models. *Mol Cell Neurosci* 2016; **73**: 63-83 [PMID: 26608002 DOI: 10.1016/j.mcn.2015.11.006]
34 **Gibney SM**, Drexhage HA. Evidence for a dysregulated immune system in the etiology of psychiatric disorders. *J Neuroimmune Pharmacol* 2013; **8**: 900-920 [PMID: 23645137 DOI: 10.1007/s11481-013-9462-8]
35 **Davies W**. Does steroid sulfatase deficiency influence postpartum psychosis risk? *Trends Mol Med* 2012; **18**: 256-262 [PMID: 22475435 DOI: 10.1016/j.molmed.2012.03.001]
36 **Mortaud S**, Donsez-Darcel E, Roubertoux PL, Degrelle H. Murine steroid sulfatase gene expression in the brain during postnatal development and adulthood. *Neurosci Lett* 1996; **215**: 145-148 [PMID: 8899734 DOI: 10.1016/0304-3940(96)12944-X]
37 **Tagawa N**, Hidaka Y, Takano T, Shimaoka Y, Kobayashi Y, Amino N. Serum concentrations of dehydroepiandrosterone and dehydroepiandrosterone sulfate and their relation to cytokine production during and after normal pregnancy. *Clin Chim Acta* 2004; **340**: 187-193 [PMID: 14734211]
38 **Grigoriadis S**, Seeman MV. The role of estrogen in schizophrenia: implications for schizophrenia practice guidelines for women. *Can J Psychiatry* 2002; **47**: 437-442 [PMID: 12085678]
39 **Jones I**, Craddock N. Searching for the puerperal trigger: molecular genetic studies of bipolar affective puerperal psychosis. *Psychopharmacol Bull* 2007; **40**: 115-128 [PMID: 17514190]
40 **Unigene**. Available from: URL: https://www.ncbi.nlm.nih.gov/unigene
41 **Gratton AM**, Ye L, Brownfoot FC, Hannan NJ, Whitehead C, Cannon P, Deo M, Fuller PJ, Tong S, Kaitu'u-Lino TJ. Steroid sulfatase is increased in the placentas and whole blood of women with early-onset preeclampsia. *Placenta* 2016; **48**: 72-79 [PMID: 27871476 DOI: 10.1016/j.placenta.2016.10.008]
42 **Lykkesfeldt G**, Bennett P, Lykkesfeldt AE, Micic S, Møller S, Svenstrup B. Abnormal androgen and oestrogen metabolism in men with steroid sulphatase deficiency and recessive X-linked ichthyosis. *Clin Endocrinol* (Oxf) 1985; **23**: 385-393 [PMID: 3864567 DOI: 10.1111/j.1365-2265.1985.tb01096.x]
43 **Fernandes NF**, Janniger CK, Schwartz RA. X-linked ichthyosis: an oculocutaneous genodermatosis. *J Am Acad Dermatol* 2010; **62**: 480-485 [PMID: 20080321 DOI: 10.1016/j.jaad.2009.04.028]
44 **Meltzer-Brody S**, Maegbaek ML, Medland SE, Miller WC, Sullivan P, Munk-Olsen T. Obstetrical, pregnancy and socio-economic predictors for new-onset severe postpartum psychiatric disorders in primiparous women. *Psychol Med* 2017: 1-15 [PMID: 28112056 DOI: 10.1017/S0033291716003020]
45 **Platia MP**, Fencl MD, Elkind-Hirsch KE, Canick JA, Tulchinsky D. Estrone sulfatase activity in the human brain and estrone sulfate levels in the normal menstrual cycle. *J Steroid Biochem* 1984; **21**: 237-241 [PMID: 6492790]
46 **Stergiakouli E**, Langley K, Williams H, Walters J, Williams NM, Suren S, Giegling I, Wilkinson LS, Owen MJ, O'Donovan MC, Rujescu D, Thapar A, Davies W. Steroid sulfatase is a potential modifier of cognition in attention deficit hyperactivity disorder. *Genes Brain Behav* 2011; **10**: 334-344 [PMID: 21255266 DOI: 10.1111/j.1601-183X.2010.00672.x]
47 **Chatterjee S**, Humby T, Davies W. Behavioural and Psychiatric Phenotypes in Men and Boys with X-Linked Ichthyosis: Evidence from a Worldwide Online Survey. *PLoS One* 2016; **11**: e0164417 [PMID: 27711218 DOI: 10.1371/journal.pone.0164417]
48 **Milunsky J**, Huang XL, Wyandt HE, Milunsky A. Schizophrenia susceptibility gene locus at Xp22.3. *Clin Genet* 1999; **55**: 455-460 [PMID: 10450863 DOI: 10.1034/j.1399-0004.1999.550610.x]
49 **Trent S**, Dennehy A, Richardson H, Ojarikre OA, Burgoyne PS, Humby T, Davies W. Steroid sulfatase-deficient mice exhibit endophenotypes relevant to attention deficit hyperactivity disorder. *Psychoneuroendocrinology* 2012; **37**: 221-229 [PMID: 21723668 DOI: 10.1016/j.psyneuen.2011.06.006]
50 **Marrs CR**, Ferraro DP, Cross CL. Hormones and mood across the first postpartum year. *Eur J Obstet Gynecol Reprod Biol* 2010; **149**: 121-122 [PMID: 20022686 DOI: 10.1016/j.ejogrb.2009.11.006]
51 **Marrs CR**, Ferraro DP, Cross CL, Rogers SL. A potential role for adrenal androgens in postpartum psychiatric distress. *Eur J Obstet Gynecol Reprod Biol* 2009; **143**: 127-128 [PMID: 19181432 DOI: 10.1016/j.ejogrb.2008.12.008]
52 **Rhodes ME**, Li PK, Burke AM, Johnson DA. Enhanced plasma

DHEAS, brain acetylcholine and memory mediated by steroid sulfatase inhibition. *Brain Res* 1997; **773**: 28-32 [PMID: 9409701]
53 **Trent S**, Cassano T, Bedse G, Ojarikre OA, Humby T, Davies W. Altered serotonergic function may partially account for behavioral endophenotypes in steroid sulfatase-deficient mice. *Neuropsychopharmacology* 2012; **37**: 1267-1274 [PMID: 22189290 DOI: 10.1038/npp.2011.314]
54 **Humby T**, Cross ES, Messer L, Guerrero S, Davies W. A pharmacological mouse model suggests a novel risk pathway for postpartum psychosis. *Psychoneuroendocrinology* 2016; **74**: 363-370 [PMID: 27728876 DOI: 10.1016/j.psyneuen.2016.09.019]
55 **Giakoumaki SG**, Bitsios P, Frangou S, Roussos P, Aasen I, Galea A, Kumari V. Low baseline startle and deficient affective startle modulation in remitted bipolar disorder patients and their unaffected siblings. *Psychophysiology* 2010; **47**: 659-668 [PMID: 20233338 DOI: 10.1111/j.1469-8986.2010.00977.x]
56 **Epperson CN**, Ballew J. Postpartum depression: a common complication of childbirth. In: Hendrick V, ed., Psychiatric disorders in pregancy and the postpartum: Principles and treatment. Humana Press: New York, 2006; 61-81
57 **Henderson ND**, Turri MG, DeFries JC, Flint J. QTL analysis of multiple behavioral measures of anxiety in mice. *Behav Genet* 2004; **34**: 267-293 [PMID: 14990867 DOI: 10.1023/B: BEGE.0000017872.25069.44]
58 **Malik AR**, Liszewska E, Jaworski J. Matricellular proteins of the Cyr61/CTGF/NOV (CCN) family and the nervous system. *Front Cell Neurosci* 2015; **9**: 237 [PMID: 26157362 DOI: 10.3389/fncel.2015.00237]
59 **Lubbers BR**, Smit AB, Spijker S, van den Oever MC. Neural ECM in addiction, schizophrenia, and mood disorder. *Prog Brain Res* 2014; **214**: 263-284 [PMID: 25410362 DOI: 10.1016/B978-0-444-63486-3.00012-8]
60 **Winterhager E**, Gellhaus A. The role of the CCN family of proteins in female reproduction. *Cell Mol Life Sci* 2014; **71**: 2299-2311 [PMID: 24448904 DOI: 10.1007/s00018-014-1556-9]
61 **Ray S**, Tzeng RY, DiCarlo LM, Bundy JL, Vied C, Tyson G, Nowakowski R, Arbeitman MN. An Examination of Dynamic Gene Expression Changes in the Mouse Brain During Pregnancy and the Postpartum Period. *G3* (Bethesda) 2015; **6**: 221-233 [PMID: 26596646 DOI: 10.1534/g3.115.020982]
62 **Pedroso I**, Lourdusamy A, Rietschel M, Nöthen MM, Cichon S, McGuffin P, Al-Chalabi A, Barnes MR, Breen G. Common genetic variants and gene-expression changes associated with bipolar disorder are over-represented in brain signaling pathway genes. *Biol Psychiatry* 2012; **72**: 311-317 [PMID: 22502986 DOI: 10.1016/j.biopsych.2011.12.031]
63 **Pantoni L**, Pescini F, Inzitari D, Dotti MT. Postpartum psychiatric disturbances as an unrecognized onset of CADASIL. *Acta Psychiatr Scand* 2005; **112**: 241; author reply 242 [PMID: 16095483 DOI: 10.1111/j.1600-0447.2005.00595.x]
64 **Sakuma K**, Komatsu H, Maruyama M, Imaichi S, Habata Y, Mori M. Temporal and spatial transcriptional fingerprints by antipsychotic or propsychotic drugs in mouse brain. *PLoS One* 2015; **10**: e0118510 [PMID: 25693194 DOI: 10.1371/journal.pone.0118510]
65 **Ito T**, Hiraoka S, Kuroda Y, Ishii S, Umino A, Kashiwa A, Yamamoto N, Kurumaji A, Nishikawa T. Effects of schizophrenomimetics on the expression of the CCN1 (CYR 61) gene encoding a matricellular protein in the infant and adult neocortex of the mouse and rat. *Int J Neuropsychopharmacol* 2007; **10**: 717-725 [PMID: 17608974 DOI: 10.1017/S1461145707007882]
66 **Stankiewicz AM**, Goscik J, Majewska A, Swiergiel AH, Juszczak GR. The Effect of Acute and Chronic Social Stress on the Hippocampal Transcriptome in Mice. *PLoS One* 2015; **10**: e0142195 [PMID: 26556046 DOI: 10.1371/journal.pone.0142195]
67 **Chen PC**, Cheng HC, Yang SF, Lin CW, Tang CH. The CCN family proteins: modulators of bone development and novel targets in bone-associated tumors. *Biomed Res Int* 2014; **2014**: 437096 [PMID: 24551846 DOI: 10.1155/2014/437096]
68 **Ye DJ**, Kwon YJ, Shin S, Baek HS, Shin DW, Chun YJ. Induction of Integrin Signaling by Steroid Sulfatase in Human Cervical Cancer Cells. *Biomol Ther* (Seoul) 2016; **25**: 321-328 [PMID: 27956712 DOI: 10.4062/biomolther.2016.155]
69 **Le Dréau G**, Kular L, Nicot AB, Calmel C, Melik-Parsadaniantz S, Kitabgi P, Laurent M, Martinerie C. NOV/CCN3 upregulates CCL2 and CXCL1 expression in astrocytes through beta1 and beta5 integrins. *Glia* 2010; **58**: 1510-1521 [PMID: 20648642 DOI: 10.1002/glia.21025]
70 **Lombet A**, Planque N, Bleau AM, Li CL, Perbal B. CCN3 and calcium signaling. *Cell Commun Signal* 2003; **1**: 1 [PMID: 14606958 DOI: 10.1186/1478-811X-1-1]
71 **Harrison PJ**. Molecular neurobiological clues to the pathogenesis of bipolar disorder. *Curr Opin Neurobiol* 2016; **36**: 1-6 [PMID: 26210959 DOI: 10.1016/j.conb.2015.07.002]
72 **Riley DM**, Watt DC. Hypercalcemia in the etiology of puerperal psychosis. *Biol Psychiatry* 1985; **20**: 479-488 [PMID: 3986256]
73 **Vendrell JA**, Magnino F, Danis E, Duchesne MJ, Pinloche S, Pons M, Birnbaum D, Nguyen C, Theillet C, Cohen PA. Estrogen regulation in human breast cancer cells of new downstream gene targets involved in estrogen metabolism, cell proliferation and cell transformation. *J Mol Endocrinol* 2004; **32**: 397-414 [PMID: 15072547]
74 **Park M**, Baek IJ, Kim H, Woo DK, Park YJ, Shim S. CCN3 overexpression inhibits growth of callosal projections *via* upregulation of RAB25. *Biochem Biophys Res Commun* 2015; **461**: 456-462 [PMID: 25871796 DOI: 10.1016/j.bbrc.2015.04.016]
75 **Slavin TP**, Feng T, Schnell A, Zhu X, Elston RC. Two-marker association tests yield new disease associations for coronary artery disease and hypertension. *Hum Genet* 2011; **130**: 725-733 [PMID: 21626137 DOI: 10.1007/s00439-011-1009-6]
76 **Berbel P**, Navarro D, Román GC. An evo-devo approach to thyroid hormones in cerebral and cerebellar cortical development: etiological implications for autism. *Front Endocrinol* (Lausanne) 2014; **5**: 146 [PMID: 25250016 DOI: 10.3389/fendo.2014.00146]
77 **Argos M**, Tong L, Pierce BL, Rakibuz-Zaman M, Ahmed A, Islam T, Rahman M, Paul-Brutus R, Rahaman R, Roy S, Jasmine F, Kibriya MG, Ahsan H. Genome-wide association study of smoking behaviours among Bangladeshi adults. *J Med Genet* 2014; **51**: 327-333 [PMID: 24665060 DOI: 10.1136/jmedgenet-2013-102151]
78 **Gueugnon F**, Thibault VC, Kearley J, Petit-Courty A, Vallet A, Guillon A, Si-Tahar M, Humbles AA, Courty Y. Altered expression of the CCN genes in the lungs of mice in response to cigarette smoke exposure and viral and bacterial infections. *Gene* 2016; **586**: 176-183 [PMID: 27080955 DOI: 10.1016/j.gene.2016.04.022]
79 **Ricard AS**, Pain C, Daubos A, Ezzedine K, Lamrissi-Garcia I, Bibeyran A, Guyonnet-Dupérat V, Taieb A, Cario-André M. Study of CCN3 (NOV) and DDR1 in normal melanocytes and vitiligo skin. *Exp Dermatol* 2012; **21**: 411-416 [PMID: 22507556 DOI: 10.1111/j.1600-0625.2012.01473.x]
80 **Roig B**, Franco-Pons N, Martorell L, Tomàs J, Vogel WF, Vilella E. Expression of the tyrosine kinase discoidin domain receptor 1 (DDR1) in human central nervous system myelin. *Brain Res* 2010; **1336**: 22-29 [PMID: 20380825 DOI: 10.1016/j.brainres.2010.03.099]
81 **Roig B**, Virgos C, Franco N, Martorell L, Valero J, Costas J, Carracedo A, Labad A, Vilella E. The discoidin domain receptor 1 as a novel susceptibility gene for schizophrenia. *Mol Psychiatry* 2007; **12**: 833-841 [PMID: 17440435 DOI: 10.1038/sj.mp.4001995]
82 **Creeth H**, McNamara G, Tunster S, Eddy J, Isles A, John R. Programming of maternal behaviour by the placenta: A novel animal model. *Psychoneuroendocrinology* 2015; **61**: 4 [PMID: 26383283 DOI: 10.1016/j.psyneuen.2015.07.397]
83 **Tunster SJ**, Creeth HD, John RM. The imprinted Phlda2 gene modulates a major endocrine compartment of the placenta to regulate placental demands for maternal resources. *Dev Biol* 2016; **409**: 251-260 [PMID: 26476147 DOI: 10.1016/j.ydbio.2015.10.015]
84 **Fujimoto S**, Hamasaki K, Ueda H, Kagawa H. Immunoelectron microscope observations on secretion of human placental lactogen (hPL) in the human chorionic villi. *Anat Rec* 1986; **216**: 68-72 [PMID: 3767004 DOI: 10.1002/ar.1092160112]
85 **Salido EC**, Yen PH, Barajas L, Shapiro LJ. Steroid sulfatase

expression in human placenta: immunocytochemistry and in situ hybridization study. *J Clin Endocrinol Metab* 1990; **70**: 1564-1567 [PMID: 2347893 DOI: 10.1210/jcem-70-6-1564]

86 **Burren CP**, Wilson EM, Hwa V, Oh Y, Rosenfeld RG. Binding properties and distribution of insulin-like growth factor binding protein-related protein 3 (IGFBP-rP3/NovH), an additional member of the IGFBP Superfamily. *J Clin Endocrinol Metab* 1999; **84**: 1096-1103 [PMID: 10084601 DOI: 10.1210/jcem.84.3.5577]

87 **Roddy KA**, Boulter CA. Targeted mutation of NOV/CCN3 in mice disrupts joint homeostasis and causes osteoarthritis-like disease. *Osteoarthritis Cartilage* 2015; **23**: 607-615 [PMID: 25541297 DOI: 10.1016/j.joca.2014.12.012]

88 **Jun JI**, Lau LF. Taking aim at the extracellular matrix: CCN proteins as emerging therapeutic targets. *Nat Rev Drug Discov* 2011; **10**: 945-963 [PMID: 22129992 DOI: 10.1038/nrd3599]

89 **Marti HP**, Jeffs A, Scherer A, Leader J, Leader C, Bedford J, Walker R. Renal Fibrosis mRNA Classifier: Validation in Experimental Lithium-Induced Interstitial Fibrosis in the Rat Kidney. *PloS One* 2016; **11**: e0168240 [PMID: 28002484 DOI: 10.1371/journal.pone.0168240]

P- Reviewer: Gobbi G, Serafini G **S- Editor**: Kong JX **L- Editor**: A
E- Editor: Li D

World Journal of Psychiatry

Submit a Manuscript: http://www.f6publishing.com

World J Psychiatr 2017 June 22; 7(2): 89-97

DOI: 10.5498/wjp.v7.i2.89

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Basic Study

Development of an instrument to measure patients' attitudes towards involuntary hospitalization

Adel Gabriel

Adel Gabriel, Departments of Psychiatry and Community Health Sciences, University of Calgary, Calgary, AB T3E 7M8, Canada

Author contributions: Gabriel A substantially contributed to the conception and design of the study, acquisition, analysis and interpretation of data; the author drafted the article and made critical revisions related to the intellectual content of the manuscript, and approved the final version of the article to be published.

Institutional review board statement: The project was granted an approval by the Conjoint Health Research Ethics Board (CHREB), of the University of Calgary. All patients participants provided their consent to the study.

Institutional animal care and use committee statement: Not applicable.

Conflict-of-interest statement: To the best of our knowledge, no conflict of interest exists.

Data sharing statement: This is an open study.

Manuscript source: Invited manuscript

Correspondence to: Dr. Adel Gabriel, Associate Clinical Professor, Departments of Psychiatry and Community Health Sciences, University of Calgary, Suite 300, 5 Richard Way SW, Calgary, AB T3E 7M8, Canada. gabriel@ucalgary.ca
Telephone: +1-403-2919122
Fax: +1-403-2916631

Received: August 23, 2016
Peer-review started: August 24, 2016
First decision: November 11, 2016
Revised: April 4, 2017
Accepted: May 3, 2017
Article in press: May 5, 2017
Published online: June 22, 2017

Abstract

AIM

To construct and assess the psychometric properties of an instrument to measure patients' attitudes towards involuntary hospitalization.

METHODS

This is a two phase study. In the first phase, based on comprehensive literature review, a twenty one item scale to measure patients' attitudes to involuntary admission was constructed. Forensic and inpatient Psychiatrists, patients' advocates and legal experts (n = 15) were invited to participate in the validation process of the written instrument, by formally rating each item of the instrument for its relevancy in measuring patients' attitudes to involuntary admission. In the second phase of the project, the instrument was administered to a sample of eighty consecutive patients, who were admitted involuntarily to an acute psychiatric unit of a teaching hospital. All patients completed the constructed attitudes towards involuntary admission scale, and the client satisfaction questionnaire.

RESULTS

Responses from psychiatry and advocacy experts provided evidence for face and content validity for the constructed instrument. The internal consistency reliability of the instrument is 0.84 (Chronbach' alpha), factor analysis resulted in three correlated, and theoretically meaningful factors. There was evidence for content, convergent, and concurrent validity.

CONCLUSION
A reliable twenty one item instrument scale to measure patients' attitudes to involuntary admission was developed. The developed instrument has high reliability, there is strong evidence for validity, and it takes ten minutes to complete.

Key words: Scales; Mmeasurements; Patients' attitudes; Involuntary admission; Psychiatric

Core tip: Examining patients' attitudes towards involuntary hospitalization is crucial for making clinical decisions and is required to administer quality patient care. This project involved the development and psychometrical assessment of a reliable instrument with demonstrated evidence of validity, to measure patients' attitudes towards involuntary hospitalization. The developed instrument consists of a 21-item, 5-point Likert questionnaire. The internal consistency reliability of the instrument is 0.84 (Chronbach' alpha), and there is an evidence for content, convergent, and concurrent validity.

Gabriel A. Development of an instrument to measure patients' attitudes towards involuntary hospitalization. *World J Psychiatr* 2017; 7(2): 89-97 Available from: URL: http://www.wjgnet.com/2220-3206/full/v7/i2/89.htm DOI: http://dx.doi.org/10.5498/wjp.v7.i2.89

INTRODUCTION

Promoting for patient care is the most important objective of mental health. This should include both effective patient day to day care, and advocating for patients' rights. Involuntary admission is one of the most ethically challenging practices in medicine, which touches patient's rights and freedom. Yet we are only beginning to learn more about patient's perspective by utilizing a reliable instruments with evidence for validity. The prevalence of patients' involuntary hospitalization, factors associated with coercion, and patients' dissatisfactions were examined internationally especially Europe. In one large of Swiss inpatients study, about 25% were admitted on an involuntary basis and there were substantial number of patients were exposed to coercion. It was demonstrated that the severity of the psychiatric disorder was the main risk factor to predict appling force during admission[1].

The prevalence of involuntary hospitalization significantly varies from country to country. For example, Zinkler and Priebe[2] (2002) found in a review that there were nearly 20-fold variations in involuntary admission rates in different European countries. However the criteria for detention of the mentally ill are broadly similar when it comes to patients at risk to themselves or others[2].

Risk factors for involuntary admission are numerous. Results from research, suggested that the diagnoses and the intensity of psychiatric illnesses were the most important risk factors for being subjected to any form of coercion[2-4].

In a cross-sectional survey, there were significant proportions among both voluntarily and involuntarily admitted patients who felt that they were forced to be hospitalized. However the majority felt that their admission was necessary[5]. Involuntary admissions were found to be associated with a history of previous hospitalizations[6], presence of psychotic symptom[7], lower levels of social functioning[8], and linguistic communication problems[9]. However, those who were admitted involuntarily were more likely to report significantly more adverse circumstances around the admission procedures such as exposure to verbal or physical force[10-13].

Both clinical outcomes and future adherence to treatment appear to be negatively affected by involuntary hospitalization or by the experience of coercion. For example, Katsakou *et al*[14] (2010), examined 778 involuntary psychiatric inpatients admissions. Perception of coercion was associated with less satisfaction with treatment. Also Swartz *et al*[15] (2003), reported that only 36% of consumers with chronic psychiatric disorders, reported fear of coerced treatment as a barrier to seeking help.

Objectives of the present study

To the best of author's knowledge, there is no published reliable scale with evidence of validity that was developed to measure patients' perceptions towards involuntary hospitalization.

The objective of this study is to examine the reliability, and validity of an instrument that was constructed to measure patients' attitudes towards involuntary hospitalization.

MATERIALS AND METHODS

Participants

Expert participants (psychiatrists, review panel, and patient advocate experts): Fifteen experts from both males and females, volunteered to participate in the validation process of the scale. Among participants, there were nine psychiatrists affiliated with the University of Calgary, three provincial mental health advocacy staff, one lawyer, and two community mental health coordinators. Among psychiatrist experts, there were two at the rank of professor, four at the associate professor in the area of forensic psychiatry, and three at the level of assistant professor in general psychiatry. Table 1 describes the demographicc details of patient participants.

Letters of invitations were delivered inviting experts to participate in the validation process. In addition to the formal validation, there was one-on-one discussion, and feedback, about each item of the proposed scale with regard its relevancy to sample attitudes of patients

Table 1 Demographics of the participating experts (n = 15)

Variable	mean (SD)
Age (yr)	52 (9.5)
Sex: Male/female	11/4
Years of experience as independent Psychiatrist, consultants, lawyers or advocate	22 (12.5)
Professorial experts' professions	*n*
Psychiatrists affiliated with the University of Calgary	9
Professors of psychiatry	2
Associate Clinical Professors (U of C)	4
Assistant Professors	3
Mental Health Advocacy Staff	3
Community order coordinators	2
Lawyers of the Mental health Review Panel	1

towards involuntary admission of psychiatric patients.

Patient participants

Invited to participate in this study, consecutive sample of consenting patients, who were involuntarily admitted to an acute psychiatry teaching unit within the University of Calgary. Patients were included if they were admitted at least on one certificate under section 2 of the Alberta Mental Health Act (2010)[16]. Form one certificate of section 2 is completed by a physician allows detention of a patient up to 24 h. When a person is detained in a facility under a form one certificate, the detained person must be examined as soon as possible by a physician who is on staff, at the receiving facility. According to the Act, these two admission forms (certificates) are sufficient authority to detain and control the person in a facility for 30 d, to allow diagnosing, care for, observation, assessments, and treatments (section 7 of the Act). If a second admission certificate is not signed within 24 h of the person's arrival at the designated facility, the person can no longer be detained involuntarily and shall be released (section 5 of the Mental Health Act)[16].

The researchers approached eligible, consenting patients and invited them to participate in the study. All patients who participated in this study were diagnosed with formal psychiatric disorders, and were deemed danger to themselves or others, on admission. Excluded from the study, patients who are mentally handicapped, the severely ill or aggressive patients, suicidal patients, and those who deemed unable to provide consent. For the purpose of this study, we excluded patients with a score > 50, on The Brief Psychiatric Rating Scale (BPRS) total maximum score[17]. The Mini-International Neuropsychiatric Interview (M.I.N.I. Screen 2001-2005) was utilized to confirm the diagnosis of each included patient[18].

Instruments administered to patients

In addition to the constructed attitudes towards involuntary admission (ATIA) scale Hospitalization scale ATIA (Table 2), all patients completed the following questionnaires: (1) The Client Satisfaction Questionnaire (CSQ)[19]. The CSQ is intended to measure satisfaction with healthcare services. The scale consists of eight items, has a high levels of internal consistency, with alphas ranging from 0.86-0.94; and (2) The Brief Psychiatric Rating Scale (BPRS)[17]. The BPRS is an 18 - item scale that measures symptom severity of major psychiatric disorders, with ratings on a seven point scale (1 = not present, 7 = extremely severe). The rating is made on observations during a 15 to 30 min interview to assess attention, emotional withdrawal, psychomotor symptoms, anxiety, psychotic symptoms depressed mood, and hostility. All patients consented to the study, and provided their demographics including; age, education, occupation, if they were brought to hospital by police force, and if mechanical restraints were used.

Procedure

The procedure of the project aimed at examining the psychometric properties of a developed scale to measure patients' perceptions towards involuntary admissions to acute psychiatric unit. The project was granted an approval by the Conjoint Health Research Ethics Board (CHREB), of the University of Calgary.

Phase 1 of the study: This phase of the study included the construction of the scale items, and the validity assessment by experts. Following literature review using PubMed, and MEDLINE, a table of specification with the initial items describing patients ATIA was prepared as a reference for writing the items of the newly developed scale. The literature was searched for recent evidence from published research projects and reviews to adequately cover the domain of patients' perceptions towards involuntary hospitalization. This was the first step of the project to improve content validity of the items selected. We were able to identify twenty one items that best describe patients' perceptions of involuntary admission[20].

Measuring attitudes is always challenging because attitudes represent such subtle affective domain Applying a scale such as a 5-point liket scale best assesses this domain[20,21]. The twenty one item list of patients' attiudes to involuntary hospitalzation were converted to a 21-item, 5-point Likert scale, resulting in the ATIA scale (Table 2).

Administration to experts

Face validity, was assessed by inviting the experts to provide their views on the overall layout and the content of the instrument. Formal content validity was assessed by asking the volunteer panel of experts to review each items and to examine its relevancy and clarity. Investigators invited experts which included forensic and general psychiatrists, independent mental health advocacy specialists, community health coordinators, and lawyers, to assess each item of the scale for its relevance in measuring patients' attitudes to involuntary admission, on a five-point Likert scale (1 = extremely irrelevant, 2 = irrelevant, 3 = slightly relevant, 4 = relevant, and 5 =

Table 2 The administered version of the constructed attitudes towards involuntary admission scale

	1	2	3	4	5
Instructions: Please rate your perception about the following statements in relation to your involuntary admission to hospital (1 = strongly disagree and 5 = strongly agree)					
I think that being detained as an involuntary patient has averted further harm to me					
I believe that I was offered the opportunity to recover in a safe place					
I could not recognize that I needed help when I was very ill					
I felt that I was pressured excessively					
My problem could have been managed without being pressured					
I think that my hospitalization was not necessary at all					
I think that my hospitalization was unfair					
I think that hospitalization was against my rights					
I felt that I was not heard					
Hospitalization against my will posed a permanent threat to my independence					
My problems might have been managed through a voluntary hospitalization					
My problems might have been managed through a shorter hospitalization					
This admission had a negative impact upon the relationship with my family					
My relationship with my psychiatrist was negatively impacted by this involuntary admission					
I felt that that my current or future job could be affected by being in hospital against my will					
I know my rights as an involuntary patient					
I was given passes and other privileges outside the unit when my doctors felt it was ok					
Admission to hospital was a humiliating experience					
I was given the chance to appeal my involuntary admission					
Overall, I was treated with respect					
I think my family should have been involved in the decision about my admission					

strongly relevant). All participating experts also provided their ratings on the clarity of each item, about absence of abrasive language and about the overall comprehensives of the instrument.

Phase Ⅱ of the study: This phase of the study included the administration of the instrument (Table 2) to patients, data collection, and examining the psychometric properties of the scale. While administration to experts was utilized to assess face and content validity, the administration to patients aimed at establishing internal consistency reliability, and exploring evidence for validity. The scale was pilot tested with four patients. Patients were asked to comment on the clarity of each item, and the time that needed to complete the scale.

After patients' feedback and experts' reviews of each item, the constructed ATIA Scale (ATIA = 21 items), was administered to eighty consenting adult consecutive patinets who were admitted involuntararily to a psychiatric teaching unit. Patients rated ATIA scale on a 5-point Likert type scale (from 1 = strongly disagree to 5 = strongly agree), their perceptions and experiences towards involuntary admission.

Table 3 shows the constructed scale after revision. Seven items scoring were reversed to avoid response patterns. All patients completed the ATIA scale, and the CSQ. A semi structured interview with patients was conducted to complete the BPRS to assess eligibility for inclusion in the study, and to confirm psychiatric diagnoses. Patients were also asked to provide their demographics including age, marital status, education, employment status and all patients were asked if force was used to bring patient to hospital, and if mechanical restraints were used to hold them during hospitalization.

RESULTS

Participated in the study eighty patients who were admitted on an involuntary basis. There were fifty two males, and twenty eight females (M/F = 65%/35%), with mean age 38 (SD = 13.0). Twenty three patients (28.7%) suffered from schizophrenia and schizoaffective disorders, thirty three patients (4.3%) from mood disorders, fourteen patients (17.5%) suffered from alcohol and substance abuse, and ten patients (12.5%) were diagnosed with adjustment disorder. In eleven patients (13.8%), mechanical restraints were applied (Table 4) displays the details of patients' demographics.

The internal consistency reliability (Cronbach's alpha) was 0.84 for the 21 items of the ATIA. Between group differences were analyzed employing Analyses of Variance. There were no significant differences, between males and females, marital status, different age groups, occupational and diagnostic categories, or any difference between the mechanically restrained groups, in the attitudes mean scores of the instrument.

Experts' responses

There were no significant differences ($P < 0.08$) in ratings among experts based on their length of experience. Expert's ratings for all items on the scale ranged from 4.2/5 to 4.8/5. The mean rating the instrument' items was 4.5/5, which results in an overall 90% agreement of experts for the relevancy of the ATIA instrument as a measure for patients attitudes towards involuntary hospitalization (Tables 5 and 6).

Patients' responses

Table 5 displays patients' attitudes mean scores on each

Table 3 The Final version of the attitudes towards involuntary admission scale

	1	2	3	4	5
Please rate your perception about the following statements (1 = strongly disagree to 5 = strongly agree)					
I think that hospitalization was against my rights					
I felt that I was not heard					
Admission to hospital was humiliating experience					
I think that my hospitalization was unfair					
My relationship with my psychiatrist was negatively impacted by this involuntary admission					
This admission had a negative impact upon the relationship with my family					
I felt that my current or future job could be affected by being in hospital against my will					
My problem might have been managed through a shorter hospitalization					
My problem might have been managed through a voluntary hospitalization					
Hospitalization against my will posed a permanent threat to my independency					
My problem could have being managed without being pressured					
I felt that I was pressured excessively					
I think that my hospitalization was not necessary at all					
I think my family should have been involved in the decision about my admission					
Please rate your perception about the following statements (1 = strongly agree to 5 = strongly disagree)					
I know my rights as an involuntary patient					
I was given the chance to appeal my involuntary admission					
I think that being detained as an involuntary patient has averted further harm to me					
I could not recognize that I need help when I was very ill					
Overall, I was treated with respect					
I believe that I was offered the opportunity to recover in a safe place					
I was given passes and other privileges outside the unit when my doctors felt it was ok					

Table 4 Demographics of patients (n = 80)

Categorical variables	Frequency (%)
Sex	
Male	52 (65)
Female	28 (35)
Marital status	
Single	48 (68)
Married	14 (17.5)
Divorced	17 (21.3)
Widow	1 (1.3)
Education	
Elementary	4 (5.0)
Junior high	3 (3.8)
High school	35 (43.8)
College	20 (25.0)
University degree	18 (22.5)
Occupation	
Unemployed	37 (46.3)
Own business	9 (11.3)
Non-skilled/temporary	3 (3.8)
Skilled	26 (32.5)
Professional	5 (6.3)
Brought to hospital by police	
Yes	35 (43.8)
No	45 (56.2)
Psychiatric diagnosis	
Mood disorders	33 (41.3)
Psychotic disorders	23 (28.7)
Alcohol and substance abuse	14 (17.5)
Adjustment disorder	10 (12.5)
Mechanical restraints	
Mechanical restraints used	11 (13.8)
Mechanical restraints not used	69 (86.2)
Continuous variables	M (SD)
Age	37.7 (13.0)
Number of psychiatric admission	3.4 (2.9)
Number of involuntarily admission	2.2 (2.0)

item towards involuntary admission. There were mixed patients' perceptions about involuntary hospitalization. Overall, there was an average rating for all the instruments' items of 2.9/5. However, in the current study, there were some important items which received a favorable positive attitude scores (> 3/5), including the following four items; "Being detained as an involuntary patient has prevented further harm to me", "I believe that I was offered the opportunity to recover in a safe place", "overall, I was treated with respect during this admission", and "I was given the chance to appeal my involuntary admission". In contrast, there were items that overall, received negative attitudes (< 3/5) scores from patients such as the following items; "My hospitalization was unfair", "I think that the hospitalization was against my rights", "I felt that I was not heard", and "Hospitalization against my will posed a permanent threat to my independence" (Tables 5 and 6).

Factor analysis

Exploratory factor analyses were performed on the 21-item scale. Three-factors were extracted, accounting for 44% of the variance in responses related to patients' perceptions of involuntary hospitalization.

Factor 1: Violation of legal rights and autonomy: This factor consists of thirteen items, has an internal consistency of 0.85, and explains 25.6% of the observed variance. It refers to the perceptions that involuntary admission violated legal rights, was not justified, and unfair. There were perceptions of threat to independency, feelings of humiliation, and of being stigmatized by others.

Factor 2: Ambivalent perceptions: This factor consists of six items, has an internal consistency of 0.68, and

Table 5 Experts' ratings, and patient's responses to the items (n = 21) of the attitudes towards involuntary admission scale

Items of the constructed list of specifications patients' and experts' ratings of the	Experts ratings for the relevancy of items[a]		Patients' responses[b]	
	Min-Max	mean (SD)	Min-Max	mean (SD)
I think that being detained as an involuntary patient has prevented further harm to me	3-5	4.6 (0.65)	1-5	3.1 (1.90)
I believe that I was offered the opportunity to recover in a safe place	3-5	4.5 (0.66)	1-5	3.9 (1.21)
I could not recognize that I needed help when I was very ill	4-5	4.8 (0.38)	1-5	2.7 (1.50)
I felt that I was pressured excessively	4-5	4.7 (0.44)	1-5	2.5 (1.46)
My problem could have been managed without being pressured	4-5	4.6 (0.65)	1-5	3.3 (1.38)
I think that my hospitalization was not necessary at all	4-5	4.5 (0.66)	1-5	2.4 (1.36)
I think that my hospitalization was unfair	3-5	4.4 (0.96)	1-5	2.4 (1.47)
I think that the hospitalization was against my rights	3-5	4.3 (0.63)	1-5	2.4 (1.45)
I felt that I was not heard	2-5	4.4 (0.96)	1-5	2.5 (1.45)
Hospitalization against my will posed a permanent threat to my independence	3-5	4.3 (0.63)	1-5	2.3 (1.50)
My problems might have been managed through a shorter hospitalization	2-5	4.3 (0.85)	1-5	3.6 (1.40)
My problems might have been managed through a voluntary hospitalization	3-5	4.6 (0.66)	1-5	2.9 (1.44)
This admission had a negative impact upon the relationship with my family	2-5	4.4 (0.96)	1-5	2.2 (1.41)
My relationship with my psychiatrist was negatively impacted by this involuntary admission	3-5	4.4 (0.65)	1-5	1.9 (1.29)
I felt that that my current or future job could be affected by being in hospital against my will	3-5	4.2 (1.2)	1-5	2.5 (1.48)
I know my rights as an involuntary patient	2-5	4.7 (0.48)	1-5	3.4 (1.51)
I was given passes and other privileges outside the unit when my doctors felt it was ok	3-5	4.5 (1.1)	1-5	4.3 (1.12)
Admission to hospital was a humiliating experience	1-5	4.3 (0.85)	1-5	2.6 (1.48)
I was given the chance to appeal my involuntary admission	4-5	4.5 (0.66)	1-5	3.2 (1.50)
Overall, I was treated with respect during this admission	2-5	4.6 (0.51)	1-5	3.9 (1.20)
I think my family should have been involved in the decision about my admission	1-5	4.6 (0.51)	1-5	3.2 (1.51)
Mean (SD) for the total samples	2.8-5	4.5 (0.70)	1-5	2.9 (1.2)

[a]Experts' responses: 1 = extremely irrelevant to 5 = very relevant; [b]Students' responses: 1 = strongly disagree to 5 = strongly agree.

Table 6 Experts' ratings of the attitudes towards involuntary admission scale format

Experts' ratings (n = 15)	Min-Max	mean (SD)
Clarity of the items (1 = not clear, 5 = very clear)	4-5	4.4 (0.65)
Absence of abrasive language (1 = presence of abrasive, 5 = absence of abrasive language	4-5	4.5 (0.52)
Comprehensiveness of the instrument (1 = not comprehensive, 5 = comprehensive)	4-5	4.5 (0.66)

explains 10% of the observed variance. This factor refers to mixed perceptions. Despite the recognition that there was a need for treatment and that the admission have averted further harm, patients felt that the admission could have been carried out on a voluntary basis and without pressure.

Factor 3: Appreciating procedural justice: This factor consists of five items has an internal consistency of 0.57 and explains 8.8% of the observed variance. It refers mainly to the positive attitudes that the admission was justified, and that there was appreciation for being treated with respect, for being provided the opportunity to appeal their involuntary admission, and for being allowed privileges outside the psychiatry unit when appropriate (Table 7).

There were significant correlation (P < 0.05-0.01) between the three factor scores on the Pearson product moment correlations (Table 8), providing an evidence for convergent validity.

There was significantly negative correlations (r = -0.44, P < 0.01) between the CSQ mean score, and ATIA factor 1 score, "violation of legal rights and autonomy". Also, there were negative correlations between the CSQ mean score, and the other two ATIA factor scores (Table 8).

DISCUSSION

In the present study, patients' ATIA, were included in a 21-Likert-type item scale that have an overall reliability internal consistency of 0.84. There was 95% overall agreement among experts about the relevance of its contents to measure patients' perceptions towards involuntary admission, providing an evidence for content validity. The scale was administered in a timely manner, when patients were able to make fair judgement about their perceptions. This was guided by ensuring a low scores (< 50) of the BPRS.

In the current study, patients who completed the ATIA scale, reported variable perceptions on the 21 item questionnare administered. There is strong evidence from published research to support the same findings and to suggest that the negative attitude towards involuntary hospitalization changes over time. For example, in number of studies, authors found retrospectively that, between 33% and 81% of patients regarded the admission as justified and the treatment as beneficial. Also, patients with more marked clinical improvement had more positive retrospective judgments[22-24].

It was demonstrated in the EUNOMIA prospective research project which included involuntary (n = 2326)

Table 7 Rotated factor matrix, attitude towards involuntary hospitalization scale scores[1]

Items perceptions of involuntary hospitalizations scale (n = 21)			
Factors extracted	**Factor loadings**		
	F1	**F2**	**F3**
I think that my hospitalization was unfair	0.80		
I think that hospitalization was against my rights	0.71		
I think that my hospitalization was not necessary at all	0.70		
Hospitalization against my will posed a permanent threat to my independency	0.59		
I felt that I was not heard	0.60		
Admission to hospital was humiliating experience	0.58		
I believe that I was offered the opportunity to recover in a safe place	0.56		
This admission had a negative impact upon the relationship with my family	0.54		
My relationship with my psychiatrist was negatively impacted by this involuntary admission	0.51		
My problem might have been managed through a shorter hospitalization	0.51	0.46	
I felt that my current or future job could be affected by being in hospital against my will	0.51		
I think my family should have been involved in the decision about my admission	0.40		
My problem might have been managed through a voluntary hospitalization		0.74	
I could not recognize that I need help when I was very ill		0.65	
My problem could have been managed without being pressured	0.39	0.52	
I think that being detained as an involuntary patient has averted further harm to me		0.51	
I was given the chance to appeal my involuntary admission			0.67
I was given passes and other privileges outside the unit when my doctors felt it was ok			0.59
I know my rights as an involuntary patient		0.55	0.56
Overall, I was treated with respect			0.56
I felt that I was pressured excessively			0.48
Internal consistency (Cronbach's alpha) for each factor	0.85	0.68	0.57
Proportion of observed variance for each factor (%)	25.6	10.0	8.8

[1]Principal components extraction, Varimax rotation with Kaiser Normalization. Rotation converged in twelve iterations, factor loadings < 0.35 have been excluded. Factor 1: Violations of legal rights and autonomy; Factor 2: Ambivalent perceptions; Factor 3: Appreciating procedural justice.

Table 8 Pearson product moment correlations between factor scores and client satisfaction questionnaire scores

PIH factors	Factor 2	Factor 3	Client satisfaction questionnaire
Factor 1	0.48[2]	0.27[1]	-0.44[2]
Factor 2		0.36[2]	-0.07
Factor 3			-0.21

[1]Correlation is significant at the 0.05 level (2-tailed); [2]Correlation is significant at the 0.01 level (2-tailed).

patients that between 39% and 71% considered that their admission was justifiable after one month, and this positive attitude changed to 86% after three months[25].

Perceptions of coercion

In the current study, significant proportion of patients perceived being pressured to the admission, or perceived humiliation. These findings replicate findings from other studies. For example, it was demonstrated that negative experiences of being coerced such as by exposure to physical or verbal force during the admission process were more common among patients with involuntary admission. However, coercion was also observed among those who were voluntarily admitted[22,23,26]. Also, Kallert *et al*[27] (2011), reported that perceptions of coercion were found to be significantly more prevalent (89%) among the involuntarily admitted patients, than among the voluntarily admitted patients (48%)[11,28].

It was emphasized by other authors that minimizing patient's perception of coercion during hospital admission may impact positively on the course and adherence to treatment. Authors emphasized that there is need, to minimize the patient's perception of coercion during hospital admission which may affect treatment course and adherence to it[28].

The results from the current study, demonstrated that the Scale's items, on atitudes towards involuntary admission clustered into three constructs (*i.e.*, factors), which resulted in three components. The factors are theoretically meaningful and cohesive, as it was demonstrated by the significant correlations between their scores, supporting evidence for convergent validity.

The three extracted factors, factor 1, "violations of legal rights and autonomy", factor 2, "ambivalent perceptions", factor 3, and "appreciating procedural justice", are consistent with previous research, and theoretically provide a meaning to our hypothseis, which provide evidence for construct valididty. Findings from the current study replicate the findings from other studies. For example, Katsakou *et al*[29] (2011), identified three groups of patients with distinct views on their involuntary hospitalization: Those who believed that it was right, those who thought it was wrong and those with ambivalent views.

Evidence for content validity

The evidence from the published literature leading to the development of a list of patients' ATIA, the cohesive construct of the scale items, and the formal input from experts, provide an evidence for content and construct validity of the scale.

Evidence for concurrent validity

This was demonstrated by the negative correlations between the mean scores of the three factors, and the CSQ mean score. There was significantly (r = -0.44, P < 0.01) negative correlation between the mean score of factor 1, and the CSQ mean score. This negative relationship is meaningful and expected, and supports the findings that patients who had negative perceptions were significantly less likely to be satisfied with services.

Limitations of the study

There was a small sample size, and all patients were recruited from the same psychiatric inpatient sitting.

Conclusion

Advocating for patients should include both effective patient day to day care, and advocating for patients' rights. It is crucial to ensure that patients' rights during hospitalization is protected. In the current study, an instrument to measure patients' perceptions towards involuntary hospitalization was developed. The instrument has a strong reliability. Utilizing confirmatory factor analysis in future research, should be performed to explore the construct validity of the instrument. Also, future research should examine the relationship between involuntary admission risk factors and the clinical outcomes associated with involuntary hospitalization.

ACKNOWLEDGMENTS

Author wishes to thank all those who participated in the formal validity process of the instruments' items, to bring it to final version. In particular author would like to thank Ms. Carol Baker, Ms. Fay Orr, and Mr. Rayan Bielby from the Alberta Advocate office. Many thanks to Mr. Fraser Gordon, chair of the review panel, and to other panel members including; Drs. Grabke and Ismail. Also many thanks to the psychiatrists of the Calgary Health Region, including: Drs. Morrison, Abdel-Keriem from Forensic psychiatry, and to Drs. Stokes, Lam, Muir, and Olouboka of the inpatient psychiatry division. Finally many thanks to Drs. Mona Nematian and Hala Bashay, for assisting in the data entry.

COMMENTS

Background

This project explored the most prevalent perceptions of patients who were admitted to an acute psychiatric unit involuntararily. It aimed at the development and psychometric assessment of an instrument to reliably measure attitudes towards involuntary hospitalization.

Research frontiers

In the first phase of the study, to ensure content validity of the instruemt, all items were written carfefully after a thourough literature review, and psychiatry experts provided a formal ratings on each item of the instrument with regard its relevancy in measuring patients' attitudes, before the instrument was administered to patients.

Innovations and breakthroughs

To the best knowledge of the author, this is the first developed instrument with acceptable reliability to systematically examine patients' attitudes to involuntary psychiatric hospitalization. Results from this study, might shed further light into providing better patient care while protecting patients' legal rights.

Applications

Future researchers, should consider testing the reliability and validity of this instrument in larger sample of patients, from different cultures and in different inpatient settings. There are number of recommendations that could be made which might include the following; better understanding of patients attitudes towards involuntary hospitalization, emphasizing the need to providing psychoeducation to patients and their relatives about the reasons that led to hospitalization and its expected duration; protecting patients' rights during their hospital stay, and improving the communication between relatives and professional hospital staff.

Peer-review

This is a highly relevant paper dealing with the assessment of patient satisfaction in the case of involuntary admission. The authors developed a reliable 21-item likert scale questionnaire with evidence of validity that seems well constructed.

REFERENCES

1 **Lay B**, Nordt C, Rössler W. Variation in use of coercive measures in psychiatric hospitals. *Eur Psychiatry* 2011; **26**: 244-251 [PMID: 21296560 DOI: 10.1016/j.eurpsy.2010.11.007]
2 **Zinkler M**, Priebe S. Detention of the mentally ill in Europe--a review. *Acta Psychiatr Scand* 2002; **106**: 3-8 [PMID: 12100342]
3 **Myklebust LH**, Sørgaard K, Røtvold K, Wynn R. Factors of importance to involuntary admission. *Nord J Psychiatry* 2012; **66**: 178-182 [PMID: 21936731 DOI: 10.3109/08039488.2011.611252]
4 **Ng XT**, Kelly BD. Voluntary and involuntary care: three-year study of demographic and diagnostic admission statistics at an inner-city adult psychiatry unit. *Int J Law Psychiatry* 2012; **35**: 317-326 [PMID: 22560406 DOI: 10.1016/j.ijlp.2012.04.008]
5 **Bonsack C**, Borgeat F. Perceived coercion and need for hospitalization related to psychiatric admission. *Int J Law Psychiatry* 2005; **28**: 342-347 [PMID: 15936078 DOI: 10.1016/j.ijlp.2005.03.008]
6 **Brunner R**, Parzer P, Resch F. [Involuntary hospitalization of patients with anorexia nervosa: clinical issues and empirical findings]. *Fortschr Neurol Psychiatr* 2005; **73**: 9-15 [PMID: 15666219 DOI: 10.1055/s-2004-830078]
7 **Craw J**, Compton MT. Characteristics associated with involuntary versus voluntary legal status at admission and discharge among psychiatric inpatients. *Soc Psychiatry Psychiatr Epidemiol* 2006; **41**: 981-988 [PMID: 17041737 DOI: 10.1007/s00127-006-0122-7]
8 **Kallert TW**, Glöckner M, Schützwohl M. Involuntary vs. voluntary hospital admission. A systematic literature review on outcome diversity. *Eur Arch Psychiatry Clin Neurosci* 2008; **258**: 195-209 [PMID: 18080170 DOI: 10.1007/s00406-007-0777-4]
9 **Künzler N**, Garcia-Brand E, Schmauss M, Messer T. [German language skills among foreign psychiatric patients: influence on voluntariness and duration of hospital treatment]. *Psychiatr Prax* 2004; **31** Suppl 1: S21-S23 [PMID: 15570490 DOI: 10.1055/s-2004-828421]
10 **Katsakou C**, Marougka S, Garabette J, Rost F, Yeeles K, Priebe S. Why do some voluntary patients feel coerced into hospitalisation? A mixed-methods study. *Psychiatry Res* 2011; **187**: 275-282 [PMID: 21272940 DOI: 10.1016/j.psychres.2011.01.001]
11 **Sheehan KA**, Burns T. Perceived coercion and the therapeutic relationship: a neglected association? *Psychiatr Serv* 2011; **62**: 471-476 [PMID: 21532071 DOI: 10.1176/ps.62.5.pss6205_0471]
12 **O'Donoghue B**, Lyne J, Hill M, O'Rourke L, Daly S, Larkin C, Feeney L, O'Callaghan E. Perceptions of involuntary admission and risk of subsequent readmission at one-year follow-up: the influence of insight and recovery style. *J Ment Health* 2011; **20**: 249-259 [PMID: 21574790 DOI: 10.3109/09638237.2011.562263]
13 **Johansson IM**, Lundman B. Patients' experience of involuntary psychiatric care: good opportunities and great losses. *J Psychiatr Ment Health Nurs* 2002; **9**: 639-647 [PMID: 12472816]

14 **Katsakou C**, Bowers L, Amos T, Morriss R, Rose D, Wykes T, Priebe S. Coercion and treatment satisfaction among involuntary patients. *Psychiatr Serv* 2010; **61**: 286-292 [PMID: 20194406 DOI: 10.1176/ps.2010.61.3.286]

15 **Swartz MS**, Swanson JW, Hannon MJ. Does fear of coercion keep people away from mental health treatment? Evidence from a survey of persons with schizophrenia and mental health professionals. *Behav Sci Law* 2003; **21**: 459-472 [PMID: 12898502 DOI: 10.1002/bsl.539]

16 **Alberta Health Services**. Guide to the Alberta Mental Health Act & Community Treatment Order Legislation. 2010. Available from: URL: https://www.albertahealthservices.ca/assets/info/hp/mha/if-hp-mha-guide.pdf

17 **Lachar D**, Bailley SE, Rhoades HM, Varner RV. Use of BPRS-A percent change scores to identify significant clinical improvement: accuracy of treatment response classification in acute psychiatric inpatients. *Psychiatry Res* 1999; **89**: 259-268 [PMID: 10708272]

18 **Sheehan DV**, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; **59** Suppl 20: 22-33; quiz 34-57 [PMID: 9881538]

19 **Greenwood N**, Key A, Burns T, Bristow M, Sedgwick P. Satisfaction with in-patient psychiatric services. Relationship to patient and treatment factors. *Br J Psychiatry* 1999; **174**: 159-163 [PMID: 10211171]

20 **Gabriel A**. Perceptions and Attitudes towards Involuntary Hospital Admissions of Psychiatric Patients. *J J Psych Behav Sci* 2016; **2**: 013

21 **Krathwohl D**, Bloom B, Masia B. Taxonomy of educational objectives: The classification of educational goals. Handbook II: The affective domain. New York David McKay, NY, 1964

22 **Katsakou C**, Priebe S. Outcomes of involuntary hospital admission--a review. *Acta Psychiatr Scand* 2006; **114**: 232-241 [PMID: 16968360 DOI: 10.1111/j.1600-0447.2006.00823.x]

23 **Katsakou C**, Priebe S. Patient's experiences of involuntary hospital admission and treatment: a review of qualitative studies. *Epidemiol Psichiatr Soc* 2007; **16**: 172-178 [PMID: 17619549]

24 **Priebe S**, Katsakou C, Amos T, Leese M, Morriss R, Rose D, Wykes T, Yeeles K. Patients' views and readmissions 1 year after involuntary hospitalisation. *Br J Psychiatry* 2009; **194**: 49-54 [PMID: 19118325 DOI: 10.1192/bjp.bp.108.052266]

25 **Priebe S**, Katsakou C, Glöckner M, Dembinskas A, Fiorillo A, Karastergiou A, Kiejna A, Kjellin L, Nawka P, Onchev G, Raboch J, Schuetzwohl M, Solomon Z, Torres-González F, Wang D, Kallert T. Patients' views of involuntary hospital admission after 1 and 3 months: prospective study in 11 European countries. *Br J Psychiatry* 2010; **196**: 179-185 [PMID: 20194537 DOI: 10.1192/bjp.bp.109.068916]

26 **Svindseth MF**, Dahl AA, Hatling T. Patients' experience of humiliation in the admission process to acute psychiatric wards. *Nord J Psychiatry* 2007; **61**: 47-53 [PMID: 17365789 DOI: 10.1080/08039480601129382]

27 **Kallert TW**, Katsakou C, Adamowski T, Dembinskas A, Fiorillo A, Kjellin L, Mastrogianni A, Nawka P, Onchev G, Raboch J, Schützwohl M, Solomon Z, Torres-González F, Bremner S, Priebe S. Coerced hospital admission and symptom change--a prospective observational multi-centre study. *PLoS One* 2011; **6**: e28191 [PMID: 22140543 DOI: 10.1371/journal.pone.0028191]

28 **Pawłowski T**, Kiejna A, Rymaszewska J. [Involuntary commitment as a source of perceived coercion]. *Psychiatr Pol* 2005; **39**: 151-159 [PMID: 15771162]

29 **Katsakou C**, Rose D, Amos T, Bowers L, McCabe R, Oliver D, Wykes T, Priebe S. Psychiatric patients' views on why their involuntary hospitalisation was right or wrong: a qualitative study. *Soc Psychiatry Psychiatr Epidemiol* 2012; **47**: 1169-1179 [PMID: 21863281 DOI: 10.1007/s00127-011-0427-z]

P- Reviewer: Kravos M, Schweiger U **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Li D

World Journal of Psychiatry

Submit a Manuscript: http://www.f6publishing.com

World J Psychiatr 2017 June 22; 7(2): 98-105

DOI: 10.5498/wjp.v7.i2.98

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Randomized Controlled Trial

Group psychological intervention for maternal depression: A nested qualitative study from Karachi, Pakistan

Nusrat Husain, Nasim Chaudhry, Christine Furber, Hina Fayyaz, Tayyeba Kiran, Farah Lunat, Raza Ur Rahman, Saira Farhan, Batool Fatima

Nusrat Husain, University of Manchester, Honorary Consultant Psychiatrist Lancashire Care NHS Trust, Manchester M13 9PL, United Kingdom

Nusrat Husain, Manchester Academy of Health Sciences Centre, Manchester M13 9NT, United Kingdom

Nasim Chaudhry, Greater Manchester West Mental Health Trust, University of Manchester, Manchester M25 3BL, United Kingdom

Nasim Chaudhry, Hina Fayyaz, Tayyeba Kiran, Batool Fatima, Pakistan Institute of Living and Learning, Karachi 75500, Pakistan

Christine Furber, School of Nursing, Midwifery and Social Work, University of Manchester, Manchester M13 9PL, United Kingdom

Farah Lunat, Lancashire Care NHS Foundation Trust, Preston PR5 6AW, United Kingdom

Raza Ur Rahman, Dow University of Health Sciences, Karachi 74200, Pakistan

Saira Farhan, United Medical and Dental College, Karachi 74900, Pakistan

Author contributions: Husain N, Chaudhry N, Furber C and Lunat F were involved in designing the study, ongoing supervision and feedback in the process of qualitative analysis, writing the manuscript and final approval of the manuscript; Fayyaz H, Kiran T and Fatima B were involved in delivering training to the participants, qualitative analysis and writing the manuscript; Rahman RU and Farhan S provided supervision during data collection.

Supported by Pakistan Institute of Living and Learning, Dow University of Health Sciences Pakistan and University of Manchester, United Kingdom.

Institutional review board statement: The study was reviewed and approved by the Institutionalized Review Board of Dow University of Health Sciences, Karachi, Pakistan.

Clinical trial registration statement: NCT01309516. The study is registered at https://clinicaltrials.gov/ct2/show/NCT01309516?term=NCT01309516&rank=1.

Informed consent statement: All the study participants provided informed written consent prior to their inclusion in the study.

Conflict-of-interest statement: None.

Data sharing statement: Informed consent for data sharing was not obtained but the presented data are anonymized and the risk of identification is minimum.

Manuscript source: Invited manuscript

Correspondence to: Nusrat Husain, MBBS, MCPS (Psych), DPH, MPH, Dip (Psych), MD, Proffesor of Psychiatry, University of Manchester, Honorary Consultant Psychiatrist Lancashire Care NHS Trust, Jean McFarlane Building, Oxford Road, Manchester M13 9PL, United Kingdom. nusrat.husain@manchester.ac.uk
Telephone: +44-16-13067921

Received: December 3, 2016
Peer-review started: December 5, 2016
First decision: April 17, 2017
Revised: May 16, 2017
Accepted: May 30, 2017
Article in press: May 31, 2017

Published online: June 22, 2017

Abstract

AIM

To understand the experience of maternal depression, the factors implicated in accessing health, and the acceptability of the psychosocial intervention.

METHODS

The participants were recruited from the paediatrics outpatient department of Civil Hospital Karachi, Pakistan. The study started in December 2009 and completed in December 2010. Women with maternal depression, aged 18-44 years with children aged 0-30 mo who had received nutritional supplements, and participated in the intervention programme [called Learning through Play (LTP) plus] were included in the study. Qualitative interviews were conducted with 8 participants before the intervention and 7 participants after the intervention. A semi structured topic guide was used to conduct the interviews.

RESULTS

Framework analysis procedures were used to analyse the qualitative data. Four themes emerged: (1) the women's contextual environment: Interpersonal conflicts, lack of social support and financial issues being the major barriers in assessing healthcare; (2) women's isolation and powerlessness within the environment: Sense of loneliness was identified as a restricting factor to access healthcare; (3) the impact of the intervention (LTP-Plus): Women felt "listened to" and seemed empowered; and (4) empowered transformed women within the same contextual environment: The facilitator provided a "gardening role" in nurturing the women resulting in a positive transformation within the same environment. The women's homes seemed to be more happy homes and there was a positive change in their behaviour towards their children.

CONCLUSION

Findings informed the further development and testing of culturally-appropriate psychosocial intervention (LTP^{+}) for addressing maternal depression.

Key words: Low income Country; Thinking Healthy Program; Learning through play; Maternal depression; Framework analysis; Exploratory analysis

Core tip: To our knowledge this is the first qualitative study from Pakistan exploring the experiences of depressed mothers participating in a group psychosocial intervention trial. This was part of a randomized control trial testing the acceptability and feasibility of a parenting intervention Learning through Play (LTP)-Plus among depressed women in a low-income setting. The LTP^{+} intervention focused on two key objectives. First was to stimulate early child development through a pictorial calendar among children from birth to 3 years. Second was to change negative thoughts patterns of mothers through culturally adapted cognitive behavioural therapy intervention. The intervention was acceptable and the qualitative data informed the further development of the intervention.

Husain N, Chaudhry N, Furber C, Fayyaz H, Kiran T, Lunat F, Rahman RU, Farhan S, Fatima B. Group psychological intervention for maternal depression: A nested qualitative study from Karachi, Pakistan. *World J Psychiatr* 2017; 7(2): 98-105 Available from: URL: http://www.wjgnet.com/2220-3206/full/v7/i2/98.htm DOI: http://dx.doi.org/10.5498/wjp.v7.i2.98

INTRODUCTION

Childbirth has been recognized as an important life event that alters responsibilities of a woman permanently[1]. The transition to motherhood is characterized by rituals, prohibitions, and guidelines that facilitate mothers' adaptation to their new roles[2]. However, lack of social support and stressful life events during this significant transition may lead to depression[3,4]. In the West, 10%-15% of women are affected by maternal depression[4] and its prevalence is much higher in developing countries such as India (28%)[5] and South Africa (34.7%)[6]. The prevalence rate is even higher among Pakistani women, *i.e.*, 36%[3]. Increased psychological distresses during the antenatal period[3,5], worry about debt[7] poverty, and disturbed marital relationships[5] have been identified as risk factors for maternal depression.

Furthermore, a phenomenological study in Hong Kong highlighted feelings of "being trapped" in women with postnatal depression and explained that lack of support in the form of uncaring husbands and controlling in-laws were emergent themes along with mothers' ambivalent feelings of love and hate towards their baby[8]. The mother is responsible for breastfeeding, maintaining hygiene for the child, and immunization. She is expected not only to recognize illness, but also to seek appropriate care and treatment for her child[9]. Symptoms of maternal depression such as tiredness, inability to concentrate, preoccupation with guilt, worthlessness, and hopelessness adversely affect a mother's ability to provide adequate care[10]. This may have a long-term impact on the child's physical as well as psychological and cognitive well-being[11]. Results of cohort studies from developing countries including South Africa, Pakistan and India report strong associations between maternal depression and stunted growth[5,12,13]. Similarly, the damaging effects of maternal depression on intellectual and psychological development are also well documented[14,15].

The effectiveness of different psychological interventions such as cognitive behavioural therapy (CBT), interpersonal psychotherapy, and problem-solving therapy is well

established in the treatment of depression in developed[16] as well as developing countries[17]. A multicomponent intervention that involved psychoeducational treatment adherence, support, and pharmacotherapy was found to be effective in reducing depression in women with postnatal depression in Santiago[18]. In Pakistan, intervention based on the principles of CBT was found to be effective in reducing depression and disability and in improving social functioning[19].

A qualitative systematic review by Dennis and Chung-Lee[20] highlighted inability to disclose feelings, the presence of myths and lack of knowledge as barriers to help-seeking behaviours in women suffering from depression. Furthermore, this review also reported a preference for "talking therapies" for the treatment of postnatal depression[20].

As far as we are aware, the present study is the first qualitative research in Pakistan which explores the experiences of women suffering from maternal depression in Pakistan and their related experiences of participation in a group psychosocial intervention trial. A mixed-method study was conducted that comprised a randomized controlled trial (RCT) to test a psychosocial intervention for reducing maternal depression and improve child outcomes. A qualitative method was also used to understand the experience of maternal depression, factors implicated in accessing help, and the acceptability of the group psychosocial intervention in the participants.

MATERIALS AND METHODS

A qualitative approach was adopted as the research design. This approach was chosen in order to understand the experience of maternal depression in the cultural context of these participants, and to explore the antecedents, manifestation, and consequences of depression. Another area that was targeted in this study was the experience of participation in a group psychosocial intervention by particularly focusing on the helpful parts of the intervention, and the difficulties faced by the participants. The participants were interviewed before and after taking part in the intervention. Data was analysed using framework analysis principles[21,22]. All the mothers aged 18-44 years with children between 0-30 mo, diagnosed with depression on Edinburgh Postnatal Depression Scale (EPDS score $\geqslant$ 14) and residents in the trial catchment site were included in the study. Mothers with a medical disorder that could prevent their participation in the trial and those with active suicidal ideation or any other severe physical/mental disorder were excluded.

Ethical approval for the study was sought from the Institutional Review Board of Dow University of Health Sciences, Karachi, Pakistan. A Participant Information Sheet was provided to all participants at the time of recruitment and queries were addressed. After providing a detailed description of the study, written informed consent was obtained from all participants. Participants were assured of confidentiality and permission was obtained to audio record interviews. Codes were assigned to each participant and all transcripts were anonymised during transcription to keep personal data confidential. Data was kept safe on encrypted and password protected computers and were transferred electronically using encrypted files. A Lone Working Policy was used by Pakistan-based researchers in order to ensure their safety in the field. Furthermore, a Distress Policy was in place to enable the researchers to have a framework for accessing further support for participants when it was clear that someone could be at risk. The participants were interviewed at Civil Hospital Karachi, because it was a convenient place for the participants.

This study was a part of an RCT in which the acceptability and feasibility of a group psychosocial intervention [Learning through Play (LTP) Plus] was tested to reduce maternal depression and improve child outcomes. The LTP program focuses on the strategies to stimulate early child development. A pictorial calendar is the main feature of this program that is designed for parents and includes eight successive stages of child development from birth to 3 years. The second component of the psychosocial intervention was cognitive behaviour therapy (CBT) that was aimed at changing negative thought patterns. This study comprised of 98 participants; half of whom were randomized into the intervention group (n = 49) and half into the control group (n = 49). Participants were included in an in-depth interview study through convenient sampling. Interviews were conducted with 7 participants from the routine treatment group and 8 participants from the LTP plus in addition to routine treatment. Initially, 25 participants were invited at random to participate in qualitative interviews; 10 refused to participate because they did not want their interviews to be recorded whereas 15 participants consented. In-depth, semi-structured interviews were conducted by trained researchers. All were trained psychologists and received additional training on qualitative research and data analysis. All interviews were audio recorded after obtaining participant consent. Two separate topic guides were prepared for pre-intervention interviews and post-intervention interviews. The purpose of the interviews with the routine treatment group was to explore experience of maternal depression, its causes and manifestation, and the state of available treatment options. However, interviews conducted with the LTP Plus group were focused on exploring the experience of participation in a group psychosocial intervention, and to identify facilitators and barriers to accessing the intervention. After each interview, field notes were made by the researcher to document the body language of the participant in response to questions along with any other relevant information.

All interviews were transcribed verbatim in Urdu and then translated into English for data analysis. The routine treatment group data and LTP plus group data were analysed separately and then integrated during the mapping and interpretation phases[23]. The five stages of

framework analysis were used to analyse data[21]. During the initial familiarization stage, three researchers (HF, TK, BF) read through the transcripts and field notes collected during the interviews several times to fully immerse themselves in the data. After all data were familiarized, and in order to identify the key themes, a draft theoretical framework was constructed in which major and minor themes were identified from all interviews. Indexing was then carried out in order to apply the draft theoretical framework systematically to the data. Here the data from transcripts were copied and pasted alongside the relevant themes that were listed in the draft theoretical framework. Data and themes were then compared again and the draft theoretical framework revised. During the charting process, data were summarized into table developed using MS Word software for each theme listed in the draft theoretical framework[24]. This process provided a clear and concise overview of the data. Finally, these tables were reviewed during the mapping and interpretation phase. This enabled all key ideas and the data to be compared and discussed by researchers and supervisors, and to identify the final theoretical framework that synthesized and interpreted the data as a whole. To maintain credibility and trustworthiness of the data and subsequent findings, the researchers in Karachi were supervised by experienced mental health and qualitative researchers (NC, FL, CF) based in the United Kingdom. Regular fortnightly Skype meetings were held to discuss progress with the study team during the data collection and analysis phases. Drafts of analyses were electronically mailed to researchers in the United Kingdom who were able to study these before the Skype meetings. The organization (structure and pace) of the supervision process enabled the Pakistan-based researchers to develop experience, skills and confidence in qualitative methods. Engagement in discussion and regular reviews by all researchers ensured fit of the data to the final analysis, and supported minimization of bias[24]. Team members met for the final review of the theoretical framework, and came up with similar ideas. Furthermore, translations from Urdu to English were back-translated to ensure accuracy. For respondent validation[25], 15 participants were approached for feed-back, out of those 9 agreed to give feedback on accuracy of the data. Researchers and group members agreed on the key themes and interpretations.

RESULTS

All participants were home maker women aged 36-40 years, married, with children aged of 0-36 mo. After completion of data analysis, the following 4 key themes were identified in the final theoretical framework.

Context-the women's environment

This theme identifies the psychosocial factors that co-existed with women suffering from maternal depression. Interpersonal conflict and lack of support from extended family members were highlighted in many interviews. For example, the data suggest that several women were experiencing financial hardship which was the main barrier to accessing healthcare facilities. In this setting, it is common for healthcare to be paid for by the service user as state-funded services are minimal. The following quotes illustrate these points.

My sister-in-law often has arguments with me. She does not take care of my children when they cry (Participant 1). Who will understand? My husband thinks that I am bad. My children also think that I am bad (Participant 3). Participants reported that they were suffering from severe financial hardship because of their partners' unemployment and were unable to access treatment for their ill children which they also had to pay for. My husband stays at home not doing anything. He has not been going to work for the last 2 years (Participant 6). Yes he earns but how much can an ill person earn? (Participant 4). My child falls ill very frequently (Participant 1). There is illness but the actual problem is poverty. We don't have money (Participant 2). Children are becoming timid and frightened; they cry because of the circumstances (Participant 5). Participants were unable to contribute financially to the household because of cultural attitudes against their going out to work[16]. It does not happen in our home (community) that women go for work and men do not go. I will go secretly after my husband will leave for work (Participant 8).

Participants also expressed dissatisfaction with the healthcare services available to them. The participant reported that most of the doctors did not provide adequate attention and appropriate treatment to the patients. She does not provide (proper) treatment; simply gives medicine and injection (Participant 1). Sometimes when a good doctor is available he attends us well, but most of the time they just ignore (Participant 2). He (doctor) does not check properly. Here doctors are just like this. No one checks, they just come and leave (Participant 3). You know well how doctors in the government setup are. They do not listen to us. There are so many patients and doctors do not bother with them (Participant 4). What kind of treatment? I had spiritual treatment but it did not have any benefit; reduced my anger just a little bit (Participant 6). Treatment can be provided by a doctor. He should give medicine and also listen to us (Participant 8).

Women isolated and powerless within the environment

The data suggest that prior to the intervention, women were thinking very little about themselves and felt very alone. They were unable to seek support outside the home and described a sense of "paralysis". Some women reported symptoms of physical illness. They were keeping themselves isolated and felt they had no support. There is no use to share this. Who will understand our problems? (Participant 3). I do work. What can I do? There is no one else who can do my work (Participant 4). Whom should I talk to, who would understand, who

would help? (Participant 7). Because of the lack of support and feelings of helplessness, the participants experienced sadness. Before (intervention) I felt sadness and a lot of anxiety and also felt myself alone (Participant 7). I remained sad and worried all the time before (intervention) and I could not find a solution for any of my problems (Participant 6). Because they were keeping themselves isolated and little support was available to them, the participants expressed this sadness in the form of anger. I get very angry (Participant 1). I cry, remain worried. What else can I do? (Participant 2). I get upset, not knowing what to do. I pray but also get angry (Participant 8). I feel like I want to take poison and kill myself and my children too (Participant 7). I started fighting with others without trying to understand what they were saying. If my husband said anything I would start fighting immediately. I used to say anything in state of anger (Participant 4). Furthermore, because of their emotional state, the participants lost interest in participating in routine activities of their daily life, such as looking after the house and their children. I just sit at home, cannot do anything. I just sit idle (Participant 6). I did not have interest in anything (Participant 1). I do not want to play with my children although I know it's important but still I am not interested in doing this (Participant 5). The disturbed emotional state often provoked them to beat their children which consequently made them feel more upset and guilty. When I was angry, I often used to beat my children (Participant 3). Earlier I used to think bad about myself (Participant 2).

The impact of the intervention

After completing the intervention, the participants were clearly demonstrating a more positive nurturing role. They appeared lesser isolated and were interacting more positively with others. They displayed a sense of empowerment following the intervention and demonstrated that the intervention enabled them to be more confident in their roles.

Now I have become more confident (Participant 2). They appeared now to have the strength and courage to attend to and interact with their children. They were more involved in the care of their children, for example, washing them adequately, teaching them etiquette, and playing with them. Some misconceptions seemed to be present in the community such as mothers believing that showing children their reflection in the mirror will make them ill-that if they showed a mirror to their child, he/she will get mad or get diarrhoea. After participating in the LTP Plus intervention, mothers learned to challenge this belief and appreciate the positive outcomes of using a mirror during child play. These quotes explain these behaviours. Now I feel good, take care of myself and the children as well. Now I do not get obsessed with worries like I was before (Participant 3). Through this program I got more information regarding children; like I did not show mirror to my child before but now I show them mirror (Participant 2).

Yes, we should play with children. They like their parents behaving like a child in front of them. This makes children happy and me as well (Participant 1). What I learned about children is that we should teach them etiquette when they are young. When elders use abusive language children understand that and also repeat that in their mind (Participant 4). I liked the part related to children because I feel happy when my child is happy (Participant 6). I liked the part related to children because before (intervention) I did not treat my children well, dealt with them harshly, but after attending the intervention I learned how to spend time with children and how to understand them (Participant 7). They also developed skills in observing and evaluating others and themselves, and also thinking about others. They were now able to solve problems when faced with difficulties and appeared to be more rational in their thinking about daily life activities. They were now thinking more outwardly, rather than inwardly. My mind has been changed since I participated in the program; now I try to solve my problems myself (Participant 5). We should keep on looking for other solutions; at least one (solution) will definitely work. This encouraged me a lot (Participant 7). Yes, all negative thoughts are gone away (Participant 1).

Empowered, transformed women within the same environment

The facilitator was seen as the catalyst for the change in the women. This was a novel experience for the participants as; previously, many of them did not have anyone to share their personal feelings with. They were happy that the facilitator was a female, and they felt that she provided more support and understood them and their feelings well. The facilitator's role can therefore be likened to a "gardeners role", nurturing the women to enable them to foster and transform within their environment.

She focused on each and every point, talked slowly and thoughtfully (Participant 1). Yes, doctor (interventionist) elaborated things very well and I did not have any problem in understanding. She tried to teach us things very calmly and in a good manner (Participant 2). I liked her style of teaching the most. She used to tell everything very slowly and calmly (Participant 3). No, there was no difficulty (in understanding session) (Participant 5). Sister (interventionist) used to teach us slowly and with love. She repeated the things we did not understand (Participant 6). She tried to teach slowly and with love (Participant 7).

To summarize these findings, the environment that these women lived in before taking part in the intervention can be likened to an "infertile garden landscape" where flora is not able to grow and thrive. Furthermore, the "gardeners", or healthcare providers in this case, are not able to provide any support freely, or to nurture their inhabitants in the surrounding area. When medical help was sought by these women, the assistance was not appropriate and did not meet their needs. This

can be likened to the "gardeners" being somewhat irresponsible and reckless as they did not pay adequate attention to these women and their health concerns. Before the intervention these women can be described metaphorically as "closed, dormant rosebuds in the garden", who were experiencing feelings of loneliness and sadness. However, the data indicate that after participating in the LTP Plus intervention the women can be compared to a "vase of blossoming roses" who are now blooming and prominently emitting confidence, knowledge, and self-assurance. Furthermore, the facilitator or deliverer of the intervention was observed as a nurturer/cultivator who attended to their needs with care, love, and attention. Hence, this role can be likened to a "nurturing gardener" who tends carefully to the plants and foliage in their surrounding landscape. Following the LTP Plus intervention, most of the women's homes (the landscape) were transformed into happy homes where the women were interacting more positively with their children.

DISCUSSION

The qualitative approach and framework analysis method of data analysis has clearly identified themes that provide a detailed explanation for the participants' feelings of psychological distress before the intervention. The method has also enabled the changes to be identified after participating in the study. The participants' environment was characterized by deprivation of financial and economic support. Worry about the employment of the partner and interpersonal conflict have been reported by the participants as a contributing factor for maternal depression. Social adversity has been reported to be associated strongly with maternal depression in differing contexts in previous studies[7]. A study in India reported economic deprivation as a risk factor for maternal depression[26]. Studies reported that unhealthy social environment and experiencing lack of social support (including difficulties in relation to people: Friends, partners, trusted people, and relatives) have strong associations with maternal depression[27]. Results of a qualitative study conducted in four cities of south-western Finland reported that lack of a caring attitude from the husband and controlling and powerful in-laws were associated factors for symptoms of hopelessness. Helplessness and loss of control were noted among Chinese women in Hong Kong suffering from maternal depression[8]. A previous study conducted in Pakistan reported that social support and stress contributed greatly to postnatal depression compared to poverty and financial issues[3]. Women in the present study reported that they were unable to contribute financially as many women in their culture are not allowed to go out for work. South Asian women are dependent on men socially and economically[28] and are restricted not only in their mobility but also in decision-making and use of resources[29]. A qualitative study of postnatal depression across countries and cultures reported that a universally accepted remedy to deal with postnatal depression was to increase social support from the family and emotional support from the husband[1].

A second theme of this study was related to women being isolated and powerless in their environment. This theme was basically about the expression of depression among women. They expressed their depression in the form of sadness, hopelessness, anger, physical symptoms, and lack of interest in the environment. They also reported that they directed their anger to their children. Depression has been reported to be a debilitating disorder with symptoms of low mood, low self-esteem, tiredness, and lack of interest[30]. Research also supports that depressed mothers are tired and unable to concentrate and they experience feelings of guilt, worthlessness, and hopelessness[10]. As these women were often unable to provide proper attention to their children because of their depression, they directed anger towards their children and ultimately felt guilty. Moreover, medically unexplained symptoms (MUS) have been recognized as the most prevalent type of symptoms in primary care[31]. MUS can be the representation of recognized psychiatric disorders such as depression or anxiety and can be manifested in various forms including chronic fatigue syndrome, irritable bowel syndrome, fibromyalgia, or simply as symptoms that exist in the absence of a defined organic diagnosis. Evidence suggests that MUS being more common in Asian and African cultures[32]. Findings from a previous study conducted in Pakistan reported that although the proportion of MUS (35%) was similar to what is reported in the West, unlike western studies MUS were twice as common in women than in men and these symptoms led to inability to perform work[32]. Results of a previous qualitative study reported that women with postnatal depression felt helpless and they somatised their depression[33].

The third theme was related to women reporting the positive effects of the LTP Plus intervention. They felt that they became more empowered after the intervention and their knowledge about child rearing improved. They reported better ways of dealing with their children and improvement in problem-solving and their feelings after attending the intervention. In an earlier qualitative study assessing the role of psychosocial intervention in postnatal depression, women described the intervention as a positive experience and found it acceptable and successful. They also reported a positive impact of the CBT approach in influencing thought patterns that led to positive and negative feelings[34]. The LTP intervention was reported to be effective in increasing mother's knowledge of child development[35]. Results of a previous study testing the Thinking Healthy Program (THP) based on the principles of CBT reported that rates of depression were reduced among women receiving this intervention compared to those receiving enhanced routine care. Women in the intervention group experienced more symptomatic relief, and better social adjustment than the comparison group[19]. This was the first time a combination of both interventions was tested, *i.e.*, LTP and CBT (THP).

It led to improvement in mother-child interaction and reduction in depression, as reported by the participants.

The final theme was about the satisfaction of the participants with the LTP Plus group facilitator. They reported that the facilitator helped them to feel empowered even within their difficult environment. Participants appreciated the communication style and patience of the facilitator. The relationship between the role of communication and the effectiveness of intervention for reducing depression in primary care has already been explored[36]. It is recommended that all the healthcare providers dealing with maternal depression should adopt a non-judgmental and accepting approach[34].

Strengths and limitations of the study

There was a high participation rate, with 15 out of 25 (60%) eligible women agreeing to participate in the study. The framework analysis process and the integral phases work well when supervising at a distance as each stage provides a logical opportunity for discussion and review with team members. This fostered a thorough and comprehensive consideration of all aspects of the research process. The multidisciplinary backgrounds of the research team (mental health, midwife, clinical psychologist, research) facilitated emergence of key ideas in the data. Because of the small sample size, the findings cannot be generalized. Moreover, female facilitators were more acceptable to the participants. The findings from women with mild to moderate depression may not be extrapolated to women with severe depression. Some interviews were not as detailed as others because women in this context are not used to accessing services and discussing their problems. Seeing health professionals is not a common practice and thus they are not familiar with talking about their feelings. Thus, the interview experience is slightly novel to them.

Reducing child mortality and morbidity has received attention as a Millennium Development Goal worldwide. However, in low and middle-income countries the process of development of cost-effective psychosocial interventions to achieve such a goal is slow. The present study gives direction in developing and testing culturally-appropriate psychosocial interventions for reducing maternal depression in order to work towards the sustainable development goal.

ACKNOWLEDGMENTS

We want to thank our participants.

COMMENTS

Background

Prevalence is much higher in developing countries such as India (28%) and South Africa (34.7%). The prevalence rate is even higher among Pakistani women, *i.e.*, 36%. Results of cohort studies from developing countries including South Africa, Pakistan and India report strong associations between maternal depression and stunted growth. In Pakistan, intervention based on the principles of cognitive behaviour therapy (CBT) was found to be effective in reducing depression and disability and in improving social functioning. However studies highlighted inability to disclose feelings, the presence of myths and lack of knowledge as barriers to help-seeking behaviours in women suffering from depression.

Research frontiers

Major changes occur during the postnatal period which determines the well-being of mothers and newborns, but unfortunately this is the most neglected period in terms of provision of quality services. Maternal depression accounts for the largest proportion of burden associated with mental or neurological disorders and have strong association with increased child mortality. There is now evidence from some low income countries that effectively delivered psychosocial interventions that are cost effective for improving maternal and child health.

Innovations and breakthroughs

This study was a part of a randomized controlled trial in which the acceptability and feasibility of a group psychosocial intervention [Learning through Play (LTP) Plus] was tested to reduce maternal depression and improve child outcomes. The LTP program focuses on the strategies to stimulate early child development. A pictorial calendar is the main feature of this program that is designed for parents and includes eight successive stages of child development from birth to 3 years. The second component of the psychosocial intervention was CBT that was aimed at changing negative thought patterns. CBT based intervention called Thinking Healthy Program (THP) was successfully tested to reduce postnatal depression in rural area of Pakistan. A parent based intervention LTP was also tested in the same setting that led to the improvement in knowledge, attitude and practices of depressed mothers about child development, however no reduction was found in maternal distress. Therefore the aim of the present study was to explore the acceptability and feasibility of combination of two interventions, *i.e.*, LTP plus THP (LTP Plus) to reduce maternal depression and improve child health.

Applications

The present study is the first qualitative study conducted in Pakistan to explore the role of culturally adapted intervention to improve maternal mental health and child health outcomes for undernourished children brought to paediatric units. There is a need to conduct such studies so that this low cost culturally appropriate intervention can be integrated into the existing health care system to improve maternal and child health in Pakistan and other low income countries.

Terminology

Framework analysis: Framework analysis is a method of qualitative analysis and it is case and theme based approach, reduces data through summarization, retains links to original data, and allows comprehensive and transparent data analysis; THP: THP is based on principles of CBT like listening, identifying and changing negative thoughts and emotions, problem solving skills, *etc.*; Cultural adaptation: Cultural adaptations are changes to intervention content or process that addition, deletion, or alteration to the components, changes in intensity of the intervention and cultural or other contextual modifications.

Peer-review

It is well written.

REFERENCES

1 **Oates MR**, Cox JL, Neema S, Asten P, Glangeaud-Freudenthal N, Figueiredo B, Gorman LL, Hacking S, Hirst E, Kammerer MH, Klier CM, Seneviratne G, Smith M, Sutter-Dallay AL, Valoriani V, Wickberg B, Yoshida K. Postnatal depression across countries and cultures: a qualitative study. *Br J Psychiatry Suppl* 2004; **46**: s10-s16 [PMID: 14754813 DOI: 10.1192/bjp.184.46.s10]

2 **Cox JL**. Perinatal mental disorder-a cultural approach. *Int Rev Psychiatr* 1996; **8**: 9-16 [DOI: 10.3109/09540269609037813]

3 **Husain N**, Bevc I, Husain M, Chaudhry IB, Atif N, Rahman A. Prevalence and social correlates of postnatal depression in a low income country. *Arch Womens Ment Health* 2006; **9**: 197-202 [PMID: 16633740 DOI: 10.1007/s00737-006-0129-9]

4 **O'hara MW**, Swain AM. Rates and risk of postpartum depression-a meta-analysis. *Int Rev Psychiatr* 1996; **8**: 37-54 [DOI: 10.3109/095

40269609037816]
5 **Patel V**, DeSouza N, Rodrigues M. Postnatal depression and infant growth and development in low income countries: a cohort study from Goa, India. *Arch Dis Child* 2003; **88**: 34-37 [PMID: 12495957 DOI: 10.1136/adc.88.1.34]
6 **Cooper PJ**, Tomlinson M, Swartz L, Woolgar M, Murray L, Molteno C. Post-partum depression and the mother-infant relationship in a South African peri-urban settlement. *Br J Psychiatry* 1999; **175**: 554-558 [PMID: 10789353 DOI: 10.1192/bjp.175.6.554]
7 **Reading R**, Reynolds S. Debt, social disadvantage and maternal depression. *Soc Sci Med* 2001; **53**: 441-453 [PMID: 11459395 DOI: 10.1016/S0277-9536(00)00347-6]
8 **Chan SW**, Levy V, Chung TK, Lee D. A qualitative study of the experiences of a group of Hong Kong Chinese women diagnosed with postnatal depression. *J Adv Nurs* 2002; **39**: 571-579 [PMID: 12207755 DOI: 10.1046/j.1365-2648.2002.02326.x]
9 **Rahman A**, Iqbal Z, Harrington R. Life events, social support and depression in childbirth: perspectives from a rural community in the developing world. *Psychol Med* 2003; **33**: 1161-1167 [PMID: 14580070 DOI: 10.1017/S0033291703008286]
10 **Stewart RC**. Maternal depression and infant growth: a review of recent evidence. *Matern Child Nutr* 2007; **3**: 94-107 [PMID: 17355442 DOI: 10.1111/j.1740-8709.2007.00088.x]
11 **Murray L**, Cooper PJ, Wilson A, Romaniuk H. Controlled trial of the short- and long-term effect of psychological treatment of post-partum depression: 2. Impact on the mother-child relationship and child outcome. *Br J Psychiatry* 2003; **182**: 420-427 [PMID: 12724245 DOI: 10.1192/bjp.182.5.420]
12 **Rahman A**, Iqbal Z, Bunn J, Lovel H, Harrington R. Impact of maternal depression on infant nutritional status and illness: a cohort study. *Arch Gen Psychiatry* 2004; **61**: 946-952 [PMID: 15351773 DOI: 10.1001/archpsyc.61.9.946]
13 **Tomlinson M**, Cooper PJ, Stein A, Swartz L, Molteno C. Post-partum depression and infant growth in a South African peri-urban settlement. *Child Care Health Dev* 2006; **32**: 81-86 [PMID: 16398794 DOI: 10.1111/j.1365-2214.2006.00598.x]
14 **Cheung YB**, Khoo KS, Karlberg J, Machin D. Association between psychological symptoms in adults and growth in early life: longitudinal follow up study. *BMJ* 2002; **325**: 749 [PMID: 12364303 DOI: 10.1136/bmj.325.7367.749]
15 **Grantham-McGregor S**. Linear growth retardation and cognition. *Lancet* 2002; **359**: 542 [PMID: 11867104 DOI: 10.1016/S0140-6736(02)07719-X]
16 **Churchill R**, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, Wessely S. A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression. *Health Technol Assess* 2001; **5**: 1-173 [PMID: 12387733 DOI: 10.3310/hta5350]
17 **Patel V**, Araya R, Chatterjee S, Chisholm D, Cohen A, De Silva M, Hosman C, McGuire H, Rojas G, van Ommeren M. Treatment and prevention of mental disorders in low-income and middle-income countries. *Lancet* 2007; **370**: 991-1005 [PMID: 17804058 DOI: 10.1016/S0140-6736(07)61240-9]
18 **Rojas G**, Fritsch R, Solis J, Jadresic E, Castillo C, González M, Guajardo V, Lewis G, Peters TJ, Araya R. Treatment of postnatal depression in low-income mothers in primary-care clinics in Santiago, Chile: a randomised controlled trial. *Lancet* 2007; **370**: 1629-1637 [PMID: 17993363 DOI: 10.1016/S0140-6736(07)61685-7]
19 **Rahman A**, Malik A, Sikander S, Roberts C, Creed F. Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial. *Lancet* 2008; **372**: 902-909 [PMID: 18790313 DOI: 10.1016/S0140-6736(08)61400-2]
20 **Dennis CL**, Chung-Lee L. Postpartum depression help-seeking barriers and maternal treatment preferences: a qualitative systematic review. *Birth* 2006; **33**: 323-331 [PMID: 17150072 DOI: 10.1111/j.1523-536X.2006.00130.x]
21 **Ritchie J**, Spencer L. Qualitative data analysis for applied policy research. In: Bryman A, Burgess R (eds) Analysing qualitative data. Routledge, London, 1994: 173-194
22 **Spencer L**, Ritchie J, O'Connor W. Analysis: practices, principles and processes. Qualitative research practice: A guide for social science students and researchers, 2003: 199-218
23 **Furber CM**, McGowan L. A qualitative study of the experiences of women who are obese and pregnant in the UK. *Midwifery* 2011; **27**: 437-444 [PMID: 20483513 DOI: 10.1016/j.midw.2010.04.001]
24 **Furber C**. Framework analysis: a method for analysing qualitative data. *BJM* 2013; **4**: 97-100
25 **Torrance H**. Triangulation, respondent validation, and democratic participation in mixed methods research. *JMMR* 2012; **6**: 111-123 [DOI: 10.1177/1558689812437185]
26 **Patel V**, Rodrigues M, DeSouza N. Gender, poverty, and postnatal depression: a study of mothers in Goa, India. *Am J Psychiatry* 2002; **159**: 43-47 [PMID: 11772688 DOI: 10.1176/appi.ajp.159.1.43]
27 **Pajulo M**, Savonlahti E, Sourander A, Helenius H, Piha J. Antenatal depression, substance dependency and social support. *J Affect Disord* 2001; **65**: 9-17 [PMID: 11426516 DOI: 10.1016/S0165-0327(00)00265-2]
28 **Narayan-Parker D**, Patel R. Voices of the poor: can anyone hear us?: World Bank Publications, 2000
29 **Jejeebhoy SJ**, Sathar ZA. Women's autonomy in India and Pakistan: the influence of religion and region. *Population and Development Review* 2001; **27**: 687-712 [DOI: 10.1111/j.1728-4457.2001.00687.x]
30 **Rahman A**, Harrington R, Bunn J. Can maternal depression increase infant risk of illness and growth impairment in developing countries? *Child Care Health Dev* 2002; **28**: 51-56 [PMID: 11856187 DOI: 10.1046/j.1365-2214.2002.00239.x]
31 **Henningsen P**, Zimmermann T, Sattel H. Medically unexplained physical symptoms, anxiety, and depression: a meta-analytic review. *Psychosom Med* 2003; **65**: 528-533 [PMID: 12883101 DOI: 10.1097/01.PSY.0000075977.90337.E7]
32 **Husain N**, Chaudhry I, Afsar S, Creed F. Psychological distress among patients attending a general medical outpatient clinic in Pakistan. *Gen Hosp Psychiatry* 2004; **26**: 277-281 [PMID: 15234822 DOI: 10.1016/j.genhosppsych.2004.03.005]
33 **Rahman A**. Challenges and opportunities in developing a psychological intervention for perinatal depression in rural Pakistan--a multi-method study. *Arch Womens Ment Health* 2007; **10**: 211-219 [PMID: 17676431 DOI: 10.1007/s00737-007-0193-9]
34 **Slade P**, Morrell CJ, Rigby A, Ricci K, Spittlehouse J, Brugha TS. Postnatal women's experiences of management of depressive symptoms: a qualitative study. *Br J Gen Pract* 2010; **60**: e440-e448 [PMID: 21062541 DOI: 10.3399/bjgp10X532611]
35 **Rahman A**, Iqbal Z, Roberts C, Husain N. Cluster randomized trial of a parent-based intervention to support early development of children in a low-income country. *Child Care Health Dev* 2009; **35**: 56-62 [PMID: 18991970 DOI: 10.1111/j.1365-2214.2008.00897.x]
36 **van Os TW**, van den Brink RH, Tiemens BG, Jenner JA, van der Meer K, Ormel J. Communicative skills of general practitioners augment the effectiveness of guideline-based depression treatment. *J Affect Disord* 2005; **84**: 43-51 [PMID: 15620384 DOI: 10.1016/j.jad.2004.09.005]

P- Reviewer: Hosak L **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Li D

World Journal of Psychiatry

Submit a Manuscript: http://www.f6publishing.com

World J Psychiatr 2017 June 22; 7(2): 106-113

DOI: 10.5498/wjp.v7.i2.106

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Childhood trauma and factors associated with depression among inpatients with cardiovascular disease

Felipe José Nascimento Barreto, Frederico Duarte Garcia, Paulo Henrique Teixeira Prado, Paulo Marcos Brasil Rocha, Nádia Souza Las Casas, Felipe Barbosa Vallt, Humberto Correa, Maila Castro Lourenço Neves

Felipe José Nascimento Barreto, Frederico Duarte Garcia, Nádia Souza Las Casas, Felipe Barbosa Vallt, Maila Castro Lourenço Neves, Department of Mental Health, Federal University of Minas Gerais, Avenida Alfredo Balena, CEP 30130-100 Belo Horizonte, Brazil

Felipe José Nascimento Barreto, Postgraduation Program in Molecular Medicine, School of Medicine, Federal University of Minas Gerais, Avenida Alfredo Balena, CEP 30130-100 Belo Horizonte, Brazil

Frederico Duarte Garcia, Humberto Correa, Molecular Medicine National Institute of Science and Technology, Avenida Alfredo Balena, Federal University of Minas Gerais, CEP 30130-100 Belo Horizonte, Brazil

Paulo Henrique Teixeira Prado, Paulo Marcos Brasil Rocha, Hospital das Clínicas, Federal University of Minas Gerais, Avenida Alfredo Balena, CEP 30130-100 Belo Horizonte, Brazil

Author contributions: Barreto FJN, Garcia FD, Prado PHT, Rocha PMB, Correa H and Neves MCL contributed to the conception of the study and design; Barreto FJN, Las Casas NS and Vallt FB contributed to data acquisition and interpretation, and writing of the paper; Garcia FD and Neves MCL contribute to editing, reviewing and final approval of the paper.

Supported by the program of Young Researchers of the Federal University of Minas Gerais, No. 01/2013; and FAPEMIG (Fundação de Amparo a Pesquisa do Estado de Minas Gerais, Brazil), No. APQ-01714-13. The funder did not interfere with any procedure regarding the production of this paper.

Institutional review board statement: The Committee of Ethics in Research of UFMG approved the protocol, registered with the number CAAE 13605213.3.0000.5149.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrolment.

Conflict-of-interest statement: Garcia FD received CME grants, received paid speakership, and participated in research from Janssen and Pfizer; Correa H received paid speakership, and participated in research from Janssen; Prado PHT and Neves MCL participated in research from Janssen. The other authors have no conflicts to declare.

Data sharing statement: We would like to inform that, related to the research described on our manuscript, no additional data is available.

Manuscript source: Invited manuscript

Correspondence to: Dr. Maila Castro Lourenço Neves, Department of Mental Health, Federal University of Minas Gerais, Avenida Alfredo Balena, 190 - Sala 240, CEP 30130-100 Belo Horizonte, Brazil. mailacln@ufmg.br
Telephone: +55-31-34099786

Received: January 21, 2017
Peer-review started: January 21, 2017
First decision: February 15, 2017
Revised: March 30, 2017
Accepted: April 23, 2017
Article in press: April 24, 2017
Published online: June 22, 2017

Abstract

AIM

To identify factors associated with depressive symptoms

among inpatients with cardiovascular disease (CVD).

METHODS

This is a cross-sectional study performed in a subsample of a large cross-sectional research that investigated affective disorders and suicide behaviour among inpatients hospitalized in non-surgical wards of the University Hospital of the Federal University of Minas Gerais from November 2013 to October 2015. Sociodemographic and clinical data were obtained through a structured interview and medical record review. Depression was assessed by the depression subscale of the Hospital Anxiety and Depression Scale, with scores $\geqslant$ 8 considered as positive screening for depression. We used the Fagerström Test for Nicotine Dependence to characterize nicotine dependence. For assessing resilience and early-life trauma, we used the raw scores of the Wagnild and Young Resilience Scale and Childhood Trauma Questionnaire, respectively.

RESULTS

At endpoint, we included 137 subjects. Thirty-eight (27.7%) subjects presented depressive symptoms and nine (23.7%) of those were receiving antidepressant treatment during hospitalization. The female sex; a lower mean educational level; a greater prevalence of previous suicide attempts; a higher level of pain; a higher prevalence of family antecedents of mental disorders; a lower resilience score; and higher childhood trauma score were the factors significantly associated with screening positive for major depression ($P < 0.05$). Multivariate analysis demonstrated that the factors independently associated with the depressive symptoms were a higher childhood trauma severity (OR = 1.06; $P = 0.004$); moderate to severe nicotine dependence (OR = 8.58; $P = 0.008$); and the number of previous hospital admissions (OR = 1.11; $P = 0.034$). The obtained logistic model was considered valid, indicating that the three factors together distinguished between having or not depressive symptoms, and correctly classified 74.6% of individuals in the sample.

CONCLUSION

Our results demonstrate that inpatients presenting both CVD and a positive screening for depression are more prone to have antecedents of childhood trauma, nicotine dependence and a higher number of previous hospitalizations.

Key words: Inpatients; Depression; Cardiovascular disease; Depressive symptoms; General hospital

Core tip: The prevalence of depression is considerably higher among individuals with cardiovascular diseases (CVD) when compared to the general population. Both major depression and depressive symptoms are predictors of poor outcome in patients with CVD. Depressive disorder is frequently overlooked and untreated in individuals with CVD. Our results demonstrate that inpatients presenting both CVD and a positive screening for depression are more prone to have antecedents of childhood trauma, nicotine dependence and a higher number of previous hospitalizations. Clinicians may consider these factors in the assessment of CVD inpatients at risk for major depression. This measure can improve their treatment approach and patients' prognosis.

Barreto FJN, Garcia FD, Prado PHT, Rocha PMB, Las Casas NS, Vallt FB, Correa H, Neves MCL. Childhood trauma and factors associated with depression among inpatients with cardiovascular disease. *World J Psychiatr* 2017; 7(2): 106-113 Available from: URL: http://www.wjgnet.com/2220-3206/full/v7/i2/106.htm DOI: http://dx.doi.org/10.5498/wjp.v7.i2.106

INTRODUCTION

The prevalence of major depressive disorder (MD) is four times higher among individuals with cardiovascular diseases (CVD) when compared to the general population[1-4], and MD is a predictor for future CVD. MD increases the risk for coronary arterial disease (CAD) by 56%, independent of other traditional cardiovascular risk factors[1]. Moreover, MD and depressive symptoms are predictors of poor outcome in patients with CVD regarding morbidity and mortality[2,3].

Maltzberg[4] first reported the bidirectional relationship between MD and CVD in 1937. This author observed an increase in mortality from CVD in patients with severe depression. More recently, some authors reported that post-myocardial infarction depression increases the risk of all-cause mortality (RR = 2.25) and of cardiac events (RR = 1.59) within 24 mo after the event[5]. Even in the absence of depressive symptoms, a positive history of depression in first-degree relatives may influence the cardiovascular risk profile in adulthood, comparing to control group[6].

Various biological modifications, previously found in patients with depression, may explain these findings. An increased concentration of inflammatory biomarkers (C-reactive protein, interleukins 1 and 6), metabolic dysregulation, dysfunctions in the platelet clotting cascade, decreased variability in heart rate, hyperactivation of hypothalamus-pituitary-adrenal axis and reduction in circulating endothelial progenitor cells are some of the factors that may be at the pathophysiological origin of the association between depression and CVD[2,7-9]. Finally, both depression and CVD have notorious genetic determinants, which may underlie the development of one and another as shared risk factors[2,10]. Even acute and chronic life stressors may increase the risk for developing one of these diseases[2,10]. Adverse events in early life can directly affect genome through epigenetic mechanisms and contribute to the expression or exacerbation of a genetic susceptibility for depression, CVD or both in adulthood[2].

During hospitalization, depression decreases inpatients'

treatment adherence, increases functional disability and extends hospital length of stay[11,12]. Inpatients with CVD presenting positive screening for depression at discharge have a 2.5 fold increase in relative risk of experiencing a CVD-related hospitalization, even after adjustment for traditional cardiovascular risk factors and measures of disease severity[13].

Depression is still a frequently overlooked and untreated condition among individuals with CVD[14,15]. The same applies for those admitted to general hospitals, a population in which 28% present criteria for depressive disorders[16]. Less than one in four cases of major depression among inpatients are correctly diagnosed by assisting physicians[14]. In addition, only half the members of the American College of Cardiologists treat depression properly, according to a national survey[17].

Inpatients with CVD have increased vulnerability for depression. Improving the knowledge on how much risk factors influence the chances of becoming depressed may improve identification of MD among this population in the general hospital setting. We hypothesized that inpatients presenting both CVD and a positive screening for major depression are more prone to be of female sex; to present personal and familiar antecedents of psychiatric disorders (*e.g.*, suicide attempts, addictions); to present worse indicators of CVD (*e.g.*, increased number of previous hospital admissions, present pain and a worse score of functionality); and present lower resilience and antecedents of childhood trauma. Our primary goal was to assess the factors mentioned above in a population of inpatients with CVD in a university hospital.

MATERIALS AND METHODS

This cross-sectional design study encompassed a subsample of a larger study that investigated suicide behaviour among general hospital inpatients. We included all inpatients admitted to the wards of the University Hospital of the Federal University of Minas Gerais (UH-UFMG), hospitalized from November 2013 to October 2015. The UH-UFMG is a tertiary regional reference centre.

The Committee of Ethics in Research of UFMG approved the protocol, registered with the number CAAE 13605213.3.0000.5149. We obtained written informed consent from all participants, after providing a complete description of the study. All subjects screening positive for a psychiatric disorder received consultation-liaison psychiatric evaluations.

Subjects

For the initial study, we included inpatients aged 18-year-old or older, hospitalized in a clinical ward and excluded patients hospitalized with surgical indication. In the present study, we selected all patients with a diagnosis of CVD (*e.g.*, CAD, congestive heart failure, Chagas cardiomyopathy, cardiac arrhythmia or any other cardiac disease that required hospitalization) and excluded subjects screening positive for delirium and mild to severe cognitive impairment or dementia as well as those unable to comprehend, illiterate or with major visual or hearing impairment. We summarized the inclusion procedure in the flowchart (Figure 1).

Instruments and procedures

After a clinical assessment and stabilization, we included all subjects at admission. Experienced psychiatrists, trained to perform the assessments foreseen in the study protocol, evaluated the subjects. All the scales used in this study had been previously translated and culturally adapted to Brazilian Portuguese.

We screened delirium using the Confusion Assessment Method[18] and cognitive impairment through the Montreal Cognitive Assessment[19] using 17 as a cut-off point[20].

For screening MD, we used the Hospital Anxiety and Depression Scale (HADS-d). This scale has acceptable properties for use in inpatients with CVD[21]. Scores of $\geqslant$ 8 indicate a positive screening for depression, according to the Brazilian validation study that issued a sensibility of 84.6% and specificity of 90.3%[22].

We used the visual analogue scale to assess pain intensity[23]. We determined the basic and instrumental activities of daily living (ADL) using the Katz Index and the Pfeffer's Functional Activities Questionnaire (PFAQ), respectively[24]. We considered scores $\geqslant$ 5 in the PFAQ as characteristic of dependence on instrumental ADL[25].

We considered a score $\geqslant$ 8 on the Alcohol Use Disorders Identification Test to assess problematic alcohol use[26] and a score $\geqslant$ 4 on the Fagerström Test for Nicotine Dependence to characterize moderate to severe nicotine dependence[27].

We considered the levels of positive psychosocial adjustment given major life events, like resilience, and used the Wagnild and Young Resilience Scale (WYRS) to evaluate resilience level. The WYRS is a paper-and-pencil scale, composed of 25 likert-type items[28] and, as the validation study did not establish a cut-off point, we used the raw results in our analysis. For assessing early-life trauma we used the Childhood Trauma Questionnaire (CTQ)[29]. The CTQ is a 28-item self-report inventory that provides a valid screening for early life abuse or negligence.

Statistical analysis

In the descriptive analysis, we calculated measures of central tendency and dispersion. The Shapiro-Wilk test assessed data normality. For univariate analysis, a χ^2 test was considered for categorical variables and Mann-Whitney test for continuous variables. To determine which factors had a greater association with positive screening for depression in our sample, we conducted a multiple logistic regression with stepwise selection. Those variables with P value $\leqslant$ 0.2 in univariate analysis were apt to enter the model. The χ^2 test model and Nagelkerke's R^2 used to evaluate the predictive ability of the logistic model obtained. Calculation of odds ratios (OR) considered a 95%CI and significance of $P < 0.05$.

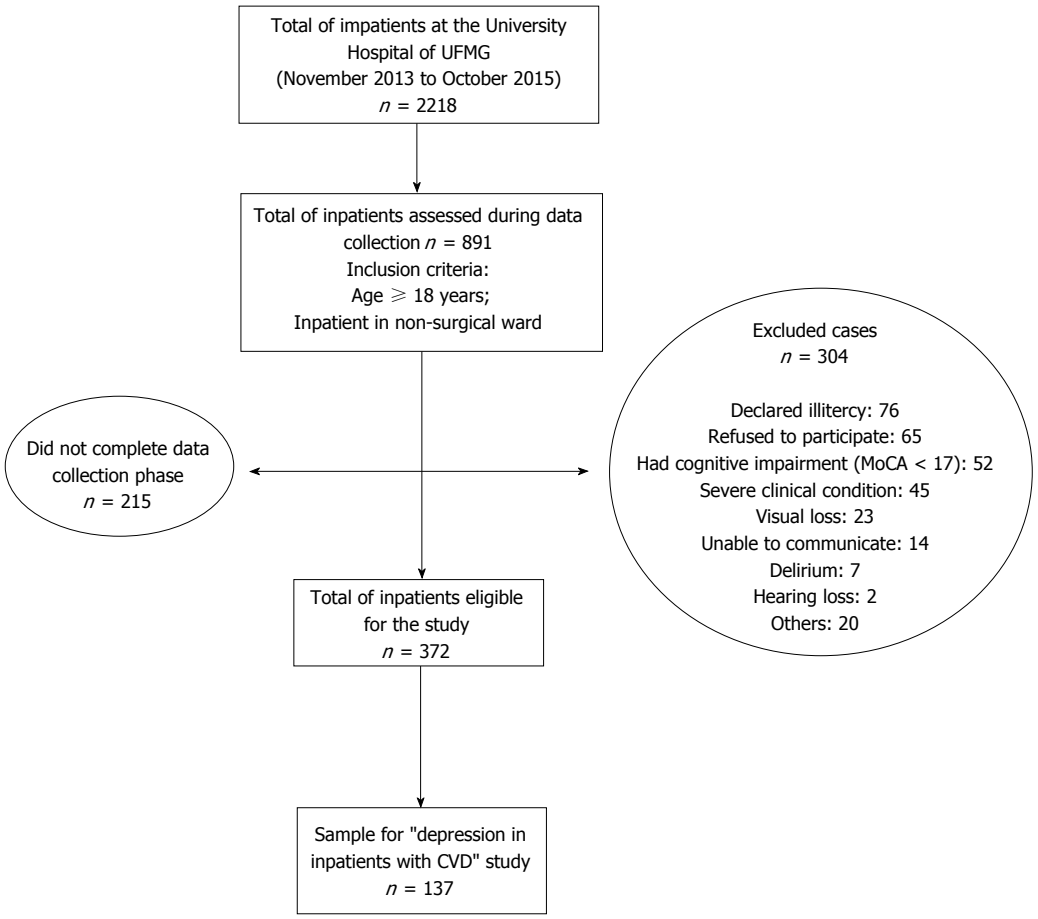


Figure 1 Flowchart of subjects included in the study. UFMG: The Federal University of Minas Gerais; CVD: Cardiovascular disease.

All analyses were performed using SPSS software version 20 (IBM Corporation© 2011).

RESULTS

Sample description

At endpoint, we included 137 subjects and found a higher prevalence of males [*n* = 92 (67.2%)], a mean age of 52.1 ± 12.5 years old and a mean educational level of 8.5 ± 4.4 years. The most prevalent CVD diagnoses were CAD (*n* = 76; 55.5%), congestive heart failure (*n* = 43; 31.4%) and cardiac arrhythmia (*n* = 15; 10.9%). CAD, the most frequent cardiovascular diagnosis, was not associated with positive screening for major depression. Seventy-five (54.7%) and 23 (16.8%) subjects presented hypertension and diabetes mellitus, respectively.

Factors associated with positive screening for depression

Thirty-eight (27.7%) subjects screened positive for depression and nine (23.7%) were taking antidepressants during hospitalization. Female sex, lower mean educational level, greater number of previous suicide attempts, higher level of pain, higher prevalence of family antecedents of mental disorders, lower resilience score and higher childhood trauma score were the factors significantly associated to screening positive for major depression (Table 1).

Three factors remained statistically associated with a positive screening for depression (Table 2) in multivariate analysis: (1) childhood trauma; (2) moderate or severe nicotine dependence; and (3) the number of hospital admissions.

Patients with moderate and severe nicotine dependence were 8.58 times more prone to screen positive for depression ($P = 0.008$).

The chance to screen positive for depression increased 11% for each hospital admission ($P = 0.034$) and 6% for each point of increase in the CTQ score for childhood trauma ($P = 0.004$).

The logistic model indicated that the three factors together distinguished between positive screening for depression or not, and correctly classified 74.6% of individuals in the sample (χ^2: 17.974, $P < 0.001$, D.F. = 1; Nagelkerke R^2: 0.33).

DISCUSSION

This study assessed the influence of the factors associated with positive screening for depression in a sample of patients with CVD hospitalized in a university hospital. After multiple comparisons, we found that positive screening for depression was significantly associated with

Table 1 Factors associated with positive screening for depression (Hospital Anxiety and Depression scale - depression subscale score ≥ 8) in inpatients with cardiovascular diseases (*n* = 137) *n* (%)

	Screening for depression		Missing data (%)	*P* value
	Yes	No		
Sociodemographic variables				
Gender				
Male	15 (39.5)	77 (77.8)	-	< 0.001[a]
Female	23 (60.5)	22 (22.2)	-	
Age, mean (SD)	53.7 ± 11.4	51.5 ± 12.8	-	0.444
Elder (aged ≥ 60 yr)	15 (39.5)	24 (24.2)	-	0.077
Educational level in years (mean ± SD)	7.4 ± 4.4	8.5 ± 4.3	1.5	0.035[b]
Married/lives with partner	25 (65.8)	70 (70.7)	0.7	0.723
Lives alone	3 (8.1)	9 (9.1)	0.7	0.857
Any son	34 (91.9)	83 (84.7)	1.5	0.272
Unemployed	9 (24.3)	23 (23.5)	1.5	0.917
Religion	35 (94.6)	91 (91.9)	0.7	0.595
Clinical variables				
N° of previous hospital admissions, mean (SD)	7.6 ± 9.1	5 ± 5.2	5.8	0.07[b]
CAD	18 (47.4)	58 (58.6)	-	0.237
Congestive heart failure	12 (31.6)	31 (31.3)	-	0.976
Cardiac arrhythmia	5 (13.3)	10 (10.1)	-	0.76
Hypertension	19 (50)	56 (56.6)	-	0.489
Diabetes mellitus	5 (13.2)	18 (18.2)	-	0.481
Pain level, mean (SD)	2.2 ± 2.9	1.3 ± 2.4	0.7	0.136
Propranolol	8 (21.1)	12 (13.5)	8.0	0.255
Dependence in basic ADL	10 (26.3)	14 (14.1)	0.7	0.09
Dependence in instrumental ADL	2 (22.2)	4 (17.4)	76.6	0.753
Psychosocial variables				
Family history of mental disorder	18 (47.4)	20 (20.2)	-	0.001[a]
Previous suicide attempt	11 (28.9)	8 (8.2)	0.7	0.002[a]
Moderate to severe nicotine dependence	7 (18.4)	10 (10.1)	-	0.186
Problematic alcohol use	7 (30.4)	13 (18.84)	32.8	0.243
Resilience score, WYS mean (SD)	138.5 ± 14.5	144.9 ± 14.9	2.9	0.029[b]
Childhood trauma score, CTQ mean (SD)	46.4 ± 20.1	37.5 ± 12.6	8.8	0.004[b]

[a]χ^2 test significant if $P < 0.05$; [b]Mann-Whitney test significant if $P < 0.05$. CAD: Coronary arterial disease; ADL: Activities of daily living; WYS: Wagnild and Young Scale; CTQ: Childhood Trauma Questionnaire.

Table 2 Logistic regression analysis of factors associated with positive screening for depression (Hospital Anxiety and Depression scale - depression subscale score ≥ 8) in inpatients with coronary arterial disease

Variable	B	EP	Wald	OR	95%CI	*P*
Moderate to severe nicotine dependence	2.15	6.91	7.135	8.58	1.77-41.57	0.008
N° of previous hospital admissions	0.106	0.06	4.505	1.11	1.01-1.23	0.034
High childhood trauma severity (CTQ)	0.06	0.02	8.2	1.06	1.02-1.11	0.004
Constant	-4.664	0.01	16.141	0.01	0.00-0.09	< 0.001

χ^2: 17.974, $P < 0.001$, D.f. = 1; Nagelkerke R^2: 0.33. CTQ: Childhood Trauma Questionnaire.

childhood trauma, the severity of nicotine dependence, and the number of previous hospital admissions. These results partially agree with our initial hypothesis as no association was found with some of the factors previously related with major depression, such as: Personal and familiar antecedents of psychiatric disorders (*e.g.*, suicide attempts, addictions), pain perception, a worse score of functionality, and a lower resilience level. To the best of our knowledge, only one study reported risk factors associated with depression in patients with CVD[30]. However, no study evaluated such a vast array of epidemiological, clinical and psychological factors associated with depression in patients hospitalized with CVD.

Our results should be regarded considering a few issues. First, our study has a cross-sectional design and, as such, hinders the evaluation of causality between the factors evaluated and major depression. Second, our sample included patients with different types of CVD. We have grouped the distinct disorders in a unique group as they share common risk factors and etiological mechanisms associated with inflammatory processes; previous studies have adopted this same strategy[30]. Finally, we have not been able to assess the severity of CVD with an objective measure within this study.

Our sample presented a rate of 27.7% of patients screening positive for depression. This result is comparable with previous studies, which reported a prevalence of

13.5% to 47% of major depression in inpatients with CVD[16,30-33]. Different from previous studies, that reported only 5% of patients with CVD and depression were being treated with antidepressants[33], in our sample, 23.7% of the subjects were taking an antidepressant.

Stressful experiences during the lifespan have been associated with CVD[34] and depression[35]. Childhood trauma is one of the most significant predictors of health problems, life expectancy, psychiatric disorders and the severity of clinical diseases' courses[36]. The occurrence of childhood trauma can influence the development of CVD through changes in metabolic, cardiovascular risk factors like dyslipidemia, central obesity, and hyperglycemia. A Dutch cohort study found that among the childhood trauma subtypes and personality traits, sexual abuse was the primary factor that correlated negatively with serum cholesterol and abdominal circumference measurements[37]. Recurrent stressful events may induce a subtle chronic inflammatory response, enough to contribute to the progression of atherosclerosis and increased the risk of developing CAD[38]. Our results highlight the importance of the assessment of childhood trauma in patients with CVD, as the severity of trauma may predict depression in this population. Clinicians must consider that one possible mechanism of the association between childhood trauma, depression and CVD is the disruption of the key stress-response system, such as the catecholamine system, the hypothalamic-pituitary-adrenal axis, and neurotrophic factors, in early stages of child development. The impairment of the stress response system can influence arousal and emotional behaviour and contribute to increase the allostatic load, impairing brain development and increasing the risk for psychopathology[36].

As reported in the paper of Caro *et al*[30], our results point that nicotine dependence is associated with a positive screening for depression in CVD inpatients. Nicotine dependence is more prevalent in individuals with depression, possibly because these subjects are less prone to engage in smoking cessation programs[9] and tend to use nicotine to alleviate anxiety and dysphoria[39]. As other risk factors for CVD, cigarette use has been associated with damage of the arterial wall. Moreover, the intensification of cigarette use maintains inflammatory response, like chronic stress, and increases risk for depression and CVD[2]. Also, both depression and CVD increase the systemic pro-inflammatory state[2,7], aggravating the pathophysiological mechanisms related to CVD and closing a vicious cycle[38].

Presenting a greater number of previous hospital admissions was another factor associated with positive screening for depression in our study. These results agree with previous findings regarding inpatients with several medical illnesses[32]. Compared to those without depression, medical inpatients suffering from depression have longer hospital stays and higher readmission rates. Both factors underline the burden of this affective disorder among CVD patients, including the financial burden[12,40]. Moreover, each hospital admission can represent an acute stressor for those who experience it, raising negative feelings about an individual's current health state and prognosis, augmenting depressive symptoms. In the same manner, a higher number of hospitalizations may represent a proxy for CVD severity. Other CVD severity measures were significantly associated with depression in inpatients, namely having an implantable cardioverter defibrillator or being in functional class Ⅲ or Ⅳ[33].

How can we link these three factors to CVD and major depression? In our view, either childhood trauma, nicotine dependence and the number of previous hospitalizations have been associated with stress arousal and pro-inflammatory states. Both conditions are well-known risk factors for major depression and CVD[36].

Our results demonstrate that inpatients presenting both CVD and a positive screening for major depression are more prone to have antecedents of childhood trauma, nicotine dependence and a higher number of previous hospitalizations. Clinicians may consider these factors in the assessment of CVD inpatients at risk for major depression. This measure can improve their treatment approach and patients' prognoses.

ACKNOWLEDGMENTS

We thank Mr. André A. C. de Freitas for performing the review and editing of this paper.

COMMENTS

Background

The prevalence of depression is considerably higher among individuals with cardiovascular diseases (CVD) when compared to the general population. Both major depression and depressive symptoms are predictors of poor outcome in patients with CVD. Depressive disorder is frequently overlooked and untreated in individuals with CVD.

Innovations and breakthroughs

This study assessed the influence of the factors associated with positive screening for depression in a sample of patients with CVD hospitalized in a university hospital. After multiple comparisons, the authors found that positive screening for depression was significantly associated with childhood trauma, the severity of nicotine dependence, and the number of previous hospital admissions.

Applications

The results demonstrate that inpatients presenting both CVD and a positive screening for major depression are more prone to have antecedents of childhood trauma, nicotine dependence and a higher number of previous hospitalizations. Clinicians may consider these factors in the assessment of CVD inpatients at risk for major depression. This measure can improve their treatment approach and patients' prognoses.

Peer-review

This is a cross-sectional survey of risk factors associated with depression in patients hospitalized in non-surgical wards and suffering in cardiovascular disease. As both cardiovascular diseases and depression are frequent and possessing a great burden on the family and the society, the study is relevant and interesting.

REFERENCES

1 **Charlson FJ**, Moran AE, Freedman G, Norman RE, Stapelberg

NJ, Baxter AJ, Vos T, Whiteford HA. The contribution of major depression to the global burden of ischemic heart disease: a comparative risk assessment. *BMC Med* 2013; **11**: 250 [PMID: 24274053 DOI: 10.1186/1741-7015-11-250]
2 **Nemeroff CB**, Goldschmidt-Clermont PJ. Heartache and heartbreak--the link between depression and cardiovascular disease. *Nat Rev Cardiol* 2012; **9**: 526-539 [PMID: 22733213 DOI: 10.1038/nrcardio.2012.91]
3 **Fuster V**, Vedanthan R. Cardiovascular disease and the UN Millennium Development Goals: time to move forward. *Nat Clin Pract Cardiovasc Med* 2008; **5**: 593 [PMID: 18813335 DOI: 10.1038/ncpcardio1353]
4 **Maltzberg B**. Mortality among patients with involutional melancholia. *Am J Psychiatr* 1937: 93
5 **Meijer A**, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research. *Gen Hosp Psychiatry* 2011; **33**: 203-216 [PMID: 21601716 DOI: 10.1016/j.genhosppsych.2011.02.007]
6 **Mannie ZN**, Williams C, Diesch J, Steptoe A, Leeson P, Cowen PJ. Cardiovascular and metabolic risk profile in young people at familial risk of depression. *Br J Psychiatry* 2013; **203**: 18-23 [PMID: 23703316 DOI: 10.1192/bjp.bp.113.126987]
7 **Elderon L**, Whooley MA. Depression and cardiovascular disease. *Prog Cardiovasc Dis* 2013; **55**: 511-523 [PMID: 23621961 DOI: 10.1016/j.pcad.2013.03.010]
8 **Seligman F**, Nemeroff CB. The interface of depression and cardiovascular disease: therapeutic implications. *Ann N Y Acad Sci* 2015; **1345**: 25-35 [PMID: 25809518 DOI: 10.1111/nyas.12738]
9 **Penninx BW**. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. *Neurosci Biobehav Rev* 2017; **74**: 277-286 [PMID: 27461915 DOI: 10.1016/j.neubiorev.2016.07.003]
10 **Mulle JG**, Vaccarino V. Cardiovascular disease, psychosocial factors, and genetics: the case of depression. *Prog Cardiovasc Dis* 2013; **55**: 557-562 [PMID: 23621965 DOI: 10.1016/j.pcad.2013.03.005]
11 **Botega NJ**, Mitsuushi GN, Azevedo RC, Lima DD, Fanger PC, Mauro ML, Gaspar KC, Silva VF. Depression, alcohol use disorders and nicotine dependence among patients at a general hospital. *Rev Bras Psiquiatr* 2010; **32**: 250-256 [PMID: 20602014]
12 **Sibitz I**, Berger P, Freidl M, Topitz A, Krautgartner M, Spiegel W, Katschnig H. ICD-10 or DSM-IV? Anhedonia, fatigue and depressed mood as screening symptoms for diagnosing a current depressive episode in physically ill patients in general hospital. *J Affect Disord* 2010; **126**: 245-251 [PMID: 20400184 DOI: 10.1016/j.jad.2010.03.023]
13 **Meyer FA**, Hugentobler E, Stauber S, Wilhelm M, Znoj H, von Känel R. Depressive symptoms at discharge from rehabilitation predict future cardiovascular-related hospitalizations. *Cardiology* 2015; **131**: 80-85 [PMID: 25870996 DOI: 10.1159/000375231]
14 **Lichtman JH**, Bigger JT, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lespérance F, Mark DB, Sheps DS, Taylor CB, Froelicher ES. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. *Circulation* 2008; **118**: 1768-1775 [PMID: 18824640 DOI: 10.1161/CIRCULATIONAHA.108.190769]
15 **Rentsch D**, Dumont P, Borgacci S, Carballeira Y, deTonnac N, Archinard M, Andreoli A. Prevalence and treatment of depression in a hospital department of internal medicine. *Gen Hosp Psychiatry* 2007; **29**: 25-31 [PMID: 17189741 DOI: 10.1016/j.genhosppsych.2006.08.008]
16 **Yanzón de la Torre A**, Oliva N, Echevarrieta PL, Pérez BG, Caporusso GB, Titaro AJ, Todaro Kicyla A, Cuatz M, Locatelli M, Nelson LM, Mac Mullen M, Baldessarini RJ, Daray FM. Major depression in hospitalized Argentine general medical patients: Prevalence and risk factors. *J Affect Disord* 2016; **197**: 36-42 [PMID: 26967917 DOI: 10.1016/j.jad.2016.02.066]
17 **Feinstein RE**, Blumenfield M, Orlowski B, Frishman WH, Ovanessian S. A national survey of cardiovascular physicians' beliefs and clinical care practices when diagnosing and treating depression in patients with cardiovascular disease. *Cardiol Rev* 2006; **14**: 164-169 [PMID: 16788327 DOI: 10.1097/01.crd.0000200977.41695.43]
18 **Fabbri RM**, Moreira MA, Garrido R, Almeida OP. Validity and reliability of the Portuguese version of the Confusion Assessment Method (CAM) for the detection of delirium in the elderly. *Arq Neuropsiquiatr* 2001; **59**: 175-179 [PMID: 11400020]
19 **Nasreddine ZS**, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; **53**: 695-699 [PMID: 15817019 DOI: 10.1111/j.1532-5415.2005.53221.x]
20 **Trzepacz PT**, Hochstetler H, Wang S, Walker B, Saykin AJ. Relationship between the Montreal Cognitive Assessment and Mini-mental State Examination for assessment of mild cognitive impairment in older adults. *BMC Geriatr* 2015; **15**: 107 [PMID: 26346644 DOI: 10.1186/s12877-015-0103-3]
21 **Zigmond AS**, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**: 361-370 [PMID: 6880820 DOI: 10.1016/j.genhosppsych.2007.06.005]
22 **Botega NJ**, Bio MR, Zomignani MA, Garcia C, Pereira WA. [Mood disorders among inpatients in ambulatory and validation of the anxiety and depression scale HAD]. *Rev Saude Publica* 1995; **29**: 355-363 [PMID: 8731275]
23 **Carvalho DSK**. P A: Avaliação da intensidade da dor. *Migrâneas and Cefaleias* 2006; **9**: 164
24 **Katz S**, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. the index of adl: a standardized measure of biological and psychosocial function. *JAMA* 1963; **185**: 914-919 [PMID: 14044222]
25 **Sanchez MAS**, Correa PCR, Lourenço RA. Cross-cultural adaptation of the "Functional Activities Questionnaire- FAQ" for use in Brazil. *Dement Neuropsychol* 2011; **5**: 322-327
26 **Saunders JB**, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addiction* 1993; **88**: 791-804 [PMID: 8329970]
27 **Fagerström KO**. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addict Behav* 1978; **3**: 235-241 [PMID: 735910]
28 **Wagnild GM**, Young HM. Development and psychometric evaluation of the Resilience Scale. *J Nurs Meas* 1993; **1**: 165-178 [PMID: 7850498]
29 **Grassi-Oliveira R**, Stein LM, Pezzi JC. [Translation and content validation of the Childhood Trauma Questionnaire into Portuguese language]. *Rev Saude Publica* 2006; **40**: 249-255 [PMID: 16583035 DOI: 10.1590/S0034-89102006000200010]
30 **Caro MA**, Sowden GL, Mastromauro CA, Mahnks S, Beach SR, Januzzi JL, Huffman JC. Risk factors for positive depression screens in hospitalized cardiac patients. *J Cardiol* 2012; **60**: 72-77 [PMID: 22436292 DOI: 10.1016/j.jjcc.2012.01.016]
31 **Pakriev S**, Kovalev J, Mozhaev M. Prevalence of depression in a general hospital in Izhevsk, Russia. *Nord J Psychiatry* 2009; **63**: 469-474 [PMID: 19551555 DOI: 10.3109/08039480903062950]
32 **Yan ZY**, Gu MJ, Zhong BL, Wang C, Tang HL, Ling YQ, Yu XW, Li MQ. Prevalence, risk factors and recognition rates of depressive disorders among inpatients of tertiary general hospitals in Shanghai, China. *J Psychosom Res* 2013; **75**: 65-71 [PMID: 23751241 DOI: 10.1016/j.jpsychores.2013.03.003]
33 **Suzuki T**, Shiga T, Kuwahara K, Kobayashi S, Suzuki S, Nishimura K, Suzuki A, Omori H, Mori F, Ishigooka J, Kasanuki H, Hagiwara N. Depression and outcomes in hospitalized Japanese patients with cardiovascular disease. - Prospective single-center observational

study-. *Circ J* 2011; **75**: 2465-2473 [PMID: 21791870]
34 **Bomhof-Roordink H**, Seldenrijk A, van Hout HP, van Marwijk HW, Diamant M, Penninx BW. Associations between life stress and subclinical cardiovascular disease are partly mediated by depressive and anxiety symptoms. *J Psychosom Res* 2015; **78**: 332-339 [PMID: 25736692 DOI: 10.1016/j.jpsychores.2015.02.009]
35 **Teicher MH**, Samson JA. Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *Am J Psychiatry* 2013; **170**: 1114-1133 [PMID: 23982148 DOI: 10.1176/appi.ajp.2013.12070957]
36 **Duarte DG**, Neves Mde C, Albuquerque MR, de Souza-Duran FL, Busatto G, Corrêa H. Gray matter brain volumes in childhood-maltreated patients with bipolar disorder type I: A voxel-based morphometric study. *J Affect Disord* 2016; **197**: 74-80 [PMID: 26970268 DOI: 10.1016/j.jad.2016.02.068]
37 **van Reedt Dortland AK**, Giltay EJ, van Veen T, Zitman FG, Penninx BW. Personality traits and childhood trauma as correlates of metabolic risk factors: the Netherlands Study of Depression and Anxiety (NESDA). *Prog Neuropsychopharmacol Biol Psychiatry* 2012; **36**: 85-91 [PMID: 22001949 DOI: 10.1016/j.pnpbp.2011.10.001]
38 **Lagraauw HM**, Kuiper J, Bot I. Acute and chronic psychological stress as risk factors for cardiovascular disease: Insights gained from epidemiological, clinical and experimental studies. *Brain Behav Immun* 2015; **50**: 18-30 [PMID: 26256574 DOI: 10.1016/j.bbi.2015.08.007]
39 **Minichino A**, Bersani FS, Calò WK, Spagnoli F, Francesconi M, Vicinanza R, Delle Chiaie R, Biondi M. Smoking behaviour and mental health disorders--mutual influences and implications for therapy. *Int J Environ Res Public Health* 2013; **10**: 4790-4811 [PMID: 24157506 DOI: 10.3390/ijerph10104790]
40 **von Ammon Cavanaugh S**, Furlanetto LM, Creech SD, Powell LH. Medical illness, past depression, and present depression: a predictive triad for in-hospital mortality. *Am J Psychiatry* 2001; **158**: 43-48 [PMID: 11136632 DOI: 10.1176/appi.ajp.158.1.43]

P- Reviewer: Gazdag G, Hosak L **S- Editor**: Song XX **L- Editor**: A **E- Editor**: Li D

World Journal of Psychiatry

Submit a Manuscript: http://www.f6publishing.com

World J Psychiatr 2017 June 22; 7(2): 114-120

DOI: 10.5498/wjp.v7.i2.114

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Relation of binge eating disorder with impulsiveness in obese individuals

Cenk Ural, Hasan Belli, Mahir Akbudak, Ali Solmaz, Zuhal Dogan Bektas, Fatih Celebi

Cenk Ural, Hasan Belli, Zuhal Dogan Bektas, Department of Psychiatry, Health Sciences University, Bagcilar Education And Research Hospital, 34100 Istanbul, Turkey

Mahir Akbudak, Department of Psychiatry, Mardin State Hospital, 47100 Mardin, Turkey

Ali Solmaz, Fatih Celebi, Department of General Surgery, Health Sciences University, Bagcilar Education And Research Hospital, 34100 Istanbul, Turkey

Author contributions: Ural C and Belli H designed the study and wrote the manuscript; Ural C and Belli H conducted the data processing and analysis; Akbudak M, Solmaz A, Bektas ZD and Celebi F collected the data.

Institutional review board statement: The study was approved by Health Sciences University, Bagcilar Education And Research Hospital.

Informed consent statement: All involved persons gave their informed constent prior to study inclusion.

Conflict-of-interest statement: I declare that we have no conflict of interests related to this research.

Data sharing statement: No.

Manuscript source: Invited manuscript

Correspondence to: Hasan Belli, MD, Associate Professor, Department of Psychiatry, Health Sciences University, Bagcilar Education And Research Hospital, Merkez Mahallesi, Bagcılar, 34100 Istanbul, Turkey. hasan.belli@saglik.gov.tr

Telephone: +90-212-4404000
Fax: +90-212-4404242

Received: December 17, 2016
Peer-review started: December 19, 2016
First decision: April 18, 2017
Revised: May 5, 2017
Accepted: May 18, 2017
Article in press: May 19, 2017
Published online: June 22, 2017

Abstract

AIM

To investigate the levels of impulsiveness, and the relationship between the binge eating disorder (BED) and the levels of impulsiveness in obese individuals.

METHODS

Two hundred and forty-one obese patients who were included in the study and candidate for bariatric surgery (weight loss surgery) were clinically interviewed to identify the BED group, and patients were divided into two groups: Those with BED and those without BED. The comorbidity rate of groups was determined by using structured clinical interview for DSM-Ⅳ (SCID-Ⅰ). A sociodemographic data form including the story of previous psychiatric treatment, structured clinical interview for DSM-Ⅳ (SCID-Ⅰ), Beck Anxiety Inventory, Beck Depression Inventory (BDI) and Barratt Impulsiveness Scale-11 were applied to both of the groups.

RESULTS

In regard to 241 obese individuals included in the study, total score and score of attention subscale for BED (+) group were significantly high ($P < 0.05$). In addition, suicide attempt, story of psychiatric consultation, and score for BDI were again significantly high in the BED (+) group ($P < 0.05$).

CONCLUSION
In assessment of obese individuals, assessment of associated psychopathology such as impulsive characteristics and suicide attempt in addition to disrupted eating behaviors will allow to have a more extensive view.

Key words: Binge eating; Obesity; Impulsiveness

Core tip: Impulsiveness is a multidimensional personality trait that leads to uncontrolled and excessive intake of food, thus contributing to development and maintenance of obesity. Obese patients who were included in the study and candidate for weight loss surgery were clinically interviewed to identify the binge eating disorder (BED) group and patients were divided into two groups: Those with BED and those without BED. Impulsivity, suicide attempt, story of psychiatric consultation, and score for depression were significantly high in the BED (+) group. Impulsive characteristics and suicide attempt in addition to disrupted eating behaviors will allow to have a more extensive view.

Ural C, Belli H, Akbudak M, Solmaz A, Bektas ZD, Celebi F. Relation of binge eating disorder with impulsiveness in obese individuals. *World J Psychiatr* 2017; 7(2): 114-120 Available from: URL: http://www.wjgnet.com/2220-3206/full/v7/i2/114.htm DOI: http://dx.doi.org/10.5498/wjp.v7.i2.114

INTRODUCTION

Over the past 30 years, the prevalence of obesity has been gradually increased worldwide and the obesity is regarded as one of the major problems for community health[1,2]. Furthermore, obesity is a condition associated with reduced life expectancy[3]. Impulsiveness is a multidimensional personality trait that leads to uncontrolled and excessive intake of food, thus contributing to development and maintenance of obesity[4,5].

After defined by Albert Stunkard for the first time[6], research on binge eating disorder (BED) has been increasingly growing in time. While BED is included in the eating disorder not otherwise specified in the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders 4th revised edition), it is reclassified alone[7] under a separate title for diagnosis in the DSM-5[8] published in May 2013. So, the BED is classified as a standard eating disorder as Anorexia Nervosa and Bulimia Nervosa[9]. Redefining BED has not changed the diagnostic criteria, but time criteria for incidence of BED attacks is reduced in order to facilitate diagnosis of BED. Such changes may be seen as increased importance of BED diagnosis category.

The binge eating behavior is largely associated with obesity and defines a subgroup of individuals with excessive eating that shows significant differences[10]. The BED may be seen in general society, but is mostly seen in obese individuals and in groups seeking a therapy for obesity[11]. The BED is characterized by compulsively eating a large amount of food without balancing behavior and it is the most common eating disorder in the obese patients[7]. Although the prevalence of BED varies in a wide range in the obese population, it may be as high as 30%-57% in obese individuals seeking for a therapy and morbidly obese individuals who are candidate for bariatric surgery[11-14]. In a multi-center fieldwork including 1984 cases, the prevalence of BED was 2% in the general population and 30.1% in the population participating in hospital-supported weight control programs[15]. The rate for BED was 23.1% in a study including 281 non-obese university students in our country[16]. In other studies performed on obese patients in our country again, the rates for BED were 22.4% and 23%, respectively[17,18].

Failures in the bariatric surgery are attributed to psychological factors and/or eating disorders rather than technical causes[19]. Impulsiveness may be a predictor for poor prognosis and negative outcomes in eating disorders[20,21]. The presence of BED may cause to regain the weight that has been lost after bariatric surgery[22-24]. However in our study, there was no significant differences between the mean body mass index (BMI) of BED (+) and BED (-) groups. The reason for this result can be related with that BED might be affecting the recovery of the lost body weight, not the initial weight loss.

Increasing number of literatures suggest that eating disorders are associated with impulsiveness especially when binge eating is prominent[25,26]. The literature has studies indicating that those with BED have higher impulsive characteristics[27-31]. There is a study performed in our country that found that impulsiveness was higher in the obese individuals than that of normal control group and overweight[32]. Another Turkish study showed that morbidly obese patients had higher impulsiveness than healthy control[33].

The obesity is an area where increasingly more studies are performed about the relationship between BED and impulsiveness. Our study has relatively higher number of patients, including morbidly obese and super morbidly obese patients who were candidate for bariatric surgery. The objective of this study was to investigate the relation of BED with impulsiveness in obese patients and to provide a more extensive view on assessment of disrupted eating behavior based on the obtained results.

MATERIALS AND METHODS

Methods

Two hundred and forty-one obese patients were successively included in the study, who admitted to Bagcilar Training and Research Hospital for bariatric surgery between July 2012 and October 2013 and transferred to psychiatry service for consultation. Thirty-four (14.1%) of 241 morbidly obese patients were obese, 150 (62.2%) were morbidly obese, and 57 (23.7%) were super-

morbidly obese. These individuals were included in this study performed as part of a comprehensive review on disorders associated with obesity. Among the individuals included in the study, 60 (24.9%) were males and 181 (75.1%) were females. A clinical interview was performed with obese patients to identify the BED group. The patients were divided into two groups according to administrated structured clinical interview for DSM-IV (SCID-I) BED comorbidity rate. The age range for patients was between 16 and 61 years. The individuals who were illiterate, who stated that they were unable to complete the scales, and who voluntarily wished to discontinue during the study were excluded from the study. The exclusion criterias were: Having a psychological disease affecting reasoning, substance use, pregnancy, and any disease restricting ability to move.

The participants were administrated a sociodemographic assessment form including eating habits and diet characteristics, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Barratt Impulsiveness Scale-11 (BIS-11).

The volunteers participated in the study were asked to sign an informed consent form. It was clearly explained in detail that responses to scales provided by participants would not affect the surgical process. Approval of ethics committee of Bagcilar Training and Research Hospital was obtained for the study.

Materials

The sociodemographic data form: Developed by the researchers to collect research data, this form included sociodemographic characteristics of volunteers (age, gender, education and marital status) and questions about disease-related characteristics.

The structured clinical interview for DSM-IV Axis I disorders: A diagnostic scale developed by First *et al*[34] (1997). SCID-I has been translated into Turkish and validity and safety studies have been performed[35].

The BDI: One of the most frequently used scales for mental health screening or research on depression. It was developed by Beck in 1961. It is a self-report measure and has 21 items with 15 including psychological symptoms and 21 including somatic symptoms. The highest score to get is 63. A higher score indicates increase in complaints for depression. The cutoff score was 17 in the study performed by Hisli for validity and safety, and the author reported that scores equal to or higher than 17 were able to differentiate a depression requiring therapy with 90% of accuracy[36,37].

The BAI: This inventory comprises of 21 questions. It is a self-report measure. Each question is assessed between 0 and 3 scores and the high scores indicate the severity of anxiety experienced by individual. So, total score to get from this inventory ranges from 0 to 63. This inventory was developed by Beck (1988) and standardized for Turkish version by Ulusoy[38] (1993).

The BIS-11: Developed by Patton *et al*[39] in 1995. It is completed by patients to assess impulsiveness. Four different sub-scores are obtained from BIS-11; total score includes non-planning, attention and motor impulsivity. The higher total score from BIS-11 indicates the higher level of impulsiveness of the patient. The validation and safety study for Turkish version of BIS-11 was performed by Güleç *et al*[40].

Statistical analysis

The data were entered into the computer using SPSS 15.0 (Statistical Package for Social Science). The data were assessed by parametric and non-parametric statistical analyses based on the distribution of data. For quantitative evaluation, Mann-Whitney *U* or Student-*t* test was used for pairwise comparison. Kruskall-Wallis test was used for triple comparisons. χ^2 test was performed for qualitative evaluation. $P < 0.05$ was considered significant.

RESULTS

After psychiatric interviews conducted, 75 (31.1%) of 241 obese patients were diagnosed with BED. The BED (+) group was composed of 62 (82.7%) female and 13 (17.3%) male patients. The mean of BMI of BED (+) and BED (-) groups was compared and there were no significant differences between values which were 46.6 and 45.5 respectively. In comparison of sociodemographic data, no statistically significant differences were found between groups (Table 1). Ceasing smoking cigarette in the last six months was assessed for groups in order to exclude the influence of ceasing smoking on the weight, and no statistically significant differences were found.

The comparison of rates for previous psychiatric admittance of BED (+) and BED (-) groups of obese individuals were 49.3% and 30.1% respectively. The differences were statistically significant ($P < 0.05$). However, no statistically significant differences were found in comparison of BED (+) and BED (-) groups 8.0% and 3.0% respectively, for psychiatric comorbidity at the time of study ($P > 0.05$) (Table 2).

The difference was statistically significant in comparison of thinking of suicide in any phases of life of BED (+) and BED (-) groups of obese individuals 34.7% and 15.7% respectively and previous attempts to suicide 21.3% and 8.4% respectively ($P < 0.05$) (Table 2).

The scores of BED (+) and BED (-) groups were 20.04 ± 11.08 and 14.77 ± 8.40, respectively, in comparison of scores from BDI of two groups. The difference was statistically significant ($P < 0.05$) (Table 3).

The groups were compared for scores from BAI and the scores of BED (+) and BED (-) groups were 16.72 ± 11.76 and 13.70 ± 9.78, respectively. The difference was not statistically significant ($P > 0.05$) (Table 3).

While no significant differences were found between BED (+) and BED (-) groups in non-planning 26.59 ± 5.32 and 25.82 ± 4.34 respectively and motor sub-scales

Table 1 Comparison of the sociodemographic and clinical characteristics of the binge eating disorder (+) and binge eating disorder (-) group

		Overall		BED (+) group		BED (-) group		*P*
Age		36.49 ± 10.14		35.05 ± 9.61		37.13 ± 10.33		0.141
Sex	Females	181	75.1%	62	82.7%	119	71.7%	0.068
	Males	60	24.9%	13	17.3%	47	28.3%	
Marital status	Maried	154	63.9%	48	64.0%	106	63.9%	0.983
	Single	87	36.1%	27	36.0%	60	36.1%	
Education level	Primary	81	33.6%	28	37.3%	53	31.9%	0.62
	Middle	107	44.4%	30	40.0%	77	46.4%	0.62
	High	53	22.0%	17	22.7%	36	21.7%	0.62
Physically active	Yes	179	74.3%	55	73.3%	124	74.7%	0.874
	No	62	25.7%	20	26.7%	42	25.3%	
Weight (kg)		124.82 ± 18.23		124.37 ± 17.57		125.03 ± 18.57		0.796
BMI		45.89 ± 6.08		46.69 ± 6.69		45.53 ± 5.76		0.195
Cigaret (yr)		6.23 ± 8.35		5.45 ± 7.56		6.58 ± 8.68		0.331
Quit smoking in the last six months		31 (12.9%)		6 (8%)		25 (15.1%)		0.130

BED (+): Group with binge eating disorder; BED (-): Group without binge eating disorder; BMI: Body mass index.

Table 2 Comparison of the psychiatric and suicidal features of the binge eating disorder (+) and binge eating disorder (-) group

		Overall		BED (+) group		BED (-) group		*P*
Previous psychiatric admittance	Yes	87	36.1%	37	49.3%	50	30.1%	0.004
	No	154	63.9%	38	50.7%	116	69.9%	0.004
Psychiatric comorbidity	Yes	11	4.6%	6	8.0%	5	3.0%	0.086
	No	230	95.4%	69	92.0%	161	97.0%	0.055
Thinking of suicide	Yes	52	21.6%	26	34.7%	26	15.7%	0.001
	No	189	78.4%	49	65.3%	140	84.3%	0.001
Previous attempts to suicide	Yes	30	12.4%	16	21.3%	14	8.4%	0.005
	No	211	87.6%	59	78.7%	152	91.6%	0.005

BED (+): Group with binge eating disorder; BED (-): Group without binge eating disorder.

21.36 ± 4.86 and 20.21 ± 3.79 respectively of BIS-11, total score 64.84 ± 9.75 and attention sub-scale 17.03 ± 3.24 were statistically significantly higher in the BED (+) group ($P < 0.05$) (Table 4).

DISCUSSION

In our study, general psychopathologic and impulsive characteristics were evaluated and examined based on the BED in obese patients (including 34 obese, 150 morbidly obese and 57 super-morbidly obese patients).

The previous psychiatric admittance of BED (+) group was higher. The relevant literature has similar results[11]. In addition, the BED (+) group has statistically significantly higher depressive symptoms in our study. This is again in agreement with previous studies[14,41-44]. The depression itself may contribute to persistence of symptoms of eating disorder[45]. Furthermore, depressive symptoms may predispose individuals to develop binge eating behavior[11]. However, there were no significant differences between the current rates for psychiatric comorbidity diagnosis in groups during the performance of study. This result, which is not consistent with the literature, was attributed to the fact that study sample included individuals who felt healthy enough to attempt seeking for treatment of obesity.

In the present study, the rate for attempting suicide, defined as an impulsive behavior, was statistically significantly higher in the BED (+) group. There are data that the rate for attempting suicide is high in eating disorders where obesity and binge eating are prominent[46-48]. In addition, a Turkish study reported that self-destructive behavior was significantly high in the group of eating disorders[49].

The relation of eating disorders with impulsiveness is complex. Impulsiveness may be characteristic only for a specific subgroup of eating disorders[26] or may manifest after eating disorder occurs[50]. Nonetheless, there is only little information about the influence of impulsiveness on the eating habits of obese individuals and individuals with BED[51]. In the present study, BIS-11 total score and score from attention sub-scale were statistically significantly higher in the BED (+) group. Inattention or cognitive impulsiveness assesses making quick decisions without thinking attentively on the matter or cognitive instability[39]. Obese individuals have an inhibition problem against stimulus in the form of food and problem with focusing attention, and such cognitive deficits are much severer in obese individuals with BED[52]. Among eating disorders, the BED may be seen as a different impulse control disorder[49]. Moreover, those with BED (+) may form a subgroup that has specific impulsive

Table 3 Comparison of the Beck Depression Inventory and Beck Anxiety Inventory between binge eating disorder (+) and binge eating disorder (-) group

	Overall	BED (+) group	BED (-) group	*P*
Beck depression inventory	16.41 ± 9.61	20.04 ± 11.08	14.77 ± 8.40	0.000
Beck anxiety inventory	14.64 ± 10.50	16.72 ± 11.76	13.70 ± 9.78	0.064

BED (+): Group with binge eating disorder; BED (-): Group without binge eating disorder.

Table 4 Comparison of the Barratt Impulsiveness Scale-11 between binge eating disorder (+) and binge eating disorder (-) group

	Overall	BED (+) group	BED (-) group	*P*
BIS-11 total	62.84 ± 8.83	64.84 ± 9.75	61.93 ± 8.25	0.018
BIS-11 attention	16.22 ± 3.28	17.03 ± 3.24	15.85 ± 3.25	0.010
BIS-11 motor	20.57 ± 4.18	21.36 ± 4.86	20.21 ± 3.79	0.072
BIS-11 non-planning	26.06 ± 4.67	26.59 ± 5.32	25.82 ± 4.34	0.275

BED (+): Group with binge eating disorder; BED (-): Group without binge eating disorder; BIS-11: Barratt Impulsiveness Scale-11.

characteristics across all obese patients[53]. In addition, there are studies establishing that individuals who have both obesity and BED more commonly have comorbid mental disorders associated with impulsiveness such as drug dependency and attention deficit/hyperactivity disorder, and many behavioral patterns[54-56].

In studies performed on eating disorders, motor impulsivity[57,58] and inattention[59] were higher in the groups with prominent binge eating. In addition, many research showed increased score for impulsiveness in individuals with BED and obesity[10,31,60,61]. In a study performed by Nasser *et al*[51] using BIS-11, individuals with BED had higher motor impulsivity and criteria for BED were positively correlated with scores from BIS-11. Furthermore, the same study identified a relationship between the variables of motor impulsivity and mood, and suggested that this relationship might be associated with possible serotonin transmission disorder in the BED[51].

Two characteristic features of BED are associated with impulsiveness, which are inability to stop eating, sense of lost control, and eating in a certain time unit in which most people would simply eat more than they could eat. Especially, impulsive characteristics were found to be high in those with BED[62]. In addition, higher rates for suicide attempt, an impulsive behavior, in the BED (+) group suggest that it might be associated with higher impulsiveness in this group. Although the BED (+) group had higher scores for depression and story of psychiatric admittance than those of other group, there were no significant differences between the rates for current psychiatric comorbidity at the time of study. In assessment of data obtained from this study, it will be reasonable to place an emphasis on impulsiveness.

For clinical efficiency, it would be useful that professionals working on eating disorders and obesity include the presence and quantity of underlying impulsive characteristics in addition to disrupted eating behavior in the assessment process. In current research on the obesity, approach to preservation of weight lost after bariatric treatment rather than losing weight is included in the research phases that become prominent. Among many important causes, inclusion of impulsive personality traits in the assessment process may increase the success rate in the field.

Limitations of our study include absence of a control group and use of a self-report scale rather than more objective methods to assess impulsiveness of participants. It would be useful that results obtained from this study should cover a larger group of cases, not only hospital samples seeking for treatment, and that this study should be repeated with more objective diagnostic instruments that are able to measure impulsiveness in the behavioral dimensions.

COMMENTS

Background

Over the past 30 years, the prevalence of obesity has been gradually increased worldwide and the obesity is regarded as one of the major problems for community health. Furthermore, obesity is a condition associated with reduced life expectancy. Impulsiveness is a multidimensional personality trait that leads to uncontrolled and excessive intake of food, thus contributing to development and maintenance of obesity. The objective of this study was to investigate the levels of impulsiveness, and the relationship between the binge eating disorder (BED) and the levels of impulsiveness in obese individuals.

Research frontiers

In assessment of obese individuals, assessment of associated psychopathology such as impulsive characteristics and suicide attempt in addition to disrupted eating behaviors will allow to have a more extensive view.

Innovations and breakthroughs

The previous psychiatric admittance of BED (+) group was higher. The relevant literature has similar results. In addition, the BED (+) group has statistically significantly higher depressive symptoms in our study. This is again in agreement with previous studies. The depression itself may contribute to persistence of symptoms of eating disorder. Furthermore, depressive symptoms may predispose individuals to develop binge eating behavior. There are data that the rate for attempting suicide is high in eating disorders where obesity and binge eating are prominent. In addition, a Turkish study reported that self-destructive behavior was

significantly high in the group of eating disorders.

Applications

For clinical efficiency, it would be useful that professionals working on eating disorders and obesity include the presence and quantity of underlying impulsive characteristics in addition to disrupted eating behavior in the assessment process.

Terminology

Bariatric surgery; weight loss surgery, binge eating disorder; is characterized by compulsively eating a large amount of food without balancing behavior and it is the most common eating disorder in the obese patients.

Peer-review

The manuscript is interesting, well written and provides important insights for understanding the characteristics of the impulsiveness that leads to uncontrolled and excessive intake of food.

REFERENCES

1 **Dixon JB**. The effect of obesity on health outcomes. *Mol Cell Endocrinol* 2010; **316**: 104-108 [PMID: 19628019 DOI: 10.1016/j.mce.2009.07.008]

2 **Stevens G**, Mascarenhas M, Mathers C. Global health risks: progress and challenges. *Bull World Health Organ* 2009; **87**: 646 [PMID: 19784438 DOI: 10.2471/BLT.09.070565]

3 **Orpana HM**, Berthelot JM, Kaplan MS, Feeny DH, McFarland B, Ross NA. BMI and mortality: results from a national longitudinal study of Canadian adults. *Obesity* (Silver Spring) 2010; **18**: 214-218 [PMID: 19543208 DOI: 10.1038/oby.2009.191]

4 **Davis C**. Psychobiological traits in the risk profile for overeating and weight gain. *Int J Obes* (Lond) 2009; **33** Suppl 2: S49-S53 [PMID: 19528980 DOI: 10.1038/ijo.2009.72]

5 **Joseph RJ**, Alonso-Alonso M, Bond DS, Pascual-Leone A, Blackburn GL. The neurocognitive connection between physical activity and eating behaviour. *Obes Rev* 2011; **12**: 800-812 [PMID: 21676151 DOI: 10.1111/j.1467-789X.2011.00893.x]

6 **Stunkard AJ**. Eating patterns and obesity. *Psychiatr Q* 1959; **33**: 284-295 [PMID: 13835451]

7 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders 4th revised edition (DSM-IV-TR). Diagnostic and Statistical Manual of Mental Disorders 4th edition TR. American Psychiatric Publishing, 2000

8 **American Psychiatric Association**. Diagnostic and statistical manual of mental disorders-5. Am J Psychiatry Arlington: American Psychiatric Publishing, 2013

9 **Knoll S**, Föcker M, Hebebrand J. [Changes to the classification of Eating Disorders in DSM-5]. *Z Kinder Jugendpsychiatr Psychother* 2014; **42**: 361-366; quiz 367-368 [PMID: 25163998 DOI: 10.1024/1422-4917/a000311]

10 **Davis C**, Levitan RD, Carter J, Kaplan AS, Reid C, Curtis C, Patte K, Kennedy JL. Personality and eating behaviors: a case-control study of binge eating disorder. *Int J Eat Disord* 2008; **41**: 243-250 [PMID: 18095308 DOI: 10.1002/eat.20499]

11 **de Zwaan M**. Binge eating disorder and obesity. *Int J Obes Relat Metab Disord* 2001; **25** Suppl 1: S51-S55 [PMID: 11466589 DOI: 10.1038/sj.ijo.0801699]

12 **de Zwaan M**, Mitchell JE, Raymond NC, Spitzer RL. Binge eating disorder: clinical features and treatment of a new diagnosis. *Harv Rev Psychiatry* 1994; **1**: 310-325 [PMID: 9384866]

13 **Saunders R**. Binge eating in gastric bypass patients before surgery. *Obes Surg* 1999; **9**: 72-76 [PMID: 10065590 DOI: 10.1381/096089299765553845]

14 **Petribu K**, Ribeiro ES, Oliveira FM, Braz CI, Gomes ML, Araujo DE, Almeida NC, Albuquerque PC, Ferreira Mde N. [Binge eating disorder in a population of morbid obese candidates to bariatric surgery at the Oswaldo Cruz University Hospital in Recife, PE]. *Arq Bras Endocrinol Metabol* 2006; **50**: 901-908 [PMID: 17160214]

15 **Spitzer RL**, Devlin MJ, Walsh BT, Hasin D, Wing R, Marcus M, Stunkard A, Wadden T, Yanovski S, Agras S, Mitchell J, Nonas C. Binge eating disorder: A multisite field trial of the diagnostic criteria. *Int J Eat Disord* 1992; **11**: 191-203 [DOI: 10.1002/1098-108X(199204)11:3<191::AID-EAT2260110302>3.0.CO;2-S]

16 **Kızıltan G**, Karabudak E, Ünver S, Sezgin E. Nutritional status of university students with binge eating disorder. *Ankara Üniversitesi Tıp Fakültesi Mecmuası* 2005; **58**: 167-171

17 **Annagür BB**, Orhan FÖ, Özer A, Tamam L. Obezitede dürtüsellik ve emosyonel faktörler: bir ön çalışma. *Nöropsikiyatri Arşivi* 2012; **49**: 14-19 [DOI: 10.4274/npa.y5961]

18 **Özbey N**. Binge eating disorder in women. *İstanbul Üniversitesi İstanbul Tıp Fakültesi Mecmuası* 1999; **62**: 36-39

19 **Busetto L**, Segato G, De Luca M, De Marchi F, Foletto M, Vianello M, Valeri M, Favretti F, Enzi G. Weight loss and postoperative complications in morbidly obese patients with binge eating disorder treated by laparoscopic adjustable gastric banding. *Obes Surg* 2005; **15**: 195-201 [PMID: 15802061 DOI: 10.1381/0960892053268327]

20 **Keel PK**, Mitchell JE. Outcome in bulimia nervosa. *Am J Psychiatry* 1997; **154**: 313-321 [PMID: 9054777 DOI: 10.1176/ajp.154.3.313]

21 **Fichter MM**, Quadflieg N, Rief W. Course of multi-impulsive bulimia. *Psychol Med* 1994; **24**: 591-604 [PMID: 7991741]

22 **Hsu LK**, Betancourt S, Sullivan SP. Eating disturbances before and after vertical banded gastroplasty: a pilot study. *Int J Eat Disord* 1996; **19**: 23-34 [PMID: 8640199 DOI: 10.1002/(SICI)1098-108X(199601)19:1<23::AID-EAT4>3.0.CO;2-Y]

23 **Hsu LK**, Sullivan SP, Benotti PN. Eating disturbances and outcome of gastric bypass surgery: a pilot study. *Int J Eat Disord* 1997; **21**: 385-390 [PMID: 9138051]

24 **Kalarchian MA**, Marcus MD, Wilson GT, Labouvie EW, Brolin RE, LaMarca LB. Binge eating among gastric bypass patients at long-term follow-up. *Obes Surg* 2002; **12**: 270-275 [PMID: 11975227 DOI: 10.1381/096089202762552494]

25 **Fernández-Aranda F**, Pinheiro AP, Thornton LM, Berrettini WH, Crow S, Fichter MM, Halmi KA, Kaplan AS, Keel P, Mitchell J, Rotondo A, Strober M, Woodside DB, Kaye WH, Bulik CM. Impulse control disorders in women with eating disorders. *Psychiatry Res* 2008; **157**: 147-157 [PMID: 17961717 DOI: 10.1016/j.psychres.2007.02.011]

26 **Waxman SE**. A systematic review of impulsivity in eating disorders. *Eur Eat Disord Rev* 2009; **17**: 408-425 [PMID: 19548249 DOI: 10.1002/erv.952]

27 **Fassino S**, Leombruni P, Pierò A, Abbate-Daga G, Giacomo Rovera G. Mood, eating attitudes, and anger in obese women with and without Binge Eating Disorder. *J Psychosom Res* 2003; **54**: 559-566 [PMID: 12781310]

28 **Davis C**, Strachan S, Berkson M. Sensitivity to reward: implications for overeating and overweight. *Appetite* 2004; **42**: 131-138 [PMID: 15010176 DOI: 10.1016/j.appet.2003.07.004]

29 **Galanti K**, Gluck ME, Geliebter A. Test meal intake in obese binge eaters in relation to impulsivity and compulsivity. *Int J Eat Disord* 2007; **40**: 727-732 [PMID: 17683093 DOI: 10.1002/eat.20441]

30 **Davis C**, Patte K, Curtis C, Reid C. Immediate pleasures and future consequences. A neuropsychological study of binge eating and obesity. *Appetite* 2010; **54**: 208-213 [PMID: 19896515 DOI: 10.1016/j.appet.2009.11.002]

31 **Mobbs O**, Crépin C, Thiéry C, Golay A, Van der Linden M. Obesity and the four facets of impulsivity. *Patient Educ Couns* 2010; **79**: 372-377 [PMID: 20399590 DOI: 10.1016/j.pec.2010.03.003]

32 **Kavakçı Ö**, Demirel Y, Kuğu N, Nur M. Dikkat eksikliği/hiperaktivitenin, dürtüsellik ve obezite ile ilişkisi üzerine bir çalışma. *Cumhur Tıp Derg* 2011; **33**: 413-420

33 **Sarisoy G**, Atmaca A, Ecemiş G, Gümüş K, Pazvantoğlu O. Obezite hastalarında dürtüsellik ve dürtüselliğin beden algısı ve benlik saygısı ile ilişkisi. *Anadolu Psikiyatr Derg* 2013; **14**: 53-61 [DOI: 10.5455/apd.34469]

34 **First M**, Spitzer R, Gibbon M, Williams J. Structured Clinical Interview for DSM-IV Axis I Disorders: Patient Edition (February 1996 Final), SCID-I/P, 1998

35 **Özkürkçügil A**, Aydemir Ö, Yıldız M, Danacı E. DSM-IV Eksen I bozuklukları için yapılandırılmış klinik görüşmenin Türkçe'ye uyarlanması ve güvenilirlik çalışması. *İlaç ve Tedavi Derg* 1999; **12**: 233-236

36 **Hisli N**. Beck Depresyon Envanterinin geçerliliği üzerine bir çalışma. *Türk Psikol Derg* 1999; **6**: 118-126

37 **Hisli N**. Beck Depresyon Envanterinin üniversite öğrencileri için geçerlilik ve güvenilirliği. *Türk Psikol Derg* 1998; **7**: 3-13

38 **Ulusoy M**. Beck Anksiyete Envanteri: Geçerlik ve güvenirlik çalışması (yayınlanmamış uzmanlık tezi). Bakırköy Ruh ve Sinir Hastalıkları Hastanesi, 1993

39 **Patton JH**, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol* 1995; **51**: 768-774 [PMID: 8778124]

40 **Güleç H**, Tamam L, Güleç MY, Turhan M, Karakuş G, Zengin M. Psychometric properties of the Turkish version of the BİS-11. *Klin Psikofarmakol Bul* 2008; **18**: 251-258

41 **Borges MB**, Jorge MR, Morgan CM, Da Silveira DX, Custódio O. Binge-eating disorder in Brazilian women on a weight-loss program. *Obes Res* 2002; **10**: 1127-1134 [PMID: 12429876 DOI: 10.1038/oby.2002.153]

42 **Fontenelle LF**, VÍtor Mendlowicz M, de Menezes GB, Papelbaum M, Freitas SR, Godoy-Matos A, Coutinho W, Appolinário JC. Psychiatric comorbidity in a Brazilian sample of patients with binge-eating disorder. *Psychiatry Res* 2003; **119**: 189-194 [PMID: 12860375]

43 **Fassino S**, Pierò A, Gramaglia C, Abbate-Daga G. Clinical, psychopathological and personality correlates of interoceptive awareness in anorexia nervosa, bulimia nervosa and obesity. *Psychopathology* 2004; **37**: 168-174 [PMID: 15237246 DOI: 10.1159/000079420]

44 **Herman BK**, Safikhani S, Hengerer D, Atkins N, Kim A, Cassidy D, Babcock T, Agus S, Lenderking WR. The patient experience with DSM-5-defined binge eating disorder: characteristics, barriers to treatment, and implications for primary care physicians. *Postgrad Med* 2014; **126**: 52-63 [PMID: 25295650 DOI: 10.3810/pgm.2014.09.2800]

45 **Mazzeo SE**, Saunders R, Mitchell KS. Gender and binge eating among bariatric surgery candidates. *Eat Behav* 2006; **7**: 47-52 [PMID: 16360622 DOI: 10.1016/j.eatbeh.2005.05.008]

46 **Favaro A**, Santonastaso P. Impulsive and compulsive self-injurious behavior in bulimia nervosa: prevalence and psychological correlates. *J Nerv Ment Dis* 1998; **186**: 157-165 [PMID: 9521351]

47 **Ackard DM**, Neumark-Sztainer D, Story M, Perry C. Overeating among adolescents: prevalence and associations with weight-related characteristics and psychological health. *Pediatrics* 2003; **111**: 67-74 [PMID: 12509556]

48 **Pompili M**, Girardi P, Tatarelli G, Ruberto A, Tatarelli R. Suicide and attempted suicide in eating disorders, obesity and weight-image concern. *Eat Behav* 2006; **7**: 384-394 [PMID: 17056416 DOI: 10.1016/j.eatbeh.2005.12.004]

49 **Maner F**, Keçeli K, Alpkan L, Ergen N E. Yeme Bozukluğu olan hastalarda kendine zarar verici davranışlar. 2. Ulusal Psikofarmakoloji Kongresi, Kongre Kitabı, 2007: 365-369

50 **Bruce KR**, Steiger H. Treatment implications of Axis-II comorbidity in eating disorders. *Eat Disord* 2005; **13**: 93-108 [PMID: 16864334 DOI: 10.1080/10640260590893700]

51 **Nasser JA**, Gluck ME, Geliebter A. Impulsivity and test meal intake in obese binge eating women. *Appetite* 2004; **43**: 303-307 [PMID: 15527933 DOI: 10.1016/j.appet.2004.04.006]

52 **Mobbs O**, Iglesias K, Golay A, Van der Linden M. Cognitive deficits in obese persons with and without binge eating disorder. Investigation using a mental flexibility task. *Appetite* 2011; **57**: 263-271 [PMID: 21600255 DOI: 10.1016/j.appet.2011.04.023]

53 **Schag K**, Schönleber J, Teufel M, Zipfel S, Giel KE. Food-related impulsivity in obesity and binge eating disorder--a systematic review. *Obes Rev* 2013; **14**: 477-495 [PMID: 23331770 DOI: 10.1111/obr.12017]

54 **Dawe S**, Loxton NJ. The role of impulsivity in the development of substance use and eating disorders. *Neurosci Biobehav Rev* 2004; **28**: 343-351 [PMID: 15225976 DOI: 10.1016/j.neubiorev.2004.03.007]

55 **Cortese S**, Angriman M, Maffeis C, Isnard P, Konofal E, Lecendreux M, Purper-Ouakil D, Vincenzi B, Bernardina BD, Mouren MC. Attention-deficit/hyperactivity disorder (ADHD) and obesity: a systematic review of the literature. *Crit Rev Food Sci Nutr* 2008; **48**: 524-537 [PMID: 18568858 DOI: 10.1080/10408390701540124]

56 **Schmidt F**, Körber S, de Zwaan M, Müller A. Impulse control disorders in obese patients. *Eur Eat Disord Rev* 2012; **20**: e144-e147 [PMID: 22367789 DOI: 10.1002/erv.2162]

57 **Rosval L**, Steiger H, Bruce K, Israël M, Richardson J, Aubut M. Impulsivity in women with eating disorders: problem of response inhibition, planning, or attention? *Int J Eat Disord* 2006; **39**: 590-593 [PMID: 16826575 DOI: 10.1002/eat.20296]

58 **Díaz-Marsá M**, Carrasco JL, Basurte E, Sáiz J, López-Ibor JJ, Hollander E. Enhanced cortisol suppression in eating disorders with impulsive personality features. *Psychiatry Res* 2008; **158**: 93-97 [PMID: 18182170 DOI: 10.1016/j.psychres.2007.06.020]

59 **Claes L**, Nederkoorn C, Vandereycken W, Guerrieri R, Vertommen H. Impulsiveness and lack of inhibitory control in eating disorders. *Eat Behav* 2006; **7**: 196-203 [PMID: 16843221 DOI: 10.1016/j.eatbeh.2006.05.001]

60 **Rydén A**, Sullivan M, Torgerson JS, Karlsson J, Lindroos AK, Taft C. A comparative controlled study of personality in severe obesity: a 2-y follow-up after intervention. *Int J Obes Relat Metab Disord* 2004; **28**: 1485-1493 [PMID: 15356662 DOI: 10.1038/sj.ijo.0802768]

61 **Arias Horcajadas F**, Sánchez Romero S, Gorgojo Martínez JJ, Almódovar Ruiz F, Fernández Rojo S, Llorente Martin F. [Clinical differences between morbid obese patients with and without binge eating]. *Actas Esp Psiquiatr* 2006; **34**: 362-370 [PMID: 17117332]

62 **Annagür BB**. Obezitede Çeşitli Risk Faktörleri ve Dürtüsellik. *Psikiyatride Güncel Yaklaşımlar* 2010; **2**: 572-582

P- Reviewer: Masaki T, Rigoli L **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Li D

World Journal of Psychiatry

Submit a Manuscript: http://www.f6publishing.com

World J Psychiatr 2017 June 22; 7(2): 121-127

DOI: 10.5498/wjp.v7.i2.121

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Three-dimensional stereotactic surface projection in the statistical analysis of single photon emission computed tomography data for distinguishing between Alzheimer's disease and depression

Eiji Kirino

Eiji Kirino, Department of Psychiatry, Juntendo University School of Medicine, Bunkyo-ku, Tokyo 113-8421, Japan

Eiji Kirino, Department of Psychiatry, Juntendo University Shizuoka Hospital, Izunokuni-shi, Shizuoka 410-2211, Japan

Eiji Kirino, Juntendo Institute of Mental Health, Koshigaya-shi, Saitama 343-0032, Japan

Author contributions: Kirino E solely contributed to this paper.

Institutional review board statement: This study was reviewed and approved by the institutional review board of Juntendo University Shizuoka Hospital.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors have no conflicts of interest to report.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Eiji Kirino, MD, PhD, Department of Psychiatry, Juntendo University Shizuoka Hospital, 1129 Nagaoka, Izunokuni-shi, Shizuoka 410-2211, Japan. ekirino@juntendo.ac.jp
Telephone: +81-55-9483111

Fax: +81-55-9485088

Received: January 30, 2017
Peer-review started: February 12, 2017
First decision: March 28, 2017
Revised: April 10, 2017
Accepted: May 3, 2017
Article in press: May 5, 2017
Published online: June 22, 2017

Abstract

AIM

To evaluate usefulness of single photon emission computed tomography (SPECT) with three-dimensional stereotactic surface projection (3D-SSP) in distinguishing between Alzheimer's disease (AD) and depression.

METHODS

We studied 43 patients who presented with both depressive symptoms and memory disturbance. Each subject was evaluated using the following: (1) the Minimal Mental State Examination; (2) the Hamilton Rating Scale for Depression; (3) Clinical Global Impression-Severity scale (CGI-S); and (4) SPECT imaging with 3D-SSP.

RESULTS

The MMSE scores correlated significantly with the maximum Z-scores of AD-associated regions. CGI-S scores correlated significantly with the maximum Z-scores of depression-associated regions. Factor analysis identified three significant factors. Of these, Factor 1 could be interpreted as favouring a tendency for AD, Factor 2 as favouring a tendency for pseudo-dementia, and Factor 3 as favouring a depressive tendency.

CONCLUSION

We investigated whether these patients could be categorized as types: Type A (true AD), Type B (pseudo-dementia), Type C (occult AD), and Type D (true depression). The factor scores in factor analysis supported the validity of this classification. Our results suggest that SPECT with 3D-SSP is highly useful for distinguishing between depression and depressed mood in the early stage of AD.

Key words: Alzheimer's disease; Three-dimensional stereotactic surface projection; Single photon emission computed tomography; Pseudo-dementia; Depression

Core tip: The present study aimed to evaluate whether statistical analysis of single photon emission computed tomography images by three-dimensional stereotactic surface projection (3D-SSP) is useful for distinguishing between Alzheimer's disease (AD) and depression. The Minimal Mental State Examination, the Hamilton Rating Scale for Depression, and Clinical Global Impression-Severity scale findings correlated significantly with the Z-scores of AD-associated and depression-associated regions as determined using 3D-SSP analysis. Furthermore, factor analysis identified three significant factors: Factor 1, a tendency for AD; Factor 2, a tendency for pseudo-dementia; and Factor 3, a depressive tendency.

Kirino E. Three-dimensional stereotactic surface projection in the statistical analysis of single photon emission computed tomography data for distinguishing between Alzheimer's disease and depression. *World J Psychiatr* 2017; 7(2): 121-127 Available from: URL: http://www.wjgnet.com/2220-3206/full/v7/i2/121.htm DOI: http://dx.doi.org/10.5498/wjp.v7.i2.121

INTRODUCTION

It is important to distinguish between depression and the depressed mood characteristic of early stage Alzheimer's disease (AD), but it can be difficult to make this distinction based solely on clinical symptoms. Brain images obtained by magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT) may be useful for distinguishing between these two conditions even at relatively early stages. Among the different imaging modalities, SPECT has been introduced clinically for making a differential diagnosis of early stage AD because it can detect brain function abnormalities before the appearance of organic changes in the brain better than other techniques. The accuracy of SPECT for diagnosing AD is reportedly 88%[1]. A meta-analysis found that SPECT has a superior specificity to clinical criteria (sensitivity 74% *vs* 81%, specificity 91% *vs* 70%) in discriminating AD from vascular dementia, fronto-temporal dementia and non-dementia subjects[2].

Three-dimensional stereotactic surface projection (3D-SSP) is a technique used for the statistical analysis of SPECT images. This technique converts images of the brains of patients with inter-individual variances in morphological features using standard brain coordinates to extract functional information (projected onto the brain surface), followed by statistical processing of the data for visual representation of the extent and severity of the reduction in brain metabolism or brain perfusion[3]. This technique was initially developed to analyze positron emission tomography (PET) images, and Minoshima *et al*[4] used 3D-SSP to show that patients with AD had reduced glucose metabolism in the posterior cingulate gyrus. H2150-PET analysis of patients with AD also showed reduced perfusion in the posterior cingulate gyrus[5], indicating that this technique can be used not only for the evaluation of brain metabolism but also for brain perfusion. 3D-SSP was first applied to SPECT by Bartenstein *et al*[6].

The present study aimed to evaluate whether statistical analysis of brain perfusion SPECT images by 3D-SSP was useful for distinguishing between AD and depression.

MATERIALS AND METHODS

Subjects

This study included 43 patients who presented with both depressive symptoms and memory disturbance (13 men and 30 women with a mean age of 67.7 years). All were clinically diagnosed with depression or AD and were ambulatory patients at the Department of Psychiatry, Juntendo University Shizuoka Hospital, Shizuoka Japan. The presence or absence of depressive symptoms was checked using the 2-item Patient Health Questionnaire depression module[7]. Depressive symptoms were considered present when either the patient or a family member reported that the patient had at least one of the symptoms suggesting "depressed mood" or "loss of interest or joy". Memory disturbance was considered present when at least one of the signs on the observation list for early signs of dementia[8] was noted. Patients showing evident signs of non-AD type dementia (vascular dementia, dementia with Lewy body, fronto-temporal lobar degeneration, *etc.*), according to clinical symptoms or diagnostic imaging findings, were excluded from the study. The study was approved by the Juntendo University Shizuoka Hospital Ethics Committee. All participants provided written informed consent.

Evaluation plan

Each patient was evaluated with following: (1) the Minimal Mental State Examination (MMSE); (2) the Hamilton Rating Scale for Depression (HAM-D); (3) Clinical Global Impression-Severity scale (CGI-S) (for evaluating AD); and (4) N-isopropyl-p-[I-123]iodine amphetamine (I-123I IMP) SPECT images with 3D-SSP. Using the CGI-S, AD severity was rated on a 7-point scale: 1 (normal), 2 (borderline), 3 (mild), 4 (moderate), 5 (moderately severe), 6 (severe), and 7 (most severe).

SPECT

Imaging was carried out while each patient lay still in a supine position, awake but with eyes closed. 111 MBq [3 mCi] of 123I-IMP (Perfusamin® Injection: IMP) was intravenously injected *via* the right cubital vein, followed by SPECT imaging 15 min later using SYMBIA-E (Siemens) with a Low-Medium Energy General Purpose collimator. The data were projected with the following parameters: Energy window, 159 KeV ± 15%; acquisition mode, step and shoot; acquisition time, 30 s × 36 Views (18 min); acquisition angle, 10°/view; rotation radius, 13.5 cm; matrix size, 128 × 128; magnification ratio, × 1.45; and pixel size, 3.3 mm.

Image reconstruction

Tomographic data were pre-processed with a Butterworth filter (order, 8; cut-off, 0.26 Nyquist) and then reconstructed from the 128 × 128 matrix of the transverse section. The Chang method was used for attenuation correction. The attenuation coefficient was set at μ = 0.06. Scatter correction was not used. Filtered back-projection by a Gaussian filter was employed for image reconstruction.

Statistical analysis

The SPECT images were statistically analysed by 3D-SSP and stereotactic extraction estimation (SEE)[9].

3D-SSP: 3D-SSP is a technique that is well-established in usefulness for the statistical analysis of images, as shown by previous studies[3,4,10] and the Society of Nuclear Medicine. Transaxial images were selected from the transaxial, coronal, and sagittal SPECT images for statistical analysis using NEUROSTAT® brain image analysis software. Image conversion was performed using standard brain coordinates followed by extraction of functional information using brain surface projection to determine the Z-score relative to the normal database (NDB).

The results of analysis with 3D-SSP can vary markedly depending on the NDB that is used. The NDB for this study was derived from data for healthy volunteers aged 50-79 years old; the data were collected at facilities equipped with the same type of SPECT system that we use. The construction of NDB was approval by ethics committee of each facility, and each participant provided written informed consent. Individuals with MMSE scores of 27 or higher and MRI/magnetic resonance angiography findings corresponding to their age were considered healthy. The SPECT device and the settings for image acquisition and reconstruction used to create the NDB were identical to those used in the present study.

SEE: SEE[9] classifies 3D-SSP brain surface projection data to regions based on neuroanatomy and Brodmann's classification. This procedure involves the assignment of anatomical and functional information to each pixel in a given image. The coordinate system for the brain surface projection data is identical to the Talairach brain coordinates[11]. Anatomical information was assigned to the 3D-SSP brain surface projection data by applying the "Talairach Daemon", which is designed to assign anatomical information to each pixel in accordance with this coordinate system[12,13]. The statistical standard deviation (Z-score) was determined for each region.

AD-associated and depression-associated regions were defined as the brain regions that exhibit characteristic perfusion reductions in the presence of AD[3-6] and depression[14] (AD-associated regions: Superior parietal lobule, inferior parietal lobule, precuneus, and posterior cingulate gyrus; depression-associated regions: Superior frontal gyrus, middle frontal gyrus, and inferior frontal gyrus).

Correlation coefficient

Spearman correlation coefficients (two tailed) were used to evaluate whether the maximum Z-scores of the AD-associated and depression-associated regions correlated with the HAM-D, MMSE, or CGI-S scores.

Factor analysis

Principal axis factor analysis with varimax rotation (df = 21) was performed for the following variables: Age, sex, HAM-D score, MMSE score, CGI-S score, and the maximum Z-scores of the AD-associated and depression-associated regions. The statistical analyses were performed in PASW® version 18 for Windows.

Evaluation criteria

Patients with HAM-D scores of 10 or higher were considered to have depressive symptoms (HAM-D-positive). Patients with MMSE scores of 24 or lower were considered to have symptoms of dementia (MMSE-positive). In evaluating the SPECT Z-score with 3D-SSP, the rating "AD-positive" was made in cases with reduction of perfusion that were 2 standard deviations (SDs) or greater (Z-score $\geqslant$ 2.00) in at least one of the AD-associated regions. Similarly, a "depression-positive" rating was given to cases showing 2 SDs or greater reductions of perfusion in at least one of the depression-associated regions.

RESULTS

MMSE-positive was confirmed in 19 cases and MMSE-negative in 24. HAM-D-positive in 14 cases and HAM-D-negative in 29 was also confirmed. The CGI-S score was 1 in 3 cases, 2 in 11 cases, 3 in 13 cases, 4 in 13 cases, 5 in 2 cases, and 6 in 1 case. In the SPECT 3D-SSP analysis, AD-positive in 9 cases and AD-negative in 34, and depression-positive in 13 cases and depression-negative in 30 was observed. The 3D-SSP results of two representative cases are presented in Figure 1.

Correlation analysis

The maximum Z-scores of AD-associated regions correlated significantly with MMSE (Spearman *r* =

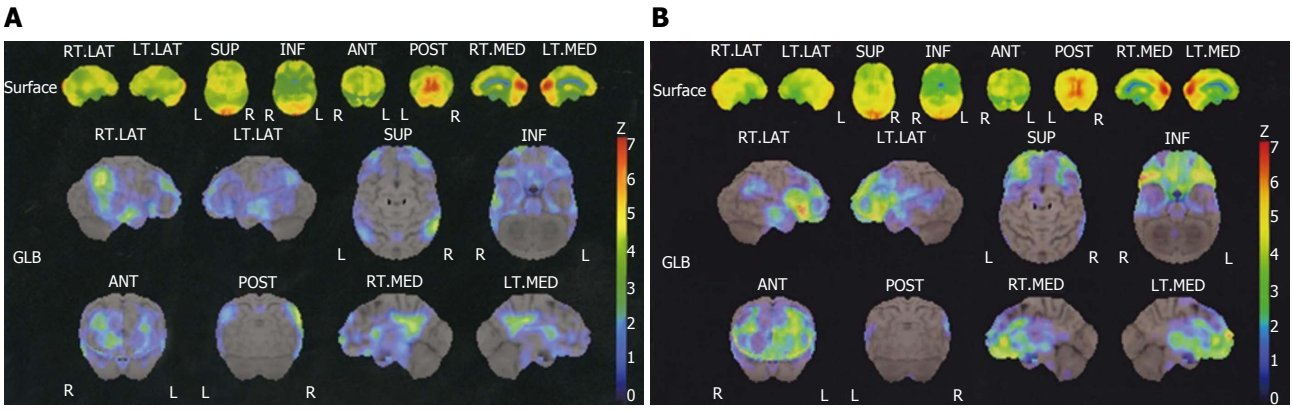


Figure 1 The three-dimensional stereotactic surface projection results of two representative cases. A: Female, 59 years old; MMSE 26, HAM-D 18, CGI 3; showed significant reduction of perfusion in the AD-associated region (the superior parietal lobule and posterior cingulate gyrus); B: Female, 64 years old; MMSE 28, HAM-D 9, CGI 2; showed significant reduction of perfusion in the depression-associated region (the inferior frontal gyrus). HAM-D: Hamilton Rating Scale for Depression; MMSE: Minimal Mental State Examination; CGI: Clinical Global Impression; AD: Alzheimer's disease.

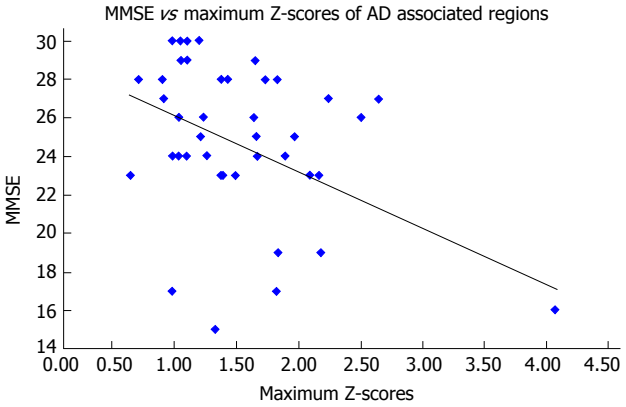


Figure 2 Correlations between Minimal Mental State Examination scores and the maximum Z scores of Alzheimer's disease-associated regions. The MMSE scores correlated significantly with the maximum Z-scores of AD-associated regions. MMSE: Minimal Mental State Examination; AD: Alzheimer's disease.

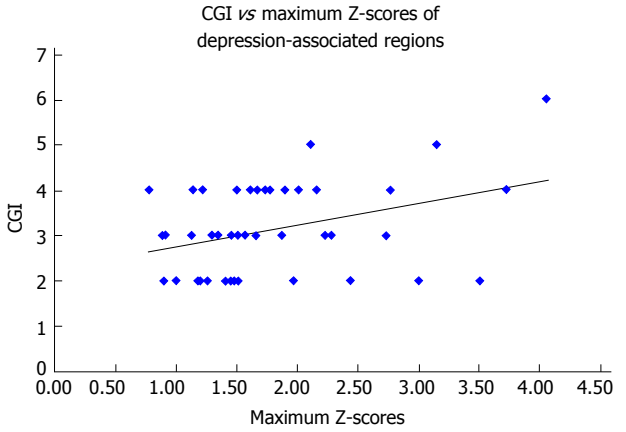


Figure 3 Correlations between Clinical Global Impression-Severity scale scores and the maximum Z scores of depression-associated regions. The CGI-S scores correlated significantly with the maximum Z-scores of depression-associated regions. CGI: Clinical Global Impression.

-0.333, n = 43, P = 0.029) (Figure 2), but not with the HAM-D score (Spearman r = 0.014, n = 43, P = 0.928) or the CGI-S score (Spearman r = 0.275, n = 43, P = 0.074). The maximum Z-scores of depression-associated regions correlated significantly with the CGI-S score (Spearman r = 0.309, n = 43, P = 0.043) (Figure 3), but not with the MMSE score (Spearman r = -0.189, n = 43, P = 0.224) or HAM-D score (Spearman r = 0.047, n = 43, P = 0.763).

Factor analysis

Three significant factors with eigenvalues over 1 were identified (Table 1). Factor 1, a tendency for AD, *i.e.*, negative correlation with MMSE and positive correlations with CGI-S and the Z-scores of AD-associated and depression-associated regions; Factor 2, a tendency for pseudo-dementia, *i.e.*, more marked in women, positive correlations with age and HAM-D and a negative correlation with MMSE; and Factor 3, a depressive tendency, *i.e.*, negative correlation with age and positive correlations with HAM-D and MMSE (Table 2).

DISCUSSION

Classifying cases in which it is difficult to distinguishing between AD and depression: Four-type classification system

In the 14 HAM-D-positive cases in which it was difficult to distinguish between AD and depression, we investigated the use of a four-type classification system (2 × 2 = 4), based on the AD rating (positive/negative) and the MMSE rating (positive/negative). The maximum Z scores of depression-associated regions correlated strongly with Factor 1 (tendency for AD) but only weakly with Factor 3 (tendency for depression). Thus, the maximum Z score of depression-associated regions was not adopted as a criterion for evaluation (Figure 4).

Each type was interpreted as follows. Type A (2 cases, both women) was interpreted as being "true AD accompanied by depressive symptoms" because both AD and MMSE were positive. Type B (3 cases, all women) was interpreted as being "pseudo-dementia" because AD was negative and MMSE was positive. Type C (3 cases;

Table 1 Results of principal axis factor analysis (df = 21)

Factors	Total of explained variance								
	Initial eigenvalues			Sums of squares of loadings after sampling			Sums of squares of loadings after rotation		
	Total	Proportion of explained variance (%)	Cumulative proportion of explained variance (%)	Total	Proportion of explained variance (%)	Cumulative proportion of explained variance (%)	Total	Proportion of explained variance (%)	Cumulative proportion of explained variance (%)
Factor 1	2.422	34.603	34.603	1.961	28.017	28.017	1.805	25.780	25.780
Factor 2	1.223	17.478	52.081	0.982	14.025	42.041	1.067	15.248	41.029
Factor 3	1.166	16.656	68.738	0.484	6.920	48.961	0.555	7.932	48.961
Factor 4	0.805	11.502	80.240						
Factor 5	0.598	8.538	88.778						
Factor 6	0.500	7.144	95.922						
Factor 7	0.285	4.078	100.000						

Methods to extract factors: Principal axis factor analysis. Principal axis factor analysis with varimax rotation (df = 21) was performed for age, gender, HAM-D score, MMSE score, CGI, and the maximum Z-scores of AD-associated and depression-associated regions. Three significant factors with eigenvalues over 1 were identified. HAM-D: Hamilton Rating Scale for Depression; MMSE: Minimal Mental State Examination; CGI: Clinical Global Impression; AD: Alzheimer's disease.

Table 2 Factor loading after varimax rotation

Factors	Factor 1	Factor 2	Factor 3
Age	0.103	0.171	-0.504
Sex	0.061	0.960	-0.107
HAM-D	0.135	0.241	0.350
MMSE	-0.679	-0.178	0.399
CGI	0.763	-0.082	-0.048
AD regions	0.674	0.078	0.063
Depression regions	0.523	0.119	0.042

Factor 1 was interpreted as indicating a tendency for AD (negative correlation with MMSE score and positive correlations with CGI-S score and maximum Z-scores of the AD-associated and depression-associated regions). Factor 2 was interpreted as indicating a tendency for pseudo-dementia (more marked in women; positive correlations with age and HAM-D score and negative correlation with MMSE). Factor 3 was interpreted as indicating a depressive tendency (negative correlation with age and positive correlations with HAM-D and MMSE scores). Colored columns represent significant correlation between the variables and Factors. HAM-D: Hamilton Rating Scale for Depression; MMSE: Minimal Mental State Examination; CGI: Clinical Global Impression; AD: Alzheimer's disease.

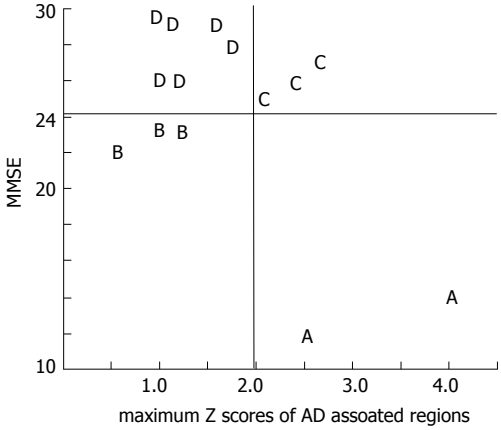


Figure 4 Schematic representation of the classification system. Types (2 × 2 = 4 types) were determined based on the AD rating (positive/negative) and on the MMSE findings (positive/negative). Data from individual patients are plotted by type (A, B, C, and D) on the graph. The X-axis indicates the AD-associated region Z-scores and the Y-axis indicates the MMSE scores. A: True AD; B: Pseud dementia; C: Occult AD; D: True depression. MMSE: Minimal Mental State Examination; AD: Alzheimer's disease.

2 women and 1 man) was interpreted as being "occult AD" because AD was positive and MMSE was negative. Type D (6 cases; 3 women and 3 men) was interpreted as being "true depression (non-AD)" because both AD and MMSE were negative (Figure 4). In the analysis of the score for each factor for each type, Type A (true AD) had high scores for Factor 1 (tendency for AD), type B (pseudo-dementia) had high scores for Factor 2 (tendency for pseudo-dementia), and type D (true depression) had high scores for Factor 3 (depressive tendency). This finding seemed to validate the use of this classification system. All of the Type B cases were women and Factor 2 loaded the variable "sex" to a greater amount (0.96), indicating that women have a higher tendency for pseudo-dementia. Type C cases (occult AD) had high scores for Factors 1 and 3, suggesting that Type C cases have a strong tendency for AD while also presenting with a depressive tendency (Figure 5).

The results of the present study indicate that the Z-scores of AD-associated regions have high sensitivity for the diagnosis of AD, while the Z scores of depression-associated regions correlated only weakly with the depressive tendency in factor analysis and lacked specific sensitivity for depressive symptoms.

Limitations

This study had some limitations, and more work needed. First, only 14 patients were included in the classification analysis, so this classification system needs to be tested in a larger number of patients. There were differences between sexes, and this, too, merits further study in a larger population. Second, we excluded patients with non-AD dementia according to their clinical symptoms or diagnostic imaging findings. A more detailed structured interview or more sophisticated evaluation for differential diagnosis would help more rigorously rule out non-AD dementia. Third, concerning the AD-associated and depression-associated regions, it would be better to

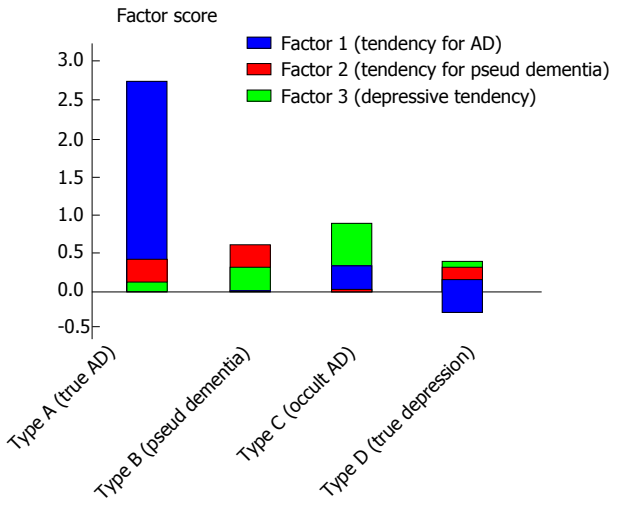


Figure 5 Scores for each factor for each type. Type A cases (true AD) had high factor scores for Factor 1 (tendency for AD); Type B cases (pseudo-dementia) had high factor scores for Factor 2 (tendency for pseudo-dementia); and Type D cases had high factor scores for Factor 3 (depressive tendency), thus validating the type determination method. Type C cases (occult AD) had high factor scores for Factors 1 and 3, suggesting that this type shows a strong tendency for AD while also presenting with a depressive tendency. AD: Alzheimer's disease.

conduct a more detailed analysis of the individual areas. The definition of depression-associated regions needs to be reviewed because the Z-scores of these regions failed to show specific sensitivity. The validity of the definition of these regions for distinguishing between AD and depression must be established based on future evaluations or meta-analyses of larger samples. Kang *et al*[15] used SPECT and found that AD patients with clinically significant depression had significantly lower perfusion in the right orbitofrontal and inferior frontal gyri than non-depressive AD patients, whereas AD patients with clinically significant apathy had had significantly lower perfusion in the right amygdala, temporal, posterior cingulate, right superior frontal, postcentral, and left superior temporal gyri than non-apathetic AD patients[15]. Thus, there may be some overlaps between AD- and depression-associated regions. On the other hand, Terada *et al*[16] investigated the cerebral blood flow of AD patients with depressive symptoms, excluding the effect of apathy and anxiety. They found that the dorsolateral prefrontal area was significantly involved in the pathogenesis of depressive symptoms in AD, and that the area on the left side in particular may be closely related to depressive symptoms[16]. In the future, AD- and depression-associated regions should be better defined to differentiate between depression and anxiety/apathy. Fourth, the use of this classification system to identify Types A-D requires validation by prospective observation. Fifth, although clinicians often find that cognitive impairment symptoms respond to treatment for depression, a substantial proportion of patients with pseudo-dementia will develop dementia during follow-up. Therefore, the use of SPECT findings to distinguish between AD and depression should be viewed with caution in terms of the clinical implications.

Conclusion

This study found that MMSE, HAM-D, and CGI-S findings correlated significantly with the Z-scores of AD-associated and depression-associated regions as determined using SPECT imaging with 3D-SSP analysis. Factor analysis identified three significant factors: (1) Factor 1, a tendency for AD; (2) Factor 2, a tendency for pseudo-dementia; and (3) Factor 3, a depressive tendency. Our results indicated that patients presenting with both depressive symptoms and memory disturbance could be divided into four types: (1) Type A, true AD; (2) Type B, pseudo-dementia; (3) Type C, occult AD; and (4) Type D, true depression. The scores for the three factors validated the identifications of these types. Thus, statistical analysis of I-123 IMP perfusion SPECT images using 3D-SSP shows great promise for distinguishing between depression and the depressed mood that is characteristic of early stage AD.

COMMENTS

Background

In clinical practice, it is often difficult to distinguish between depression and the depressed mood seen in the early stage of Alzheimer's disease (AD). Among the different imaging modalities, brain perfusion single photon emission computed tomography (SPECT) has been introduced clinically for making a differential diagnosis of early stage AD because it can detect brain function abnormalities before the appearance of organic changes in the brain better than other techniques.

Research frontiers

Three-dimensional stereotactic surface projection (3D-SSP) is a technique used for the statistical analysis of SPECT images.

Innovations and breakthroughs

The present study aimed to evaluate whether statistical analysis of brain perfusion SPECT images by 3D-SSP was useful for distinguishing between AD and depression. As results, factor analysis identified three significant factors. Of these, Factor 1 could be interpreted as favouring a tendency for AD, Factor 2 as favouring a tendency for pseudo-dementia, and Factor 3 as favouring a depressive tendency. Furthermore, the authors investigated whether these patients could be categorized as types: Type A (true AD), Type B (pseudo-dementia), Type C (occult AD), and Type D (true depression). The factor scores in factor analysis supported the validity of this classification.

Applications

The authors' results suggest that SPECT with 3D-SSP is highly useful for distinguishing between depression and depressed mood in the early stage of AD.

Terminology

3D-SSP: Three-dimensional stereotactic surface projection is a technique used for the statistical analysis of SPECT images. This technique converts images of the brains of patients with inter-individual variances in morphological features using standard brain coordinates to extract functional information (projected onto the brain surface), followed by statistical processing of the data for visual representation of the extent and severity of the reduction in brain metabolism or brain perfusion.

Peer-review

This is an interesting study on the use of SPECT in differentiating depression from dementia.

REFERENCES

1 **Bonte FJ**, Harris TS, Hynan LS, Bigio EH, White CL. Tc-99m HMPAO SPECT in the differential diagnosis of the dementias with histopathologic confirmation. *Clin Nucl Med* 2006; **31**: 376-378 [PMID: 16785801 DOI: 10.1097/01.rlu.0000222736.81365.63]

2 **Dougall NJ**, Bruggink S, Ebmeier KP. Systematic review of the diagnostic accuracy of 99mTc-HMPAO-SPECT in dementia. *Am J Geriatr Psychiatry* 2004; **12**: 554-570 [PMID: 15545324 DOI: 10.1176/appi.ajgp.12.6.554]

3 **Minoshima S**, Frey KA, Koeppe RA, Foster NL, Kuhl DE. A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. *J Nucl Med* 1995; **36**: 1238-1248 [PMID: 7790950]

4 **Minoshima S**, Foster NL, Kuhl DE. Posterior cingulate cortex in Alzheimer's disease. *Lancet* 1994; **344**: 895 [PMID: 7916431 DOI: 10.1016/S0140-6736(94)92871-1]

5 **Ishii K**, Sasaki M, Yamaji S, Sakamoto S, Kitagaki H, Mori E. Demonstration of decreased posterior cingulate perfusion in mild Alzheimer's disease by means of H215O positron emission tomography. *Eur J Nucl Med* 1997; **24**: 670-673 [PMID: 9169576 DOI: 10.1007/BF00841407]

6 **Bartenstein P**, Minoshima S, Hirsch C, Buch K, Willoch F, Mösch D, Schad D, Schwaiger M, Kurz A. Quantitative assessment of cerebral blood flow in patients with Alzheimer's disease by SPECT. *J Nucl Med* 1997; **38**: 1095-1101 [PMID: 9225797]

7 **Kroenke K**, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care* 2003; **41**: 1284-1292 [PMID: 14583691 DOI: 10.1097/01.MLR.0000093487.78664.3C]

8 **Hopman-Rock M**, Tak EC, Staats PG. Development and validation of the Observation List for early signs of Dementia (OLD). *Int J Geriatr Psychiatry* 2001; **16**: 406-414 [PMID: 11333429 DOI: 10.1002/gps.354]

9 **Mizumura S**, Kumita S, Cho K, Ishihara M, Nakajo H, Toba M, Kumazaki T. Development of quantitative analysis method for stereotactic brain image: assessment of reduced accumulation in extent and severity using anatomical segmentation. *Ann Nucl Med* 2003; **17**: 289-295 [PMID: 12932111 DOI: 10.1007/BF02988523]

10 **Minoshima S**, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol* 1997; **42**: 85-94 [PMID: 9225689 DOI: 10.1002/ana.410420114]

11 **Talairach J**, Tournoux P. Co-planar stereotaxic atlas of the human brain. Thiem Medical Publishers, New York, 1988

12 **Lancaster JL**, Rainey LH, Summerlin JL, Freitas CS, Fox PT, Evans AC, Toga AW, Mazziotta JC. Automated labeling of the human brain: a preliminary report on the development and evaluation of a forward-transform method. *Hum Brain Mapp* 1997; **5**: 238-242 [PMID: 20408222 DOI: 10.1002/(SICI)1097-0193(1997)5:4<238::AID-HBM6>3.0.CO;2-4]

13 **Lancaster JL**, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT. Automated Talairach atlas labels for functional brain mapping. *Hum Brain Mapp* 2000; **10**: 120-131 [PMID: 10912591 DOI: 10.1002/1097-0193(200007)10:3<120::AID-HBM30>3.0.CO;2-8]

14 **Navarro V**, Gastó C, Lomeña F, Mateos JJ, Marcos T. Frontal cerebral perfusion dysfunction in elderly late-onset major depression assessed by 99MTC-HMPAO SPECT. *Neuroimage* 2001; **14**: 202-205 [PMID: 11525329 DOI: 10.1006/nimg.2001.0787]

15 **Kang JY**, Lee JS, Kang H, Lee HW, Kim YK, Jeon HJ, Chung JK, Lee MC, Cho MJ, Lee DS. Regional cerebral blood flow abnormalities associated with apathy and depression in Alzheimer disease. *Alzheimer Dis Assoc Disord* 2012; **26**: 217-224 [PMID: 21959363 DOI: 10.1097/WAD.0b013e318231e5fc]

16 **Terada S**, Oshima E, Sato S, Ikeda C, Nagao S, Hayashi S, Hayashibara C, Yokota O, Uchitomi Y. Depressive symptoms and regional cerebral blood flow in Alzheimer's disease. *Psychiatry Res* 2014; **221**: 86-91 [PMID: 24296273 DOI: 10.1016/j.pscychresns.2013.11.002]

P- Reviewer: Chakrabarti S, Szekely A **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Li D

World Journal of Psychiatry

Submit a Manuscript: http://www.f6publishing.com

World J Psychiatr 2017 June 22; 7(2): 128-132

DOI: 10.5498/wjp.v7.i2.128

ISSN 2220-3206 (online)

CASE REPORT

Cognitive correlates of neuroimaging abnormalities in the onset of schizophrenia: A case report

Silvia Grassi, Giulia Orsenigo, Marta Serati, Elisabetta Caletti, Alfredo Carlo Altamura, Massimiliano Buoli

Silvia Grassi, Giulia Orsenigo, Marta Serati, Elisabetta Caletti, Alfredo Carlo Altamura, Massimiliano Buoli, Department of Psychiatry, University of Milan, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, 20122 Milan, Italy

Author contributions: Grassi S and Orsenigo G collected data; Serati M revised report; Caletti E performed neuropsychological tests; Altamura AC designed the report; Buoli M wrote the paper.

Institutional review board statement: This case report was exempted from IRB standards of University of Milan.

Informed consent statement: Patient gave his written informed consent and permission for disclosure of his protected health information.

Conflict-of-interest statement: Professor Altamura has served as a consultant or on Advisory Boards for Roche, Merck, Astra Zeneca, Bristol Myers Squibb, Janssen/Cilag and Lundbeck. Drs Grassi, Orsenigo, Serati, Caletti and Buoli do not have any affiliation with or financial interest in any organization that might pose a conflict of interest with the present article.

Manuscript source: Invited manuscript

Correspondence to: Silvia Grassi, MD, Department of Psychiatry, University of Milan, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Via F. Sforza 35, 20122 Milan, Italy. silvia.grassi1@unimi.it
Telephone: +39-02-55035983
Fax: +39-02-55033190

Received: December 17, 2016
Peer-review started: December 19, 2016
First decision: April 18, 2017
Revised: April 27, 2017
Accepted: May 12, 2017
Article in press: May 15, 2017
Published online: June 22, 2017

Abstract

Increasing evidence shows that cognitive impairment and brain abnormalities can appear early in the first episodes of schizophrenia, but it is currently debated how brain changes can correlate with clinical presentation of schizophrenic patients. Of note, this report describes the case of a young schizophrenic male presenting parietal magnetic resonance/positron emission tomography abnormalities and cognitive impairment, documented by specific neuropsychological tests. In our knowledge only few studies have investigated if neuropsychological abnormalities could be concomitant with both structural and functional neuroimaging. This case shows that impairment in specific cognitive domains is associated with structural/functional brain abnormalities in the corresponding brain areas (frontal and parietal lobes), supporting the hypothesis of disconnectivity, involving a failure to integrate anatomical and functional pathways. Future research would define the role of cognitive impairment and neurodegeneration in psychiatric nosography and, in particular, their role in the early phases of illness and long-term outcome of schizophrenic patients.

Key words: Positron emission tomography; Magnetic resonance; Schizophrenia; Neuropsychology

Core tip: Schizophrenia is associated with impairment in executive function, verbal memory, verbal fluency and attention. Neuropsychological tests are associated with structural and functional brain alterations. This

case report is an example of the potential correlation between clinical symptoms (*e.g.*, cognitive impairment) and brain changes. These data may help in the prediction of possible outcome of schizophrenia patients.

Grassi S, Orsenigo G, Serati M, Caletti E, Altamura AC, Buoli M. Cognitive correlates of neuroimaging abnormalities in the onset of schizophrenia: A case report. *World J Psychiatr* 2017; 7(2): 128-132 Available from: URL: http://www.wjgnet.com/2220-3206/full/v7/i2/128.htm DOI: http://dx.doi.org/10.5498/wjp.v7.i2.128

INTRODUCTION

A number of data would indicate schizophrenia as a progressive neurodegenerative disorder[1] whose outcome is influenced by many biological and clinical factors[2]. Of note, recent literature shows that neuropsychological deficits at onset may predict the clinical course of illness[3] being often associated with frontal and parietal lobe dysfunctions[4-6]. Moreover, a recent trial found that brain abnormalities of schizophrenic patients change according to age at onset. In particular, early onset patients show parietal abnormalities, while adult onset patients exhibit frontal and temporal ones[7].

To our knowledge there are few studies[8-10] associating cognitive frontal and parietal deficits with structural [magnetic resonance (MR)] and functional neuroimaging [positron emission tomography (PET)] and the anatomical and functional relationships underlying this deficit remain to be elucidated. Dysconnectivity, a failure in functional integration, is considered a key mechanism in the pathophysiology of cognitive impairments (in particular working memory performance) in individuals with schizophrenia[11].

The present paper deals with a recent diagnosed schizophrenic patient showing frontal and parietal lobe MR/PET abnormalities clinically associated with deficits in the corresponding cognitive domains.

CASE REPORT

The patient was a 19-year-old man admitted in our department. The patient showed nor psychiatric comorbidity with an Axis Ⅰ disorder neither personality disorders. A neurological exam, performed by a neurologist, was negative. Diagnosis of undifferentiated schizophrenia and exclusion of comorbid conditions were assessed through the administration of semi-structured interviews based on DSM-Ⅳ criteria (SCID Ⅰ and Ⅱ). Patient had family history for psychiatric disorders: The father was an alcohol abuser, one schizophrenic uncle (father's brother) committed suicide and the grandmother in mother line was affected by bipolar disorder. At the admission in our ward the patient was drug-naïve and showed persecutory delusion, auditory hallucinations, thought/behavioural disorganization and a duration of untreated psychosis of 9 mo[12]. Baseline score at Positive and Negative Syndrome Scale[13] was 84, while baseline score at Brief Psychiatric Rating Scale was 55[14]. In the first days of admission patient underwent to neuropsychological tests, cerebral MR and cerebral PET.

A neuropsychological battery was designed to encompass the areas believed to be affected by Schizophrenia[15]. Results and standard scores are summarized in Table 1. Patient's neurocognitive performances provided evidence for impairment in the following domains: Executive function (Cognitive Estimation, Verbal fluency, Trail Making Test), verbal memory, verbal ability (Boston Naming Test, phonemic Verbal Fluency) and attention (Visual Search, Trail Making Test). In addition, the patient failed in two Wechsler Adult Intelligence Scale[16] subscales: Verbal Comprehension Index and Perceptual Organization Index.

MR was performed using a circular polarized head coil and included Turbo Spin-Echo T1-weighted sequences, T2-weighted sequences and FLAIR. Imaging in three planes was performed using 5-mm slice thickness. MR revealed normal-sized ventricles, normal-sized subarachnoidal spaces, no abnormalities in gray matter, but bilaterally soft hyper-intensities in superior parietal lobe[4] periventricular white matter.

Fluorodeoxyglucose (FDG) was injected in condition of rest and fasting and after 30 min three-dimensional scan was performed. The images were compared to a cohort of normal ones. Fluoro-D-Glucose PET (Figures 1 and 2) showed glucose frontal and parietal lobes hypometabolism bilaterally. No further abnormalities in FDG distribution were observed.

MR and PET were performed by neuroradiologists collaborating within our department.

Of note, neuropsychological results are consistent with outlined MR abnormalities and PET images (fronto-parietal abnormalities)[17].

DISCUSSION

The present case report confirms data from literature of early cognitive deficits in the course of schizophrenia[18,19] and neuroimaging parietal abnormalities in early onset schizophrenic patients[7,20,21]. In addition, the correspondence between cognitive deficits and morphological/functional brain alterations[22] contributes to clarify the influence of brain changes in schizophrenia clinical presentation as well as to support the hypothesis of schizophrenia as a neurodegenerative disorder[23,24]. Recent trials found that brain abnormalities are more severe in patients with a longer duration of illness[25-27], novel antipsychotics are promising molecules for their efficacy in stopping the neurodegenerative process[28,29]. In this context cognitive and neuroimaging follow-up of our case can be useful to discriminate if neurodegenerative process of schizophrenia progresses in the course of illness or it is specific of early stages[24,30,31]. Finally, it would be important in the future to define the role of neuroimaging abnormalities in influencing outcome. MR

Table 1 Neuropsychological results

Test	Patient score	Normal value	Result	Z-score
Mini-mental state examination	27.19	24-29.19	Normal	0.45
Executive functions: Tower of London	25	20-36	Normal	-0.75
Frontal assessment battery	15.98	13.5-17.3	Normal	-0.95
Cognitive estimation task	19.97	0-18	Failed	2.43
Bizarreness	6	0-4	Failed	4
Problem solving: Raven's progressive matrices	29.05	18.6-33.05	Normal	0.89
Assessment of cognitive impairment in memory				
Verbal memory and learning				
Digit Span	5.75	3.75-8.75	Normal	-0.4
Verbal Learning	10.50	6.50-21.50	Normal	-0.93
Recall of prose: Immediate and after 10 min	3.50	8.00-27.50	Failed	-2.92
Spatial short-term memory (Corsi test)	4.50	3.50-8.50	Normal	-1.20
Attention and speed information processing				
Trail making test				
Part A	33	< 93 s	Normal	
Part B, dual task	161	< 282 s	Normal	
Part B-A	128	< 186 s	Borderline score	-1.36
Visual search	34.25	31-51.25	Borderline score	
Verbal fluency				
Phonemic	23	17-59	Borderline score	-1.43
Categories	32	25-58	Normal	-1.15
Language				
Boston naming test	31	43-60	Failed	-4.82
Token test	32	29-36	Normal	-0.29
Wechsler adult intelligence scale-revised	General IQ = 75 (verbal IQ = 81; performance IQ = 74) VCI = 5.5; POI = 6.25	80-120	Borderline score	-2.50

The standard scores, reported in the second column, are calculated considering a normal population. Our patient's scores, adjusted for age, sex and education are shown in the first column next to each test. A score is considered pathological when the score is present less than 5% of the normal population. Sometimes normal scores are considered pathological due to the clinical condition and the global performance. VCI: Verbal comprehension index; POI: Perceptual organization index.

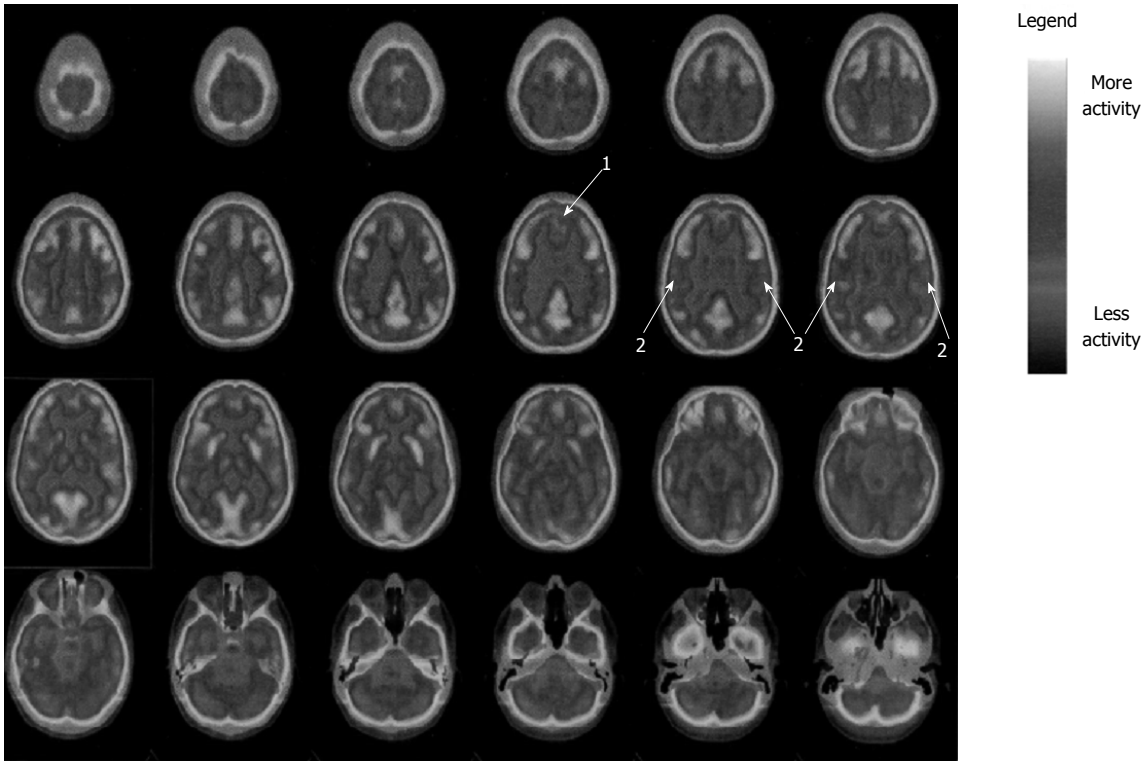


Figure 1 D-glucose (fluorodeoxyglucose) positron emission tomography, transversal sections. Pointer 1 displays the frontal lobe hypo-metabolism; pointer 2 displays the parietal lobe hypo-metabolism.

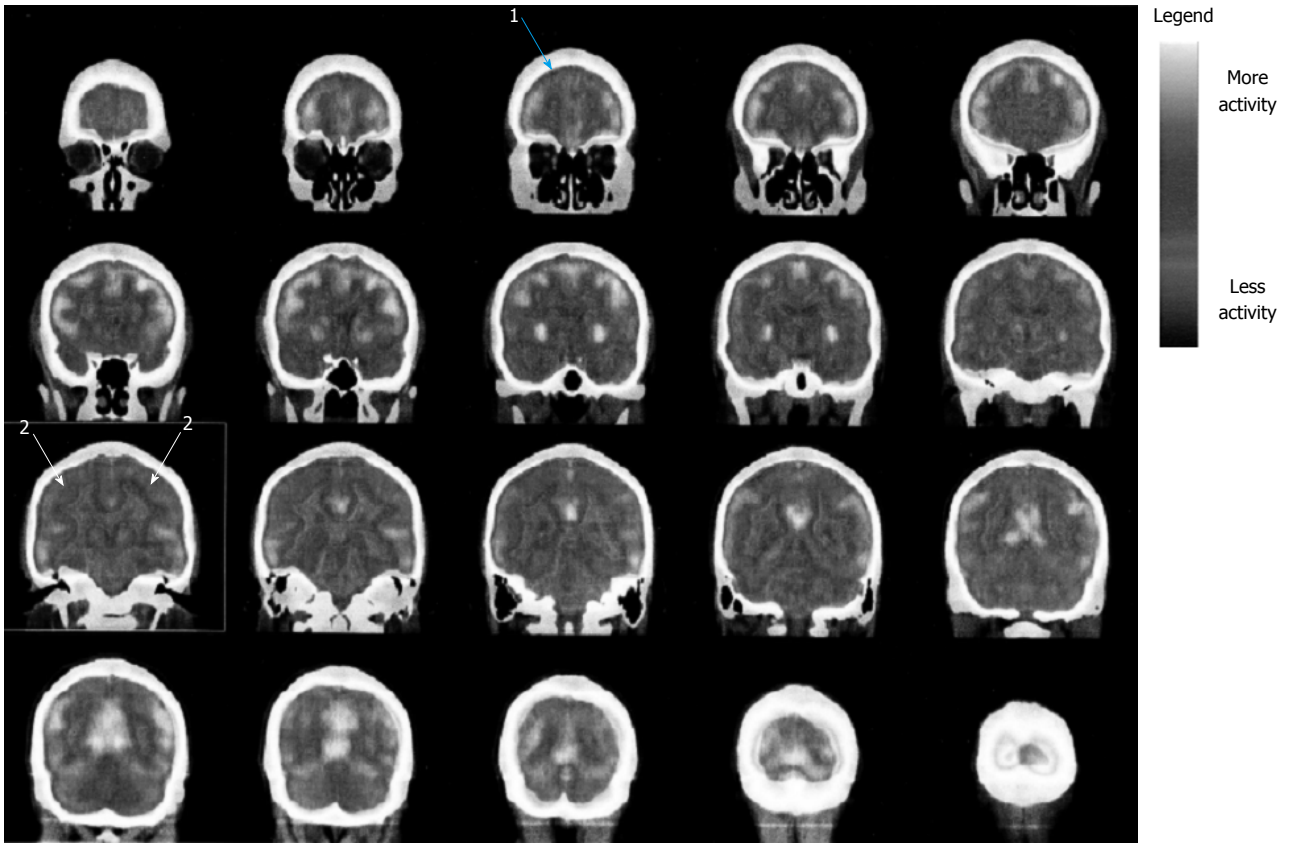


Figure 2 Fluoro-D-glucose (fluorodeoxyglucose) positron emission tomography, coronal sections. Pointer 1 displays the frontal lobe hypo-metabolism; Pointer 2 displays the parietal lobe hypo-metabolism.

and PET could be useful tools to make diagnosis and to predict long-term course of schizophrenic illness.

COMMENTS

Case characteristics

A 19-year-old male patient with severe schizophrenia presentation.

Clinical diagnosis

Patient was hospitalized because of prominent persecutory delusion, auditory hallucinations, aggressiveness and thought/behavioural disorganization.

Differential diagnosis

Bipolar disorder, substance use disorder.

Laboratory diagnosis

Routine blood tests were resulted within normal limits.

Imaging diagnosis

At magnetic resonance imaging bilaterally soft hyper-intensities in superior parietal lobe periventricular white matter were detected, while positron emission tomography showed glucose parietal lobes hypo-metabolism bilaterally.

Pathological diagnosis

Schizophrenia, acute episode.

Treatment

Ziprasidone 80 mg × 2 and Gabapentin 300 mg × 3.

Related reports

Severe cognitive impairment as showed by neuropsychological tests.

Term explanation

Dysconnectivity means abnormal functional integration among brain regions resulting in impaired modulation of neurotransmitters.

Experiences and lessons

It is important to perform imaging evaluation and neuropsychological tests to better define long-term outcome of schizophrenia patients.

Peer-review

This case report is novel and well designed.

REFERENCES

1 **van Haren NE**, Schnack HG, Cahn W, van den Heuvel MP, Lepage C, Collins L, Evans AC, Hulshoff Pol HE, Kahn RS. Changes in cortical thickness during the course of illness in schizophrenia. *Arch Gen Psychiatry* 2011; **68**: 871-880 [PMID: 21893656 DOI: 10.1001/archgenpsychiatry.2011.88]

2 **Altamura AC**, Bobo WV, Meltzer HY. Factors affecting outcome in schizophrenia and their relevance for psychopharmacological treatment. *Int Clin Psychopharmacol* 2007; **22**: 249-267 [PMID: 17690594 DOI: 10.1097/YIC.0b013e3280de2c7f]

3 **Wölwer W**, Brinkmeyer J, Riesbeck M, Freimüller L, Klimke A, Wagner M, Möller HJ, Klingberg S, Gaebel W. Neuropsychological impairments predict the clinical course in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2008; **258** Suppl 5: 28-34 [PMID: 18985291 DOI: 10.1007/s00406-008-5006-2]

4 **Brunet-Gouet E**, Decety J. Social brain dysfunctions in schizophrenia: a review of neuroimaging studies. *Psychiatry Res* 2006; **148**: 75-92 [PMID: 17088049 DOI: 10.1016/j.pscychresns.2006.05.001]

5 **Ragland JD**, Laird AR, Ranganath C, Blumenfeld RS, Gonzales SM, Glahn DC. Prefrontal activation deficits during episodic memory in schizophrenia. *Am J Psychiatry* 2009; **166**: 863-874 [PMID: 19411370 DOI: 10.1176/appi.ajp.2009.08091307]

6 **Schmidt A**, Smieskova R, Simon A, Allen P, Fusar-Poli P, McGuire PK, Bendfeldt K, Aston J, Lang UE, Walter M, Radue EW, Riecher-Rössler A, Borgwardt SJ. Abnormal effective connectivity and psychopathological symptoms in the psychosis high-risk state. *J Psychiatry Neurosci* 2014; **39**: 239-248 [PMID: 24506946 DOI: 10.1503/jpn.130102]

7 **Kyriakopoulos M**, Perez-Iglesias R, Woolley JB, Kanaan RA, Vyas NS, Barker GJ, Frangou S, McGuire PK. Effect of age at onset of schizophrenia on white matter abnormalities. *Br J Psychiatry* 2009; **195**: 346-353 [PMID: 19794204 DOI: 10.1192/bjp.bp.108.055376]

8 **Deserno L**, Sterzer P, Wüstenberg T, Heinz A, Schlagenhauf F. Reduced prefrontal-parietal effective connectivity and working memory deficits in schizophrenia. *J Neurosci* 2012; **32**: 12-20 [PMID: 22219266 DOI: 10.1523/JNEUROSCI.3405-11.2012]

9 **Pujol N**, Penadés R, Rametti G, Catalán R, Vidal-Piñeiro D, Palacios E, Bargallo N, Bernardo M, Junqué C. Inferior frontal and insular cortical thinning is related to dysfunctional brain activation/deactivation during working memory task in schizophrenic patients. *Psychiatry Res* 2013; **214**: 94-101 [PMID: 23993992]

10 **He Z**, Deng W, Li M, Chen Z, Jiang L, Wang Q, Huang C, Collier DA, Gong Q, Ma X, Zhang N, Li T. Aberrant intrinsic brain activity and cognitive deficit in first-episode treatment-naive patients with schizophrenia. *Psychol Med* 2013; **43**: 769-780 [PMID: 22883428 DOI: 10.1017/S0033291712001638]

11 **Stephan KE**, Friston KJ, Frith CD. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. *Schizophr Bull* 2009; **35**: 509-527 [PMID: 19155345 DOI: 10.1093/schbul/sbn176]

12 **Altamura AC**, Serati M, Buoli M. Is duration of illness really influencing outcome in major psychoses? *Nord J Psychiatry* 2015; **69**: 403-417 [PMID: 25768662 DOI: 10.3109/08039488.2014.990919]

13 **Kay SR**, Opler LA, Lindenmayer JP. The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. *Br J Psychiatry Suppl* 1989; **155** (Suppl 7): 59-67 [PMID: 2619982]

14 **Flemenbaum A**, Zimmermann RL. Inter- and intra-rater reliability of the Brief Psychiatric Rating Scale. *Psychol Rep* 1973; **32**: 783-792 [PMID: 4704758]

15 **Stefanopoulou E**, Manoharan A, Landau S, Geddes JR, Goodwin G, Frangou S. Cognitive functioning in patients with affective disorders and schizophrenia: a meta-analysis. *Int Rev Psychiatry* 2009; **21**: 336-356 [PMID: 20374148 DOI: 10.1080/09540260902962149]

16 **Kay SR**. Schizophrenic WAIS pattern by diagnostic subtypes. *Percept Mot Skills* 1979; **48**: 1241-1242 [PMID: 492898 DOI: 10.2466/pms.1979.48.3c.1241]

17 **Leeson VC**, Barnes TR, Harrison M, Matheson E, Harrison I, Mutsatsa SH, Ron MA, Joyce EM. The relationship between IQ, memory, executive function, and processing speed in recent-onset psychosis: 1-year stability and clinical outcome. *Schizophr Bull* 2010; **36**: 400-409 [PMID: 18682375 DOI: 10.1093/schbul/sbn100]

18 **Fitzgerald D**, Lucas S, Redoblado MA, Winter V, Brennan J, Anderson J, Harris A. Cognitive functioning in young people with first episode psychosis: relationship to diagnosis and clinical characteristics. *Aust N Z J Psychiatry* 2004; **38**: 501-510 [PMID: 15255822 DOI: 10.1111/j.1440-1614.2004.01403.x]

19 **Fatouros-Bergman H**, Cervenka S, Flyckt L, Edman G, Farde L. Meta-analysis of cognitive performance in drug-naïve patients with schizophrenia. *Schizophr Res* 2014; **158**: 156-162 [PMID: 25086658 DOI: 10.1016/j.schres.2014.06.034]

20 **Bartholomeusz CF**, Cropley VL, Wannan C, Di Biase M, McGorry PD, Pantelis C. Structural neuroimaging across early-stage psychosis: Aberrations in neurobiological trajectories and implications for the staging model. *Aust N Z J Psychiatry* 2017; **51**: 455-476 [PMID: 27733710 DOI: 10.1177/0004867416670522]

21 **Yildiz M**, Borgwardt SJ, Berger GE. Parietal lobes in schizophrenia: do they matter? *Schizophr Res Treatment* 2011; **2011**: 581686 [PMID: 22937268 DOI: 10.1155/2011/581686]

22 **Minatogawa-Chang TM**, Schaufelberger MS, Ayres AM, Duran FL, Gutt EK, Murray RM, Rushe TM, McGuire PK, Menezes PR, Scazufca M, Busatto GF. Cognitive performance is related to cortical grey matter volumes in early stages of schizophrenia: a population-based study of first-episode psychosis. *Schizophr Res* 2009; **113**: 200-209 [PMID: 19616413 DOI: 10.1016/j.schres.2009.06.020]

23 **Rund BR**. Is schizophrenia a neurodegenerative disorder? *Nord J Psychiatry* 2009; **63**: 196-201 [PMID: 19235629 DOI: 10.1080/08039480902767286]

24 **Olabi B**, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. *Biol Psychiatry* 2011; **70**: 88-96 [PMID: 21457946 DOI: 10.1016/j.biopsych.2011.01.032]

25 **Hulshoff Pol HE**, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr Bull* 2008; **34**: 354-366 [PMID: 18283048 DOI: 10.1093/schbul/sbm168]

26 **Torres US**, Duran FL, Schaufelberger MS, Crippa JA, Louzã MR, Sallet PC, Kanegusuku CY, Elkis H, Gattaz WF, Bassitt DP, Zuardi AW, Hallak JE, Leite CC, Castro CC, Santos AC, Murray RM, Busatto GF. Patterns of regional gray matter loss at different stages of schizophrenia: A multisite, cross-sectional VBM study in first-episode and chronic illness. *Neuroimage Clin* 2016; **12**: 1-15 [PMID: 27354958 DOI: 10.1016/j.nicl.2016.06.002]

27 **Buoli M**, Caldiroli A, Panza G, Altamura AC. Prominent clinical dimension, duration of illness and treatment response in schizophrenia: a naturalistic study. *Psychiatry Investig* 2012; **9**: 354-360 [PMID: 23251199 DOI: 10.4306/pi.2012.9.4.354]

28 **van Haren NE**, Hulshoff Pol HE, Schnack HG, Cahn W, Mandl RC, Collins DL, Evans AC, Kahn RS. Focal gray matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. *Neuropsychopharmacology* 2007; **32**: 2057-2066 [PMID: 17327887 DOI: 10.1038/sj.npp.1301347]

29 **Ozcelik-Eroglu E**, Ertugrul A, Oguz KK, Has AC, Karahan S, Yazici MK. Effect of clozapine on white matter integrity in patients with schizophrenia: a diffusion tensor imaging study. *Psychiatry Res* 2014; **223**: 226-235 [PMID: 25012780 DOI: 10.1016/j.pscychresns]

30 **Zanello A**, Curtis L, Badan Bâ M, Merlo MC. Working memory impairments in first-episode psychosis and chronic schizophrenia. *Psychiatry Res* 2009; **165**: 10-18 [PMID: 19046607 DOI: 10.1016/j.psychres.2007.10.006]

31 **Braw Y**, Bloch Y, Mendelovich S, Ratzoni G, Gal G, Harari H, Tripto A, Levkovitz Y. Cognition in young schizophrenia outpatients: comparison of first-episode with multiepisode patients. *Schizophr Bull* 2008; **34**: 544-554 [PMID: 17984299 DOI: 10.1093/schbul/sbm115]

P- Reviewer: Belli H, Kravos M **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Li D

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com