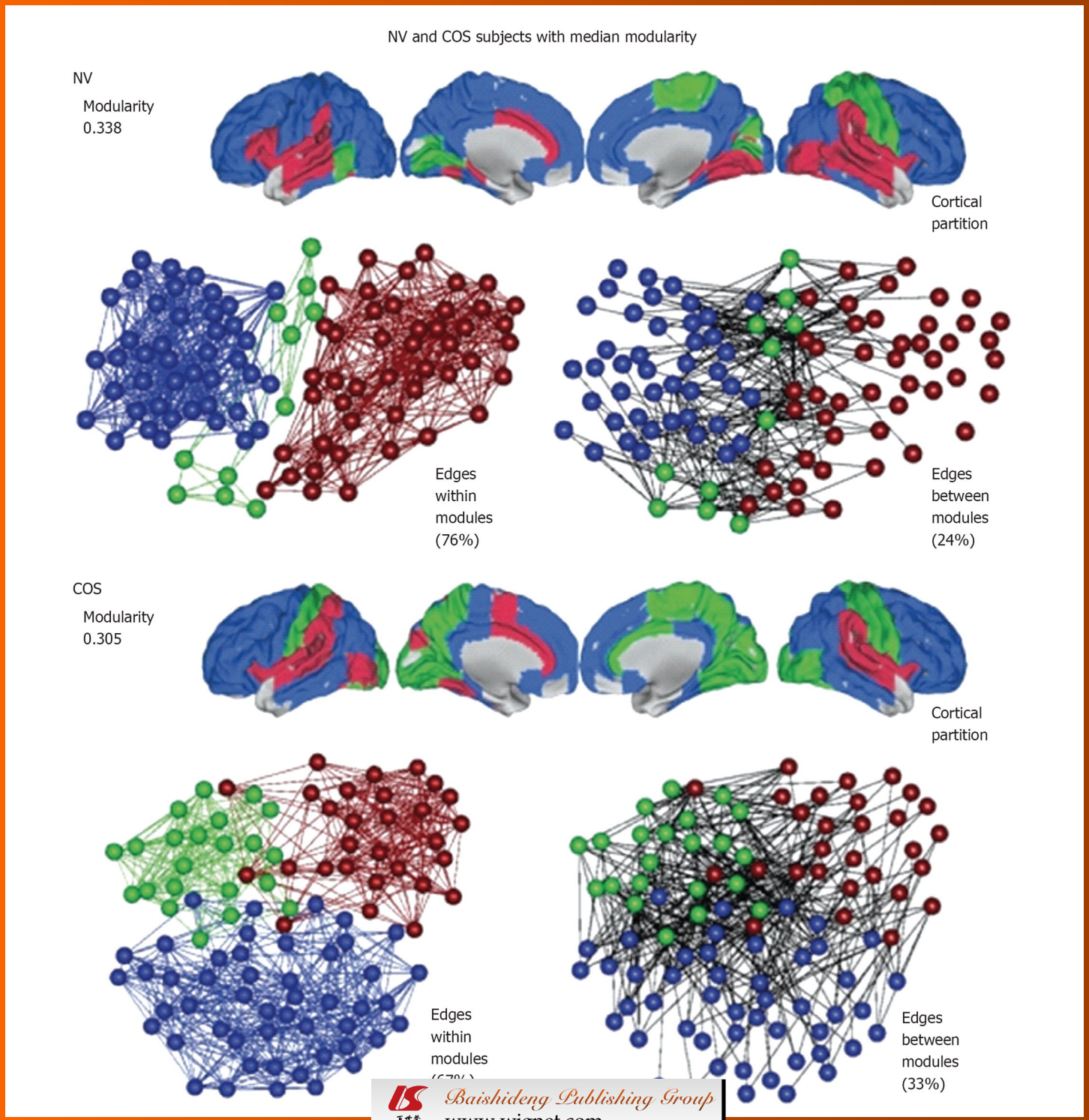
ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2012 February 22; 2(1): 1-25



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

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AIM AND SCOPE

World Journal of Psychiatry (*World J Psychiatr*, *WJP*, online ISSN 2220-3206, DOI: 10.5498) is a bimonthly peer-reviewed, online, open-access, journal supported by an editorial board consisting of 103 experts in psychiatry from 32 countries.

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NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Bimonthly

EDITING
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E-mail: wjp@wjgnet.com
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai, Hong Kong, China
Fax: +852-31158812
Telephone: +852-58042046
E-mail: bpg@baishideng.com
http://www.wjgnet.com

PUBLICATION DATE
February 22, 2012

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2220-3206/g_info_20100722180909.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Psychiatry

Online Submissions: http://www.wjgnet.com/esps/
wjp@wjgnet.com
doi:10.5498/wjp.v2.i1.1

World J Psychiatr 2012 February 22; 2(1): 1-12
ISSN 2220-3206 (online)

EDITORIAL

Graph-based network analysis in schizophrenia

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Received: October 9, 2011 Revised: December 10, 2011
Accepted: January 21, 2012
Published online: February 22, 2012

Key words: Schizophrenia; Graph theory; Small world networks; Brain networks; Brain connectivity

Peer reviewers: Judith Usall, MD, PhD, Research and development Unit Sant Joan de Déu, Dr Antoni Pujadas 42, Sant Boi de Llobregat 08830, Spain; Peter J Gebicke-Haerter, Professor, Department of Psychopharmacology, Central Institute of Mental Health, Mannheim 68159, Germany

Micheloyannis S. Graph-based network analysis in schizophrenia. *World J Psychiatr* 2012; 2(1): 1-12 Available from: URL: http://www.wjgnet.com/2220-3206/full/v2/i1/1.htm DOI: http://dx.doi.org/10.5498/wjp.v2.i1.1

Abstract

Over the last few years, many studies have been published using modern network analysis of the brain. Researchers and practical doctors alike should understand this method and its results on the brain evaluation at rest, during activation and in brain disease. The studies are noninvasive and usually performed with elecroencephalographic, magnetoencephalographic, magnetic resonance imaging and diffusion tensor imaging brain recordings. Different tools for analysis have been developed, although the methods are in their early stages. The results of these analyses are of special value. Studies of these tools in schizophrenia are important because widespread and local network disturbances can be evaluated by assessing integration, segregation and several structural and functional properties. With the help of network analyses, the main findings in schizophrenia are lower optimum network organization, less efficiently wired networks, less local clustering, less hierarchical organization and signs of disconnection. There are only about twenty five relevant papers on the subject today. Only a few years of study of these methods have produced interesting results and it appears promising that the development of these methods will present important knowledge for both the preclinical signs of schizophrenia and the methods' therapeutic effects.

INTRODUCTION

Schizophrenia is characterized by the disintegration of thought processes and emotional responsiveness. Bleuler coined the term "schizophrenia," describing it as a group of diseases[1]. Early brain damage and genetic, psychological and social factors appear to be the main elements of the disease's expression. Diagnosis is established with the use of certain criteria based on the DSM-IV diagnostic tools. The symptomatology of schizophrenia is widely divergent and there is evidence for multiple processes and disturbances in the "group of schizophrenias". After decades of research, it is evident that widely dispersed brain circuits are implicated, mainly circuits of the dorsal and dorsolateral prefrontal cortex and cortical areas of the temporal lobe[2]. Numerous magnetic resonance imaging (MRI) and tractography or diffusion tensor imaging (DTI) studies did not reveal anatomical findings characteristic of schizophrenia[3,4]. In a greater population-based MRI study, gray matter reductions and white matter deficits were found to be widespread in schizophrenics. Simultaneously, gray matter excesses were observed bilaterally in the basal ganglia, anterior cingulate and medial orbitofrontal cortices. Additionally, cerebrospinal fluid excesses were evident in the ventricles[5]. A relationship between

structural and functional connectivity has been suggested by several authors[6]. Disturbances in structural connectivity are directly related to functional connectivity. The latter is expressed in abnormal patterns of neurophysiological oscillations, especially in high frequency bands seen in the electroencephalogram (EEG) and magnetoencephalogram (MEG)[7,8]. Disturbance of these high frequency oscillations is indicative of abnormal neural synchrony as the result of a "disconnection syndrome" in schizophrenia. In recent years, attempts have been made to study connectivity and network organization using tools derived from graph theory. With these tools, brain network analyses can be performed noninvasively using bioelectrical signals or MRI.

NETWORK ANALYSIS OF THE BRAIN

Modern network analyses of the brain using tools derived from graph theory assess anatomical, functional and effective connectivity, as well as their local or widespread properties. The information from such analyses is related to the integration and segregation of brain networks at rest and during several activations. A graph, a mathematical representation of the network, consists of vertices, i.e., the nodes corresponding to brain regions and edges representing connections or statistical dependencies between nodes. Several parameters characterize the graphs and present information about their potential behavior and connection topologies. The first use of graph theory to study networks of neurons was the nervous system of the roundworm *Caenorhabditis elegans* or *C. elegans*, which is the only animal with a completely known neuronal wiring diagram. This worm has exactly 302 neurons and all neuronal connections have been recorded. The organization of this neuronal network was found to have the optimum functional properties, i.e., the so-called small world network (SWN). This organization corresponds to graphs with optimum segregation and integration: local bindings are tightening and connection to remote points is easy, with few and/or easy steps[9]. In SWNs, the average distance between two vertices is similar to the random networks', increasing logarithmically with the number of vertices[10] (Figure 1).

Several measures characterize the graphs. The cluster coefficient and path length are between the commonly used parameters. The clustering coefficient of a vertex is the probability that its neighbor vertices are also connected to each other. The average of all of the clustering coefficients (C) of a graph is a measure of the local structure of the graph. The path length expresses the paths or the ease with which the information travels from one vertex to remote vertices. The average of the path lengths is the path length (L) of the graph. This average expresses the global interaction of the network.

Low L means easy communication between remote vertices. The degree of a vertex is the number of edges and the average of all of the degrees is the degree (K) of the whole graph. The degree distribution P (K) is the probability that a randomly chosen node has the degree K. Local and global efficiency, which are analogous to C and L, express segregation and integration. Using C and L or local and global efficiency, it is possible to detect whether or not a SWN organization exists. In that case, C is high and L is low; local and global efficiency are high. Many studies have shown that SWN organization is a healthy optimum organization in the brain from which deviations are detected in pathologies, such as ADD, AD, schizophrenia and epilepsy. An additional interesting graph metric is centrality, or betweenness centrality, which measures the number of short paths between any two nodes that pass through this node and identifies hubs, i.e., the nodes with high degree; modularity, i.e., a measure of the organization in modules with high clustering; and hierarchy, i.e., a measure of the way that hubs are connected in space.

Table 1 List of graph theoretical studies in schizophrenia

Study	Method	Parameters
2006: Micheloyannis *et al*[61]	EEG	C, L, SWN
2008: Basset *et al*[17]	MRI, MEG	SWN, efficiency
2008: Liu *et al*[67]	fMRI	C, L, Eloc, Eglob, K, SWN
2009: Rubinov *et al*[64]	EEG	C, L, SWN
2009: Basset *et al*[66]	MEG	Cost efficiency
2010: Wang *et al*[77]	fMRI	SWN, efficiency
2010: van den Heuvel *et al*[40]	DTI	C, L, SWN
2010: De Vico Fallani *et al*[62]	EEG	Network density, degree
2010: Lynall *et al*[68]	fMRI	SWN, efficiency, hierarchy, degree dist, connectivity strength and diversity
2010: Alexander-Bloch *et al*[69]	fMRI	Modularity
2011: Jalili *et al*[65]	EEG	Degree, node strength, SWN, Eglob, modularity, centrality
2011: Zalesky *et al*[70]	DTI	SWN, nodal degree, C, L, efficiency
2011: Fornito *et al*[25]	fMRI	C, L, SWN, efficiency
2011: Yu *et al*[71]	fMRI	C, L, Eloc, Eglob, SWN
2011: Lord *et al*[79]	fMRI	Betweenness centrality, degree centrality, L
2011: Weiss *et al*[86]	MEG	Network cost
2011: Yu *et al*[78]	fMRI	K, C, L, Eglob, Eloc
2011: Wang *et al*[75]	DTI	SWN, Cost, Eloc, Eglob
2012: Ma *et al*[72]	fMRI	C, L, centrality
2012: He *et al*[76]	fMRI	K, C, L, Eloc, Eglob
2012: Alexander-Bloch *et al*[74]	fMRI	Modularity
2012: Alexander-Bloch *et al*[73]	MRI	Network connection distance
2012: Shi *et al*[80]	MRI, DTI	SWN, modularity, centrality, connection distance

EEG: Electroencephalogram; MRI: Magnetic resonance imaging; MEG: Magnetoencephalographic; DTI: Diffusion tensor imaging; fMRI: Functional MRI; SWN: Small world network; C: Clustering coefficients; L: Path length; K: Degree K.

Brain networks in health

The first use of graph theoretical network analysis in humans was performed with MEG signals in healthy individuals[11] (Table 1). It was found that the lower and higher frequency bands displayed the features of SWN. A vast body of literature has accumulated using network

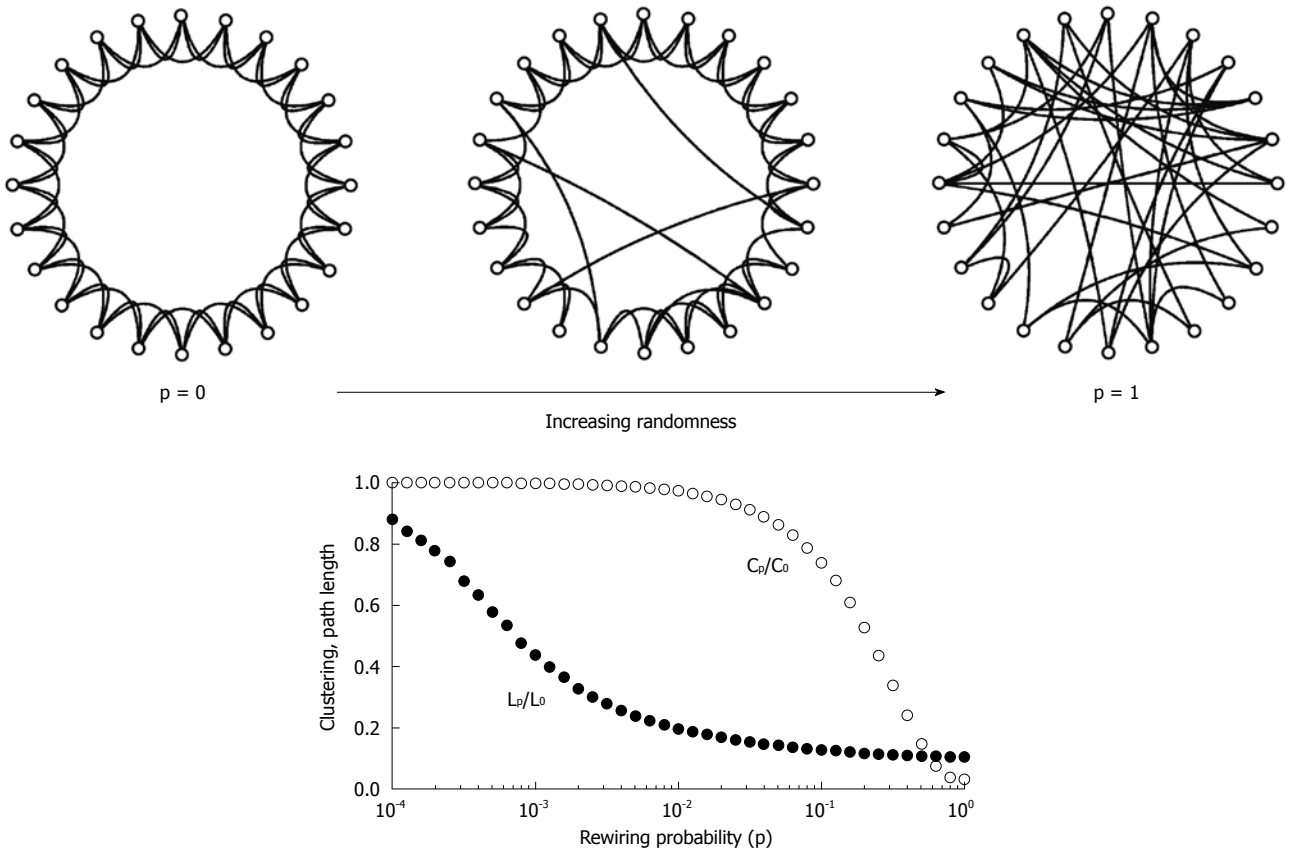

Figure 1 The Watts-Strogatz model of the small world. The network at the upper left corner represents a ring lattice with circular boundary conditions. Starting from this configuration, connections are randomly rewired with given rewiring probability p. For p = 0 (no rewiring), the network retains its regular lattice topology. For p = 1, the network is completely random, and all lattice-like features have disappeared. Intermediate values of p result in networks that consist of a mixture of random and regular connections. The plot at the bottom shows the clustering coefficient Cp and the path length Lp, both normalized by their values for the regular network (P0, L0). Note that there is a broad range for the rewiring probability p when networks have clustering similar to the regular network's clustering and a path length similar to the random network's path. Within this range, networks exhibit small-world attributes. Data computed following the procedure is described in Watts and Strogatz (66), with networks consisting of 1000 nodes and 10 000 edges (data points represent averages of 400 rewiring steps)[85].

analysis in health, at rest or during several tasks. The main characteristic of the brain network analysis is the SWN. As in other SWNs in the brain, this structure could be simultaneously scale-free with connectivity distribution following a power law. Connectivity distribution following a truncated power law distribution seems more possible. This architecture means that there is a modular organization (with clusters) and simultaneously optimized fast processing[12]. Nodes of brain networks (neurons or groups of neurons) can have different degrees. High-degree nodes are the hubs. Nodes can be organized in small subgroups consisting of only a few nodes having similar functions. These are the motifs. Clusters or modules are parts of a network with many connections between them and few connections to the other parts of the network; these clusters subserve similar brain functions[13]. Modularity corresponds to local segregation of the network (Figure 2). Another important feature of brain network organization is hierarchy. Hierarchy characterizes the structural and functional organization of neural networks and can be seen as the encapsulation of smaller elements in larger ones, a behavior that is recursive of fractal development[14].

Construction of brain graphs

There are several methods of constructing brain graphs to study parameters and visualize brain networks. Graphs can be constructed from EEG or MEG and MRI. For microelectrode recordings, the nodes of the graph are the microelectrodes. For EEG or MEG recordings, the electrodes or sensors are the nodes. Because volume conduction of electrical activity influences the electrodes, if nodes are taken from the sources under each sensor from the cortex, they give more accurate values for the construction of graphs. Adequate estimation of the sources can be performed with several softwares[15]. The edges are taken to be the correlations between nodes estimated using linear or nonlinear methods. The connections between nodes can be binarized or weighted, directed or not. Binarized connections are the simplest form, but for functional or effective connectivity estimation, weights or causal relationships between nodes must be considered[12].

The methods of construction of the graphs from MRI differ (Figure 3). Regions corresponding to Brodman areas can be taken as nodes. The automated anatomical labeling template is often used to find the nodes

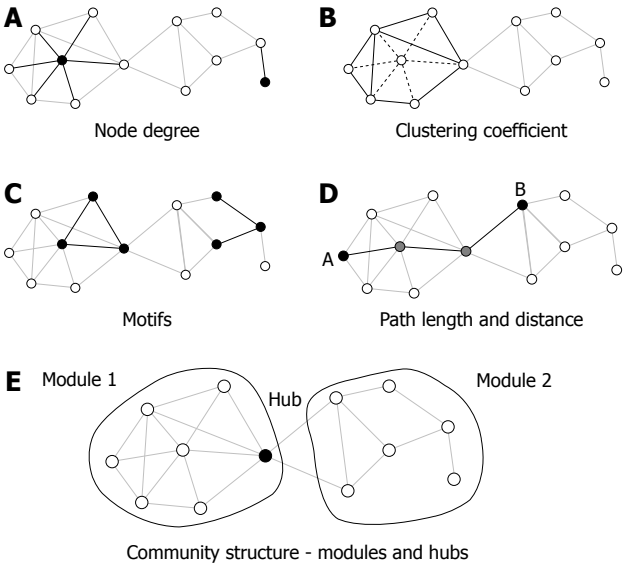

Figure 2 Key graph measures and their definitions. The measures are illustrated in a rendering of a simple undirected graph with 12 nodes and 23 edges. A: Node degree corresponds to the number of edges attached to a given node, which are shown here for a highly connected node (left) and a peripheral node (right); B: The clustering coefficient is shown here for a central node and its six neighbors. These neighbors maintain eight out of 15 possible edges for a clustering coefficient of 0.53; C: Each network can be decomposed into subgraphs of motifs. The plot shows two examples of two different classes of three-node motifs; D: The distance between two nodes is the length of the shortest path. Nodes A and B connect in three steps through two intermediate nodes (shown in gray). The average of the finite distances for all node pairs is the graph's path length; E: The network forms two modules interconnected by a single hub node[85].

for the MRI graphs[16]. The other possibility is to take nodes with equal numbers of voxels covering the whole brain[17]. An additional possibility is to construct and assess structural graphs using DTI to find the nodes and edges. Strong co-variation between cortical regions is assumed to be related to connectivity and the trophic effects of neurons. Thus, the cortical thickness or volume of multiple cortical regions can be taken as the different nodes[17,18]. The EEG or MEG signals or the time series of voxels or brain regions in MRI are used to construct an association matrix as a weighted network. They can be transformed into a binary matrix in which a threshold is used; values above one threshold exist and below another do not.

Normal brain network organization

Using EEG signals, it becomes evident that numerous neurophysiological parameters show heritability[19]. During the last several years, brain networks were studied for heritability. This methodology is important because network organization indicates brain function ability[20-22]. In EEG studies, synchronization likelihood (showing linear and nonlinear dependencies between signals), clustering coefficient, path length and small-worldness showed heritability in a great number of twins[23,24]. In a functional MRI (fMRI) study in monozygotic and dizygotic twins, the genetic influence was more evident in special regions[25].

Normal brain network organization is characterized by high clustering (existence of motifs, modules and high-degree nodes, i.e., hubs) and short path length, expressing the SWN architecture with high efficiency and organized for optimum economy and cost[26]. The SWN architecture shows differences between hemispheres and gender, as demonstrated in an fMRI study[27,28]. A fMRI study[29] found that there was a difference between men and women. Women had shorter path length and higher clustering. A DTI tractography study showed that local efficiency was higher in females[30]. Women show greater overall cortical connectivity and more efficient networks[31].

Two additional important characteristics of normal brain network organizations are modularity and hierarchy. These traits characterize not only neural networks but also most complex systems, such as biological, economic, social networks and the internet[14,32]. The achievement of this brain organization is revolutionary[33]. Structural and functional modular organization has been demonstrated analyzing anatomical and BOLD fluctuations from resting-state fMRI[34,35]. In accordance with other studies, the modular organization influence segregation and integration, high information processing and network robustness[32]. Hierarchy, the other neural network characteristic, is considered recursive of fractals[29], i.e., the network organization shows a self-similar organization. It can be visible in spatial, temporal and topological scales[36-38]. The small nervous system of C. elegans, as well as other animals and human brains, show hierarchical modularity represented by an economical wiring diagram[37]. The existence of hubs, i.e., high-degree nodes, is important for the normal function of brain networks. These hubs have a central position for efficient integration of information across the network. The hubs have above-average connections, low clustering coefficients, low path length to other nodes and a high level of betweenness centrality[39,40].

The SWN, as well as the modular organization and widespread interconnections, shows changes during several brain functions, depending on the accuracy of executive task performance and general intelligence[21,29,41]. During working memory, individuals with higher education showed lower SWN organization according to the neural efficiency hypothesis, i.e., the lower-educated needed more effort, producing more efficient network organization, as expressed by a higher SWN index[41]. Cognitive effort breaks modularity depending on effort, as shown during working memory of difficulties[21]. In a study of learning in short or longer intervals (minutes, hours, days), dynamic changes in modularity were detected[42]. A study of graph characteristics using bioelectrical signals during visual working memory maintenance found that α and β bands showed a memory-load-dependent scale-free SWN behavior[43]. Returning to graph theoretical tools and fMRI, it was found that during working memory, connectivity strength decreased as working memory load increased[44]. Intelligence is related to brain network or-

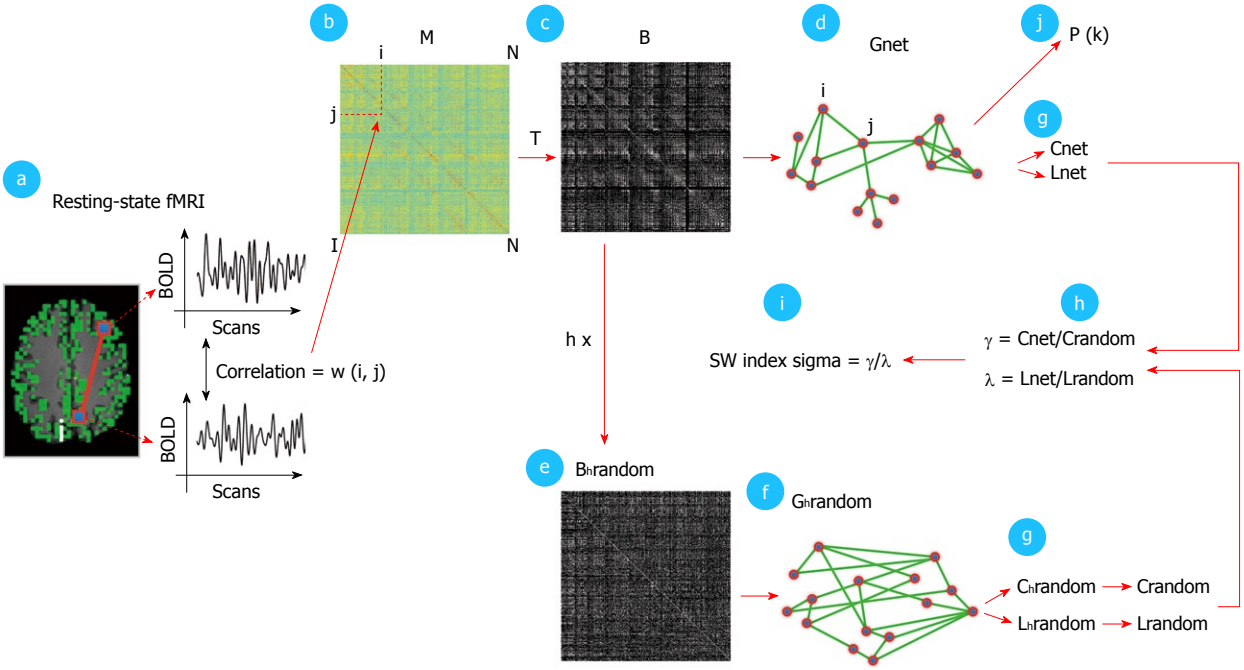

Figure 3 Detailed schematic illustration of the graph analysis. The first step (panel a) consisted of calculating the temporal zero-lag correlations between the filtered functional magnetic resonance imaging BOLD time-series of all voxels, which was believed to reflect inter-voxel functional connectivity. The computed correlations were represented as a correlation matrix M, with cell M (i, j) holding the level of functional connectivity between voxel i and voxel j (panel b). M was thresholded with a threshold T (panel c), resulting in a binary connectivity matrix B, representing an unweighted graph Gnet (panel d). T varied between 0 and 0.7 (with steps of 0.05) and a range of fixed k between 4000 and 20. For each fixed k, M was thresholded with a computed T that corresponded exactly to a connectivity degree of k for that particular individual dataset. Next, B was randomized (panel e) to create a random graph Grandom with a similar connectivity distribution P (k) as Gnet but a random organization of connections. Also, h random graphs were formed per Gnet. From Grandom and Gnet, the graph characteristics Cnet, Lnet, Crandom, Lrandom were computed (panel g). Crandom and Lrandom were created by averaging the clustering-coefficient and path length of the h random graphs. Next, γ and λ were computed, as defined as Cnet/Crandom and Lnet/Lrandom (panel h). The small-world index sigma was computed as the ratio between γ and λ (SW index, panel i) expressing the small-worldness of Gnet. In addition, the connectivity distribution P (k) of Gnet was computed (panel j). Finally, the individually computed graph characteristics were averaged over the group of subjects and the group averaged connectivity distribution P (k) was fitted with a power-law function to examine a possible scale-free organization of the functionally connected human brain[36].

ganization. Higher scores on intelligence tests are related to greater global efficiency of the brain anatomical networks, as found in a diffusion tensor tractography study using graph theoretical tools[45]. Three recent functional connectivity studies using fMRI, high-density resting state EEG or MEG had similar findings, demonstrating the correlation between global efficiency and intelligence performance[20,22,29].

In children, the long distant connections (edges) are weak in contrast with stronger short-distance edges. During development, short-distance connections weaken, while the long-distance connections increase in strength[46-49]. The SWN architecture already exists in the 1st month of life[48] and this organization seems to assume higher values in adults[50]. Modular organization changes greatly in elderly people compared with the young and middle-aged. The old showed a decrease in the connector ratio and inter-module connections[51]. In another study, older people showed a decrease in the inter-modular organization frontal and an increase in the posterior and central modules[35]. Additionally, there are age-related task-dependent effects. In a study of language perception, age-related declines in global efficiency were found[52]. During mathematical thinking, the $\alpha 2$ band showed a degree of SWN disorganization in adults compared to children, whereas β and γ bands showed lower synchronization and lower SWN organization[53]. Recently published reviews are helpful to understand the normal organization and development[54-58]. Existing studies related to network development are not sufficient to provide a conclusive and detailed picture. It is important to collect more details in the future to define first signs of disturbance in the development of brain diseases, such as schizophrenia.

BRAIN NETWORKS IN SCHIZOPHRENIA

There is a vast body of literature related to neuroanatomical abnormalities and connectivity in schizophrenia[59,60]. Brain network disturbances began to be studied in 2006, providing many interesting findings and sparking the hope that in a few years, we will understand more about schizophrenia and the signs of its onset. Because network analysis offers information about integration, segregation, connectivity and overall organization of brain networks, it promises an interesting approach to schizophrenia. The first studies using network analysis in schizophrenia were performed assessing SWN organization. In 2006, the first paper related to schizophrenia and SWN was published. The authors recorded electroencephalographic signals using 29 electrodes in which the nodes and the edges

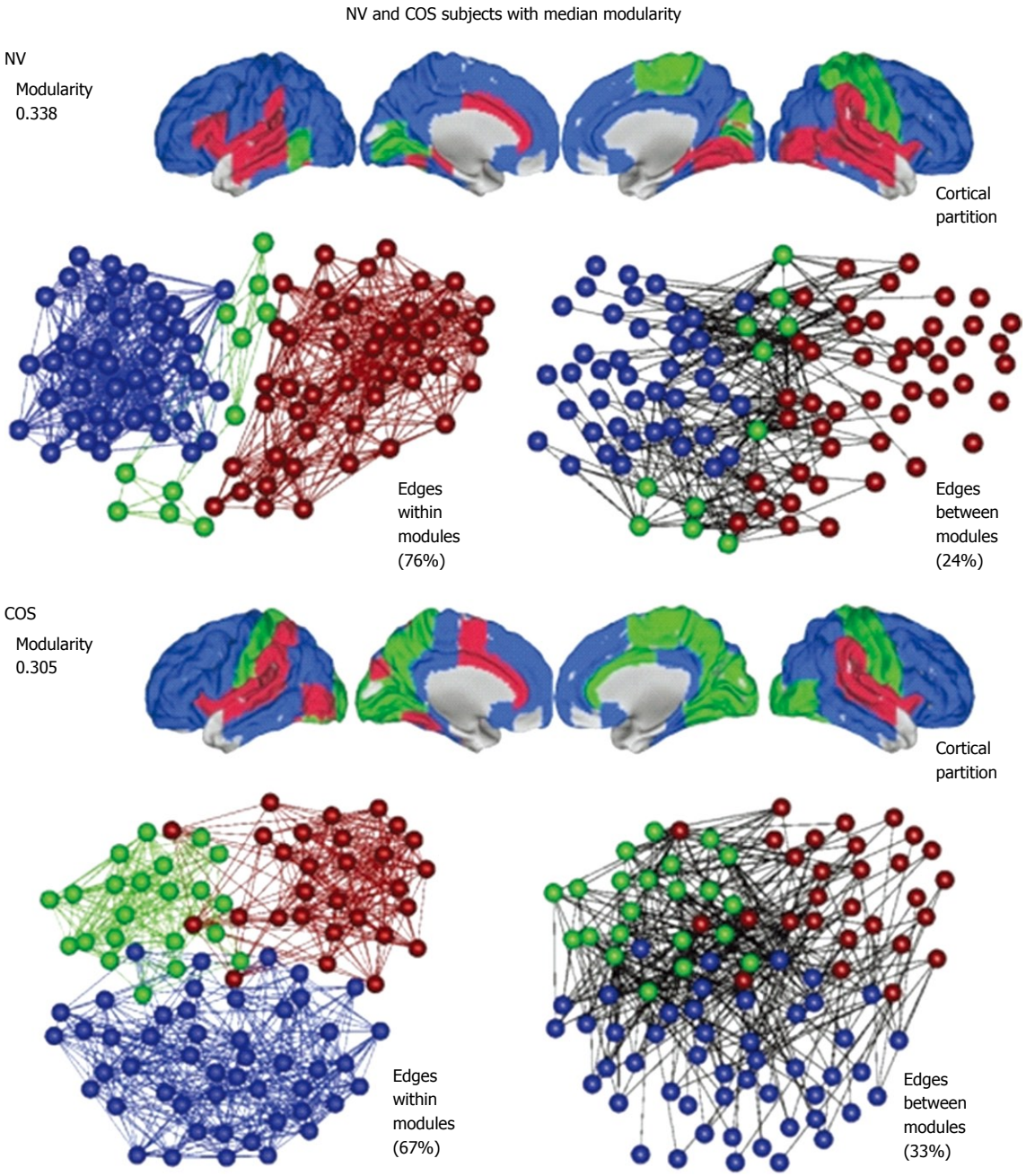

Figure 4 An illustration of modularity using representative brain networks from a childhood-onset schizophrenia population and a control (NV) population. At a local threshold of 0.22 topological cost, the modular partition is shown for the median NV subject (above) and the median childhood-onset schizophrenia (COS) subject (below). Each module is assigned a specific color and the modular structure of each subject is illustrated in three different ways. The cortical partition shows the anatomical location of modules, while the left-hand topological plot shows the density of intra-modular edges between nodes in different modules[69].

were estimated with a linear and nonlinear estimator in 20 stabilized, functional schizophrenics and 20 healthy controls. Undirected binary graphs were constructed and the clustering coefficient, path length and SWN index were evaluated at rest and during a working memory test separately in all frequency bands. Disrupted patterns of functional integration were found for $\alpha 1$, $\alpha 2$, β and $\gamma 1$ bands in schizophrenics during working memory in comparison to controls. The SWN pattern was lower in patients[61]. The same material was later analyzed with spectral analysis, coherence and construction of graphs from the coherence, and high-resolution EEG and graphs. These analyses showed the SWN disruption and, additionally, signs of hypofrontality with an asymmetry[62,63]. In another study with EEG signal recordings at rest, 40 young schizophrenics and 40 controls were estimated using a nonlinear method and the nonlinear correlation matrices were converted to weighted graphs. Clustering coefficient, path length and central hubs were evaluated. Schizophrenics showed the lower clustering and shorter path lengths indicative of lower SWN organization. The centrality of hubs was also lower in schizophrenics. These findings are indicative of a disturbance toward the randomization of schizophrenics' networks[64].

Another study used two methods of measuring between electrode values and several graph parameters of EEG signals in 14 schizophrenics and 14 controls. The correlation between electrodes was assessed using partial and non-partial cross-correlations that complemented one another. Graphs were constructed and graph parameters were measured for small-worldness, vulnerability, modularity, assortativity and synchronizability[65]. The small-worldness was reduced in schizophrenics, indicative of lower segregation and integration. The modularity index was also lower in schizophrenic patients, indicative of the lower segregation properties of their networks. This reduced modularity was more evident in the β band. Vulnerability and assortativity showed that resilience in schizophrenics was lower. The normal networks show assortative construction, while nodes with high degree tend to link with other nodes with high degree. The vulnerability shows the size of the drop in performance when a node is removed. Both of these parameters differed in patients who indicated lower resilience, except for the γ band, which showed less vulnerability in comparison to controls. Additionally, widespread synchronizability was lower in patients in the θ, α, β and γ bands. All of these differences in the components of schizophrenics' brain networks are indicative of the networks' failures in schizophrenic patients.

Bassett *et al*[66] recorded magnetoencephalographic signals from 29 healthy individuals and 28 schizophrenics performing a working memory task. The nodes were the 275 channels of the MEG. These authors used mutual information (sensitive to linear and nonlinear association) between wavelet coefficients for each pair of channels to construct graphs at each MEG band in the range between 1 and 60 Hz, and they estimated efficiency in relationship to cost, i.e., the cost-efficiency of networks' different frequency bands (connection cost estimated by the mutual information). The normal organization of brain networks maximizes efficiency for minimum cost. In this study, the schizophrenics showed reduced maximal cost-efficiency in relationship to normal individuals in the β-frequency band (15-30 Hz). There are indices that this band is a coordination frequency for large-scale networks, such as the networks for the working memory. This was more evident on nodes in the left lateral parietal and frontal areas related to working memory function.

With MRI, including tractography, network construction can include cortical and subcortical structures. Several studies in schizophrenia have been performed using MRI. Liu *et al*[67] studied SWN behavior in schizophrenics using fMRI. fMRI reveals information about the activities of cortex and subcortical structures. Liu *et al*[67] used a well-known "automated anatomical labeling" method to define 90 regions as nodes[18]. Partial correlation was used to assess between-node connectivity. Partial correlation matrices were used to construct binary undirected graphs and their parameters were compared between patients and healthy controls. The schizophrenics showed lower small-worldness in relationship to the normal controls with a lower degree of connectivity, lower strength of connectivity, lower clustering coefficient and longer path length. Additionally, there was a negative correlation between SWN index and duration of the disease. Topological estimations showed frontal, parietal and temporal functional alterations. These findings indicate the reduction of information processing more evident in the more chronic cases. Another study[68] using fMRI adds more indices towards disorganization of networks in schizophrenia, although the basic characteristic of the normal network organization, i.e., the small-worldness, is reduced but not totally disrupted, as found in other studies. Resting-state fMRI was acquired over 17 min in 12 schizophrenics and 15 healthy individuals. Seventy-two cerebral regions were used as nodes to construct undirected graphs in the 0.06-0.125 Hz frequency interval using wavelet correlation matrices. Using the wavelet correlation (a linear estimator) and wavelet mutual information (a linear and nonlinear estimator), the functional connectivity strength and diversity for each of the 72 nodes was assessed. In schizophrenia, the strength of functional connectivity was reduced and several brain regions showed increased diversity of functional connectivity. It is important to mention that while several studies show a reduction in functional connectivity, other studies have shown regional increased connectivity. Clustering was lower for most patients' cortical nodes and node degree was reduced in some places and increased in others. High-degree hubs and lower-degree nodes are more probable in healthy individuals. Interestingly, an additional finding shows that schizophrenics have a great robustness to random attack (removal of nodes). Alexander-Bloch *et al*[69] studied modules of resting-state fMRI in 13 cases of childhood-onset schizophrenia and 19 healthy individuals. Modularity is an important property of complex systems, such as the brain. Modules were defined as groups of brain regions with fMRI time series that are similar to each other and are dissimilar from other groups.

Abnormal modularity (dysmodularity) was found in schizophrenic patients (Figure 4), suggesting that it is a sign of developmental disturbance. The clustering coefficient was also reduced in this study, while complementary measures of global efficiency and robustness were increased.

In another detailed fMRI-graph theoretical study of 203 people with schizophrenia and 259 health controls, the authors used partial correlation to measure the between all possible pairs of node values[17]. The nodes were extracted from cortical thickness measurements, as these measurements are strongly correlated between regions that are axonally connected. This method has been used in several studies in recent years. From these partial correlation values, binary graphs were constructed and topological, as well as distant, metrics were evaluated. The analyses included cortical and subcortical structures at global, divisional and regional scales, including unimodal, multimodal and transmodal divisions of the cerebral cortex. Firstly, the common graph parameters

were calculated, i.e., the node degree, hierarchy, assortativity, connection distance, centrality and identified hubs. Hubs with high hierarchy have high total connectivity but low local connectivity. With assortativity, the existence of assortative or disassortative networks is estimated. The former is characterized by connections between nodes with the same degree. Thus, high-degree nodes (hubs) are likely to be connected to each other. In the disassortative networks, the hubs are not connected to each other. The connection distance represents a special or topological property of the network. The centrality measure is used to identify hubs. Altogether, in this study, detailed network analyses were performed, thereby contributing important knowledge of the organization of normal and schizophrenics' brains. The multimodal network showed a hierarchical organization in normal brains in which frontal hubs with low clustering dominated, whereas the transmodal network was assortative. In schizophrenics, the multimodal network showed reduced hierarchy, loss of frontal hubs and emergence of non-frontal hubs and increased connection distance. To explain these findings, the authors speculate that the network pattern of schizophrenia is a neurodevelopmental disturbance.

Zalesky *et al*[70] constructed graphs of 74 schizophrenics and 37 healthy controls using whole-brain tractography. By assessing corticocortical connectivity through tractography and calculating the graph parameters node degree, small-worldness, efficiency, path length and clustering, it was possible to extract valuable information. Neural fiber tract connectivity was assessed using tractography. The graph constructed had a total of 82 nodes for each individual, corresponding to 82 distinct gray-matter regions. Pairs of nodes were interconnected if they were joined by a link *via* a sufficient number of streamlines, as detected by tractography. This direct assessment of connectivity revealed impaired connectivity in three regionally distinct groups of nodes: medial frontal, parietal/occipital and left temporal. The patients showed disconnection in cingulum and corpus calosum findings understood from previous studies. The occipital nodes showed the greatest disruption. The antero- and postero-medial components of the default mode network were also affected at a high degree. Network organization as expressed by the graph parameters showed several impairments in schizophrenia. The nodal degree was reduced, indicative of sparse interconnections. Network efficiency and small-worldness in patients were also reduced. It is interesting that in non-schizophrenic subjects, the intelligence quotient showed a linear association to the clustering coefficient, path length and global efficiency. This correlation was not found in patients with schizophrenia. In summary, this study showed disconnection and disorganization in schizophrenics' brains. Recently, a few more studies were performed related to resting state using fMRI. Yu *et al*[71] used ICA and fMRI to determine a set of maximally specially independent brain networks and then graph theory methods. Small-worldness, clustering coefficient, path length, local and global efficiencies were altered in schizophrenia, in comparison to healthy controls. Ma *et al*[72] used ICA and fMRI and graph construction with the help of mutual information. Schizophrenic patients showed lower small worldness at rest. Alexander-Bloch *et al*[69,73,74] with collaborators published three articles related to modularity, anatomical distance and population differences in network community structure in health and childhood onset schizophrenia using fMRI. In schizophrenics, both modularity and the modular community were quantitatively disturbed. Another interesting finding was that there was reduced strength of functional connectivity over short distances and it could be a sign of excessive "pruning" of short-distance functional connectivity in schizophrenia. Wang *et al*[75] used diffusion tracking tractography to construct weighted anatomical networks of the brain in 79 schizophrenics and 96 controls. It was found that the anatomical networks of the patients showed decreased global efficiency, the small world network was disrupted in schizophrenia and the regional efficiency of the prefrontal cortex and the paralimbi/limbic regions were affected in patients.

A number of studies examined regional brain disturbances in schizophrenia. From previous studies, it is known that frontal and temporal gray matter show decreased integrity in schizophrenics. For this reason, van den Heuvel *et al*[40] studied these regions and their capacity to communicate with other brain regions in 40 patients and 40 healthy controls. These researchers constructed weighted graphs using DTI and magnetic transfer imaging, which shows the myelin transmitting information related to the normal function of axons. The graph's nodes were defined by the tractography and automated anatomical label template parcellating the brain into 108 unique regions. The strength of the existing connections between nodes was taken as the measure of average level of magnetic transfer imaging to calculate the weighted connections. The graph parameters assessed were clustering coefficient; path length, small-worldness, connectivity strength, which shows how strong each node is connected to the rest of the network, and betweenness centrality, which shows how centrally a node is located in the network. Hubs were identified. The patients showed decreased network connectivity of frontal and temporal areas. The magnetic transfer imaging that shows myelination in white matter revealed reduction diffusely across the frontal lobe. Increased path length was higher in the frontal, temporal and occipital regions, which are indicative of reduced global efficiency. The frontal hubs have less betweenness centrality, i.e., fewer remote connections, and are less efficient in patients. Bassett *et al*[17], as well as Lynall *et al*[68], also discovered impairment of the role of frontal hubs. Small-worldness was reduced but preserved. The reduced efficiency of frontal and temporal regions, together with the lower efficiency of frontal hubs, is of importance to the impairment of cognitive processes in schizophrenics. Additional studies related to regional brain dysfunction were performed by Yu and Ma: Yu *et al*[71] found that the network parameters extracted using ICA

and graph theory were disturbed in frontal, parietal and occipital areas; Ma *et al*[72] found disturbances in motor regions, cerebellum and parietal regions.

To examine connectivity and neural network disturbances during a cognitive task performance, Fornito *et al*[25] studied 23 first episode schizophrenics and 23 controls. They examined brain connectivity and network disturbances during a cognitive task performance as an indicator of weaknesses of cognitive disturbances in the disease. In this study, functional connectivity was measured between 78 brain nodes with a β series correlation technique examining region-wise and edge-wise connectivity, clustering coefficient, path length, local efficiency, global efficiency and small-worldness. The cognitive task used was the AX-Continuous Performance Task, which has been used previously as a clinical test in schizophrenia to examine frontal lobe function. fMRI recordings and functional connectivity were event-related, while whole-brain networks were constructed. Results showed connectivity deficits in the cognitive task in frontoparietal regions, which occur in addition to generalized impairment of connection between the frontal regions and the rest of the brain. This study is indicative of widespread, but especially frontal, dysfunction in schizophrenia. He *et al*[76] studied working memory in schizophrenics and found aberrant BOLD activations and disrupted functional connectivity during the task. An additional study assessed disturbances during cognition in schizophrenia-combined activation and functional evaluation, i.e., structural activation during a cognitive task, as well as network functional evaluation during the same task using graph theoretical tools[77]. The cognitive task was a memory task (episodic memory-for-context task). One hundred and twenty well-known words were used. During the recall phase, fMRI was recorded in 23 schizophrenics and 33 healthy controls. The cortical functional activation during the performance of the memory task showed a similar pattern in schizophrenia and healthy controls. Using more strength criteria ($P < 0.001$), the schizophrenics showed decreased activation in the bilateral prefrontal cortex, as well as the inferior and middle occipital gyrus, thalamus and caudate. Patients showed gray matter reduction in the left medial prefrontal cortex, occipital cortex, temporal pole and bilateral insula. The network measures showed SWN configuration in both groups but with reduced local efficiency in patients. Importantly, between the two groups, there were differences in the number of hubs and a few differences in their location. That several network hubs were located in different regions in schizophrenics could be the result of gray matter volume reduction in certain areas in patients. For the same reason, the normal patients had more hubs than the schizophrenics. Altogether, this structural and functional study shows important differences between normal controls and schizophrenics during the memory cognitive task. Another fMRI study was undertaken to examine the temporal lobe during an auditory oddball task in 20 schizophrenics and 20 healthy controls[78]. The authors evaluated connectivity and network properties during the cognitive task. It is known that in schizophrenia, P300 amplitude (oddball response) is reduced. Auditory cortex activation is also reduced in schizophrenics, as shown in fMRI studies. This study intended to examine the oddball differences between schizophrenics and normal controls more precisely. Firstly, the top 95 task-related voxels were detected separately on the left and right using independent component analysis during the auditory oddball task. Using partial correlation to construct graphs, clustering coefficient, shortest path length, local and global efficiency, and small worldness were subsequently evaluated. Independent-component analysis showed, as expected, the most task-related components on both temporal lobes. SWN was preserved in both sides and both groups but it was lower in patients who showed longer short path length and lower global efficiency on the left side. Thus, temporal lobe task-related dysfunction with a significant asymmetry was detected. He *et al*[76] estimated working memory in 35 schizophrenics using fMRI. They found that during working memory, the patients showed lower clustering coefficient and less local efficiency. During an auditory oddball task, Ma *et al*[72] found lower small-worldness in schizophrenic patients.

Crucial to treating schizophrenia are not only the study of the disease after the development of the symptoms but also the evaluation of at-risk individuals. Evaluation of the progress of the disease and the therapeutic effects are also important. Brain network analysis is a new method in this effort. Thus, these important evaluations are sparse, in contrast to many previous studies using clinical, neurophysiological and MRI methods. In one study[79], at-risk mental-state individuals were examined in comparison to healthy controls during a verbal fluency task performance that recruits frontal lobe networks. The study used functional MRI and graph theoretical tools to assess brain networks during the task. The network metrics used were network density (as a measure of total network connectivity), global average path length and global betweenness-centrality, indicating the compactness of the network. Because executive function and information processing are disconnected in schizophrenia and in at-risk mental states, in this study, the assessment was concentrated in the anterior cingulated cortex function. Nineteen regions of interest in this area were selected in 22 healthy people and 33 individuals in the prodromal stage of the disease. Global connectivity, as assessed by partial correlations as well as efficiency, showed no group differences. In contrast, in the cingulated region, the at-risk subjects showed a reduction in topological centrality. This finding is indicative that the disturbance exists prior to the disease in the region that supports executive functions. In an interesting study, Shi *et al*[80] estimated the brain networks of 26 neonates at high risk for schizophrenia. They showed impaired global efficiency, lower path length and lower connection distance. These findings were indicative of brain alteration in neonates at genetic risk for schizophrenia.

Conclusions and future implications

A literature search related to schizophrenia retrieves more than 100 000 papers (in Scopus, 127 770). From the time

that schizophrenia was acknowledged as a disease of the brain, several methods have been used to study the brains of schizophrenics and their relatives. Research on schizophrenia is still notably active. During the last 20 years, many structural MRI studies of schizophrenia have been performed. These have provided more knowledge than the previous (postmortem) anatomical studies related to structural and functional organization of the brains of schizophrenics. The main structural findings are gray-matter abnormalities primarily located in the frontoparietal, frontotemporal and anterior limbic regions, as well as enlargement of the ventricles[59,81]. DTI imaging visualizes connections in the white matter[4,79]. These studies, especially the DTI, are in their infancy and exhibit methodological problems. Nevertheless, widespread disconnectivity is supported by several fMRI and DTI studies in parallel with neurophysiological studies[7,82,83]. In schizophrenia, there is neither a characteristic anatomical finding nor a local disturbance. Disconnectivity is found in schizotypy and in the general population[82]. In ultra-high-risk for psychosis individuals, MRI studies have shown abnormalities in the prefrontal, temporal and anterior cingulated cortices. Attempts have been made to use MRI to find biomarkers with which to access the development of the disease, but valid results have not been reached[84]. This search for biomarkers is especially difficult because the progression of the disease produces more severe morphological brain abnormalities[5].

The modern network theory intends to provide answers to many questions related to structural and functional disturbances in the disease of schizophrenia. In just a few years, this method revealed many interesting findings. It was found that the networks of schizophrenics' brains are less efficiently wired, show less small-worldness, are less clustered and are less hierarchically organized. In short, network disturbances in schizophrenia are indicative of abnormal connectivity, abnormal integration and segregation, lower cost-efficiency and abnormal modularity. It is less probable to find high-degree hubs and there are signs of developmental disturbances in the brains of schizophrenics. All of these findings have been extracted in the last 10 years. In parallel with schizophrenia, other brain diseases, such as autistic disorders, Alzheimer's disease, depression and epilepsy, have been studied with these methods. These findings indicate that the modern method is promising. More studies are needed to clarify several questions about the disease, its pre-clinical signs and treatment effects.

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S- Editor Lu YJ **L- Editor** Roemmele A **E- Editor** Zheng XM

World Journal of Psychiatry

Online Submissions: http://www.wjgnet.com/esps/
wjp@wjgnet.com
doi:10.5498/wjp.v2.i1.13

World J Psychiatr 2012 February 22; 2(1): 13-25
ISSN 2220-3206 (online)

REVIEW

Childhood stressful events, HPA axis and anxiety disorders

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Received: September 6, 2011 Revised: October 24, 2011
Accepted: January 21, 2012
Published online: February 22, 2012

Abstract

Anxiety disorders are among the most common of all mental disorders and their pathogenesis is a major topic in psychiatry, both for prevention and treatment. Early stressful life events and alterations of hypothalamic pituitary adrenal (HPA) axis function seem to have a significant role in the onset of anxiety. Existing data appear to support the mediating effect of the HPA axis between childhood traumata and post-traumatic stress disorder. Findings on the HPA axis activity at baseline and after stimuli in panic disordered patients are inconclusive, even if stressful life events may have a triggering function in the development of this disorder. Data on the relationship between stress, HPA axis functioning and obsessive-compulsive disorder (OCD) are scarce and discordant, but an increased activity of the HPA axis is reported in OCD patients. Moreover, normal basal cortisol levels and hyper-responsiveness of the adrenal cortex during a psychosocial stressor are observed in social phobics. Finally, abnormal HPA axis activity has also been observed in generalized anxiety disordered patients. While several hypothesis have attempted to explain these findings over time, currently the most widely accepted theory is that early stressful life events may provoke alterations of the stress response and thus of the HPA axis, that can endure during adulthood, predisposing individuals to develop psychopathology. All theories are reviewed and the authors conclude that childhood life events and HPA abnormalities may be specifically and trans-nosographically related to all anxiety disorders, as well as, more broadly, to all psychiatric disorders.

Key words: Anxiety disorders; Early stressful life events; Childhood traumata; Cortisol; Hypothalamic pituitary adrenal axis; Vulnerability; Psychopathology

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Faravelli C, Lo Sauro C, Godini L, Lelli L, Benni L, Pietrini F, Lazzeretti L, Talamba GA, Fioravanti G, Ricca V. Childhood stressful events, HPA axis and anxiety disorders. *World J Psychiatr* 2012; 2(1): 13-25 Available from: URL: http://www.wjgnet.com/2220-3206/full/v2/i1/13.htm DOI: http://dx.doi.org/10.5498/wjp.v2.i1.13

INTRODUCTION

Anxiety disorders are among the most common of all mental disorders[1]. The diagnostic and statistical manual of mental disorders (DSM-IV-TR)[2] includes generalized anxiety disorder (GAD; a chronic form of anxiety characterized by excessive, uncontrollable worry), panic disorder (PD; with recurrent, unexpected paroxysms of anxiety, somatic and autonomic symptoms and fear), phobic disorders [e.g., specific phobias, agoraphobia, so-

cial phobia (SP)], posttraumatic stress disorder (PTSD; characterized by unwanted, intrusive remembrances - as daytime thoughts and night-time dreams and nightmares - and avoidance of activities and other cues associated with prior life-threatening trauma) and obsessive-compulsive disorder (OCD; with recurrent obsessions and compulsions) in this category.

Exposure to stressors (i.e., early stressful life events) and sensitivity to stress have been strongly implicated in the manifestation or exacerbation of these syndromes[3-11]. Accordingly, the available literature reports that adults with an history of adverse childhood experiences develop anxiety disorders more frequently than adults without early stress[3-5,12].

However, studies about early life stress have investigated different periods of childhood and different adverse experiences. In the present review, the authors will consider the following early stressful life events, or adverse experiences: parental neglect; physical, emotional and sexual abuse; separation or death of a parent; and living with a mentally ill parent likely to be unable to provide continuous parental care. Frequency and duration of abuse, abuse involving penetration, force or violence, and a close relationship to the perpetrator, as well as early parental loss, appear to be the most harmful factors in terms of long-lasting effects on the child[4,6,7,10]. Usually, stressful events will be considered traumatic when they involve actual or threatened death or serious injury to oneself, or another threat to one's physical integrity, to which the subjects respond with intense fear, helplessness or horror (or in children, the response must involve disorganized or agitated behavior)[2].

Preclinical studies in animals and humans suggest that an early-life stressor (e.g., maternal separation during infancy, childhood abuse and neglect) is associated with marked long-term changes in brain circuitry regulating stress reactivity, mood and behavior (e.g., corticotropin releasing factor-containing neurons)[3].

Several clinical models suggest that early stressful life events may provoke dysfunctions in the central nervous system[13] and alterations of the stress response that can endure during adulthood[14-16]. In fact, physical and psychological stress experiences activate the hypothalamic pituitary adrenal (HPA) axis[17] through the secretion of corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) by the parvocellular neurons of the paraventricular nucleus of the hypothalamus. These neuropeptides activate the synthesis and the release of adrenocorticotropin hormone (ACTH) from the anterior pituitary, which successively stimulates the adrenal cortex to synthesize glucocorticoids, i.e., cortisol in humans. Cortisol influences several physiological processes and the synthesis of neurotrophic factors, with effects on mood and behavior[18,19].

Several methods evaluate HPA axis functioning through dosage of cortisol in a 24 h urine collection, in plasma/serum, in saliva or in cerebrospinal fluid (CSF), both in a basal condition and after stimuli. The main difference between these dosages is that less than 10% of plasmatic cortisol is free and thus biologically active, whereas salivary and urinary cortisol consists completely of the free (bioactive) fraction. On the other hand, the majority of plasmatic cortisol is bound to cortisol-binding globulin or to other proteins and is biologically inactive. As plasma free cortisol is in equilibrium with salivary cortisol, the latter is preferred as it is an easily obtainable biofluid and noninvasive source for evaluating the HPA axis.

Moreover, since cortisol has a circadian rhythm, with low values at awakening, followed by peak values 30 min after awakening and a steady decline during the rest of the day, several measures across the day explore HPA axis activity and the efficacy of the physiological evening downregulation.

Several stress tests can be applied: the most widely used method is the dexamethasone (Dex) suppression test (DST), which explores HPA axis functioning by measuring the suppression of cortisol levels induced by the administration of Dex; the Dex suppression CRH stimulation test (Dex/CRH test) explores pituitary and adrenal functioning by measuring ACTH and cortisol levels after a low-DST and subsequent stimulation with CRH; the combined administration of CRH and AVP (CRH/AVP test) helps investigate the activity of the HPA axis by measuring both the response of cortisol (adrenal) and ACTH (pituitary) to a stressor; and the ACTH stimulation test explores adrenal activity by measuring cortisol levels.

The relationship between stress, HPA axis hormones and psychopathology has been demonstrated in animal and human models.

Studies on rodents have shown that early social isolation provokes behavioral abnormalities similar to human depression and anxiety disorders, while environmental enrichment displays an antidepressive and anxiolytic effect in animal models of depression and anxiety[20].

Increased plasmatic ACTH and cortisol levels have been observed during behavioral despair in neonate non-human primates when separated from the mother[21,22].

Furthermore, when CRH is injected into the cerebral nervous system of laboratory animals, it produces effects reminiscent of stress, depression, fear and anxiety through actions on specific brain regions[4,23-25].

Breier *et al*[14] observed 90 subjects exposed to early parental loss in childhood and found higher plasma cortisol and ACTH concentrations in subjects who had obtained a lifetime psychiatric diagnosis, compared to those who did not receive a psychiatric diagnosis.

More recently, some authors observed that children who experienced permanent or long-term separations from parents, or parental death, show a hyperactive HPA axis, with increased basal salivary cortisol concentrations[26,27] and cortisol non-suppression after the DST[28], as well as the combined Dex/CRH test[29].

Moreover, alterations of the HPA axis have been

widely reported in psychiatric disorders, including anxiety disorders[30-39]. For instance, Vreeburg *et al*[40] showed a modest but significantly higher 1 h cortisol awakening response among anxious patients, especially in those with PD with agoraphobia and those with comorbid depression. However, if the diagnosis of current anxiety disorder was associated with higher awakening cortisol levels, remitted anxiety only showed a trend toward higher morning cortisol and any association was observed between anxious status and evening cortisol level or cortisol suppression after Dex administration[40].

However, neither the excess of stressful events during childhood nor the abnormalities of the HPA axis seem to be specific to any diagnostic group[11,41,42]. Moreover, data concerning the HPA axis in all anxiety diagnostic subgroups are scarce and few studies have examined the role of the HPA axis as a mediating factor between childhood stressful life events and anxiety disorders[3,4,11].

The present paper aims at reviewing the data on HPA axis functioning in anxiety disorders and the relationship between childhood stressful life events and these neuroendocrine alterations. Moreover, a hypothesis attempting to explain these associations will be discussed.

CHILDHOOD STRESSFUL EVENTS, HPA AXIS AND PTSD

PTSD is a chronic psychiatric condition that may develop in subjects who have been exposed to or have witnessed an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others, experiencing fear, helplessness or horror[2]. This psychiatric condition is frequent in subjects with a history of adverse childhood experiences[4,12,43-45].

Data about HPA axis functioning and its relationship with early life stress in PTSD are reported in Table 1.

Preclinical evidence showed a long-term sensitization of the stress response after early life stress[14]. Other authors reported increased cortisol levels in women with PTSD who experienced a childhood abuse[46,47] and in prepubertal children with PTSD secondary to past childhood maltreatment experiences[48], compared to non traumatized subjects.

Recent studies have provided evidence for sustained increases in CRH activation in the CSF of PTSD patients[49-51].

According to these findings, even in anticipation of and during a stressful cognitive challenge, PTSD patients with childhood abuse showed higher mean cortisol levels compared to healthy subjects[52-54]. Moreover, after CRH and ACTH administration, PTSD patients with childhood trauma had greater ACTH and cortisol responses, as well as a later cortisol peak[55,56].

On the other hand, Santa Ana *et al*[57] found that adults with PTSD had a less robust ACTH response to a cold pressor task compared to controls, regardless of age of index trauma. Moreover, when trauma happened in childhood, cortisol at baseline and at all post-task measurements was lower and did not display the decrease in cortisol over the course of the 2 h monitoring period, which was observed in subjects with adult index trauma and controls.

Similarly, after a CRH stimulation test, De Bellis *et al*[58] and Bremner *et al*[54] reported that childhood abused women with PTSD exhibited a significantly smaller ACTH response and no difference in cortisol response, than the healthy control group. Moreover, an excessive suppression of cortisol in response to a low dose of Dex (0.5 mg) was reported in similar groups of patients, compared to controls[31,59-61].

In contrast, other studies found no difference between women with PTSD and healthy subjects in terms of circadian rhythm of cortisol, baseline cortisol and ACTH levels[56,62] and in cortisol levels after DST[47].

In summary, these data show high baseline CRH levels and low plasma cortisol levels in PTSD patients and seem to confirm the mediating effect of the HPA axis between childhood traumata and PTSD[14,55,63].

A possible explanation for this finding is that high cortisol levels reflect an initial sensitization to the persistent intrusive nature of the memories and the continued sense of threat experienced by these individuals[64], while the following blunted response may reflect a physiological adaptation of the HPA axis to chronic stress, with the downregulation of the pituitary CRH-receptors[65]. Thus, the hypothalamic CRH hypersecretion may be due to the early life stress[4].

According to these hypotheses, several studies have documented a reduced hippocampal volume in adult patients with PTSD related to childhood abuse[66], as if the long-term overexposure to glucocorticoids would lead to cell atrophy, loss or decreased neurogenesis[67].

Moreover, different activation of corticolimbic pathways may induce an "overcoming" negative feedback inhibition, which causes a blunted ACTH/cortisol response after a psychosocial and not chemical stressor[4].

Another hypothesis is that the higher availability of glucocorticoid receptors on pituitary cells of PTSD patients induces an enhanced negative feedback signal on cortisol production[68,69].

An insufficient pituitary and/or adrenal response to central stimulation, or a reduced sensitivity in response to low cortisol levels, may also explain HPA axis hypersuppression[69].

Furthermore, de Kloet *et al*[69] hypothesized that subjects with PTSD display an enhanced bioavailability of Dex or an inadequate vasopressin reaction to a low dose Dex administration.

Moreover, other factors can be involved in the altered stress regulation of PTSD patients: hormone binding proteins (e.g., CRH binding protein and corticosteroid binding globulin); the immune factors; sample differences (e.g., age, gender, inclusion and exclusion criteria, presence of a comorbidity like major depressive disorder, medication use); the diurnal rhythm and pulsatile secretion of

Table 1 Hypothalamic pituitary adrenal axis functioning and its relationship with childhood traumata and psychopathology in post-traumatic stress disordered patients

Author	Control group	Sample	Cortisol levels	ACTH levels	Suppression (DST)	Stress test	Correlations with childhood traumata and psychopathology
Lemieux *et al*[46], 1995	9 non abused women; 8 abused women w/o PTSD	11 abused women with PTSD	↑ Basal urinary levels	-	-	-	↑ Scores on Impact Event Scale related to cortisol levels in PTSD sample
De Bellis *et al*[48], 1999	10 non-traumatized children; 24 healthy controls	18 children with PTSD due to childhood maltreatment	↑ Basal urinary levels	-	-	-	↑ Psychopathology
Bremner *et al*[66], 2003	18 HC	23 patients with abuse-related PTSD	Salivary cortisol: 61% higher Waiting for test; 46% higher during test	-	-	Cognitive challenge	Neurohormonal response to stress in PTSD subjects is not impaired
Luecken[52], 1998	31 HC	30 students who lost one parent before age 16	↑ Salivary levels post task	-	-	Video clip depicting the death of a parent + speech task	Altered neurohormonal responses to stress in those who lost one parent
Elzinga *et al*[53], 2003	12 abused women without PTSD	12 abused women with PTSD	Salivary cortisol: 60% higher waiting for test; 122% higher during test; 69% higher during recovery	-	-	Personalized trauma scripts	Altered neurohormonal responses to stress in PTSD abused women
Rasmusson *et al*[56], 2001	11 HC	12 outpatients with PTSD	= Plasma basal levels; ↑ plasma and urinary post tests levels	= Basal levels; ↑ post CRF levels	-	CRF and ACTH stimulation tests	Altered neurohormonal responses to stress in PTSD subjects
Santa Ana *et al*[57], 2006	31 HC	58 subjects with PTSD (25 with childhood trauma)	↓ Plasma basal and post Task, if childhood trauma	↓ Post task	-	Cold Pressor Task	-
De Bellis *et al*[58], 1994	13 HC girls	13 sexually abused girls	= Plasma and salivary basal and post CRH	↓ Basal and post CRH	-	CRH stimulation test	↑ Adult psychopathology and altered hormonal responses to stress
Stein *et al*[61], 1997	21 non abused women	19 children and/or adolescent with sexual abuse	-	-	↑	Low dose DST (0.5 mg)	↑ Adult psychopathology
Yehuda *et al*[31], 2004	10 non traumatized subjects	52 traumatized subjects	-	-	↑	Low dose DST (0.5 mg)	-
Jovanovic *et al*[59], 2010	61 traumatized non PTSD subjects	29 traumatized PTSD subjects	= Basal plasma levels; ↓ post Dex plasma levels	↓ Post Dex	↑	Low dose DST (0.5 mg)	Abnormalities of HPA feedback and ↑ psychopathology
Altemus *et al*[62], 2003	15 HC	16 women with PTSD due to childhood abuse	= Basal plasma and salivary levels	-	-	-	-
Lindley *et al*[47], 2004	17 HC	17 subjects with PTSD (88% due to childhood trauma)	↑ Basal salivary levels	-	=	Low dose DST (0.5 mg)	No correlations between cortisol, childhood abuse and psychopathology

HC: Healthy controls; DST: Dexamethasone suppression test; PTSD: Posttraumatic stress disorder; ACTH: Adrenocorticotropin hormone; CRH: Corticotropin releasing hormone; CRF: Corticotropin releasing factor.

adrenal hormones; the time passed since the traumatic event occurred; experienced stress during the assessment; the subjectivity of the perception of stressors; and alterations in the activity of the central nervous system and/or in hormone bioavailability and/or in hormone receptor function[69].

None of these hypotheses is considered completely exhaustive; thus more studies are needed in order to explain the altered functioning of the HPA axis in PTSD patients.

CHILDHOOD STRESSFUL EVENTS, HPA AXIS AND PD

Findings on HPA axis abnormalities in patients suffering from PD are conflicting and inconsistent[36], but stressful life events are known to be contributing factors[6].

Several studies have investigated the relationship between anxiety, panic attacks (PAs) and the activation of the HPA axis. In fact, anxiety and panic seem to be qualitatively different: the former is an emotional state related

Table 2 Hypothalamic pituitary adrenal axis functioning in panic disordered patients

Author	Control group	Sample	Cortisol levels	ACTH levels	DST	Stress test
Woods *et al*[71], 1987	13 HC	18 drug-free agoraphobic patients	Plasma cortisol not increased during PA	-	-	Exposure to phobic situations
Goldstein *et al*[76], 1987	61 HC; 38 outpatients with MDE	24 outpatients PD	↑ Basal plasma cortisol *vs* HC; = plasma cortisol *vs* MDE	-	=	Dex 1 mg
Cameron *et al*[74],1987	4 HC	8 PD patients	= In basal conditions; ↑ during spontaneous PA	-	-	-
Kathol *et al*[77], 1988	37 HC	65 PD subjects	↑ Urinary cortisol	-	-	-
Uhde *et al*[75], 1988	12 HC	12 drug-free PD patients	= Basal cortisol	-	-	-
Abelson *et al*[78], 1996	12 HC	20 PD subjects	↑ Overnight plasma cortisol; ↑ amplitude of ultradian secretory episodes	If low frequency of PA→ ↑ daytime ACTH levels and ↑ ACTH ultradian amplitude. If high frequency of PA→ shifted ACTH circadian cycles	-	-
Schreiber *et al*[30], 1996	10 MDE subjects, 10 HC	13 PD subjects wth agoraphobia	↑ Plasma cortisol versus controls	= Levels in PD *vs* controls and MDE subjects	92% non suppressors (higher than MDE subjects and controls)	69% abnormal Dex-CRH test (more than controls, but lesser than MDE subjects)
Bandelow *et al*[73], 2000	23 HC	23 PD patients	↑ Urinary and salivary cortisol	-	-	-
Coryell *et al*[81], 1989	38 HC	82 PD patients	-	-	25.6% non suppressors	Dex 1 mg
Coryell *et al*[80], 1991	-	72 PD patients	-	-	36% non suppressors	
Erhardt *et al*[33], 2006	30 HC	30 PD subjects	↑ Basal plasma levels	↑ Basal	-	17% hyperresponder to Dex-CRH
Petrowski *et al*[82], 2010	34 HC	34 PD subjects	= Basal salivary levels; abnormally absent cortisol awakening response	-	-	Absent cortisol response to Trier Social Stress Test
Lieberman *et al*[79], 1983	22 MDE	10 PD	↑ Plasma cortisol	-	=	DST

HC: Healthy controls; DST: Dexamethasone suppression test; PA: Panic attack; MDE: major depressive episode; ACTH: Adrenocorticotropin hormone; PD: Panic disorder; Dex: Dexamethasone; CRH: Corticotropin releasing hormone.

to a potential threat, mostly activating HPA and the sympathoadrenal axes; the latter is an emotion evoked by the perception of an actual danger that causes major sympathetic activation with small effects on the HPA axis[70].

Several authors have reported no increased salivary or plasma cortisol levels during the PA[70,71] (Table 2), maybe due to a successful habituation to the repeated experiences of panic[72]. However, probably due to anticipatory anxiety, higher salivary cortisol levels have been reported at the beginning of the PA[73,74] (Table 2).

Furthermore, several findings indicated that real life PAs and selective panicogen stimuli (e.g., sodium lactate and carbon dioxide) do not activate the HPA axis, while non-selective agents (e.g., agonists of the colecholecystokinin receptor B) induce the release of stress hormones, regardless of the occurrence of the PA[70]. On the other hand, Flumazenil and benzodiazepine receptor antagonists seem not to activate the HPA axis or induce PAs[70]. Finally, other agents, like yohimbine, mCCP and Fenfluramine, increase anticipatory anxiety and the release of stress hormones, without inducing a true PA[70].

Findings on baseline HPA axis activity and its reactivity to some stressors in panic disordered patients seem to be inconclusive (Table 2). In fact, during a resting state, both normal[74,75] and elevated cortisol levels have been reported[76-78]. On the other hand, a clear escape or hypersuppression after Dex administration has not been demonstrated[76,79], but some DST abnormalities exist and predict risk of relapse and long term disability in panic disordered subjects[30,80,81].

Furthermore, Schreiber *et al*[30] and Erhardt *et al*[33] reported a hyperresponsivity of the HPA axis to Dex/CRH test in patients with PD (Table 2), unlike Petrowski *et al*[82] who showed a lack of cortisol responsivity to acute uncontrollable stress in PD patients (Table 2).

As far as stressful life events are concerned, only Safren *et al*[5] found higher rates of childhood abuse among women with PD, than among subjects with other anxiety disorders. In fact, in most of the literature, no significant differences were found in terms of early stressful life events between PD and GAD[83], SP[84] or depression[85].

Table 3 Hypothalamic pituitary adrenal axis functioning and its correlation with psychopathology in obsessive compulsive disordered patients

Author	Control group	Sample	Cortisol levels	Other hormones levels	DST	Correlations with psychopathology
Monteleone *et al*[91], 1994	13 HC	13 drug-free OCD patients	↑ Plasma cortisol cyrcadian rhythm	-	-	↑ Severity of OCD symptoms
Kluge *et al*[86], 2007	9 HC	9 OCD inpatients w/o comorbid depression	↑ Plasma levels	↑ Plasma ACTH	-	-
Catapano *et al*[89], 1990	20 HC	18 OCD patients	-	-	27.7% non-suppression	Correlated with sex (all non suppressors were males) and independently of depression
Coryell *et al*[92], 1989	82 panic disordered patients	20 OCD outpatients	-	-	=	-
Altemus *et al*[90], 1992	25 HC	12 OCD subjects	-	↑ CSF CRH; ↑ plasma and CSF AVP	-	↑ Psychopathology

HC: Healthy controls; DST: Dexamethasone suppression test; CSF: Cerebrospinal fluid; CRH: Corticotropin releasing hormone; AVP: Arginine vasopressin; OCD: Obsessive-compulsive disorder; ACTH: Adrenocorticotropin hormone.

In conclusion, stressful life events may have a triggering function but they are not a *conditio sine qua non* that supports the development of PD[6] and data concerning HPA axis functioning are discordant, as both normal and increased hormonal activity have been reported[70,73].

CHILDHOOD STRESSFUL EVENTS, HPA AXIS AND OCD

A large number of studies reported that the onset of OCD is often preceded by stressful events, like increased responsibility (e.g., job promotion, birth of a child), losses (e.g., death of a family member, dismissal from employment) and traumata, such as abuse or combat[86]. Moreover, it is well documented that OCD symptoms increase under stressful situations[87] and that patients with OCD suffer from daily life stress more than healthy controls[87,88].

However, data about the relationship between stress, HPA axis functioning and OCD are scarce and discordant[86], even if several studies have shown an increased activity of the HPA axis in OCD disordered patients[86,89-91] (Table 3).

For instance, Kluge *et al*[86] demonstrated that nocturnal plasma cortisol and ACTH levels were significantly elevated in patients with OCD, compared to healthy controls. The circadian rhythm of cortisol was preserved in OCD patients, although at a higher level compared with normal controls and proportional to the severity of obsessive-compulsive symptoms[91]. Furthermore, CRH and AVP levels have been found significantly elevated in the CSF and plasma of these patients, compared to healthy controls[90] (Table 3). Catapano *et al*[89] observed that a subgroup of OCD patients, particularly males, may escape the DST independently from the coexistence of depressive features. On the other hand, Coryell *et al*[92] reported normal suppression after 1 mg Dex (Table 3).

Moreover, the role of the stress responsive neurohormone AVP in the onset and maintenance of compulsive behaviors (e.g., hand-washing, cleaning and trichotillomania) has been studied in rats. The intracerebroventricular administration of ACTH or CRH in rats prolongs the maintenance of conditioned behaviors acquired during a period of stress (i.e., induction of aversive stimuli, like shocks and loud noises), and promotes grooming, which is considered a behavioral model for OCD[86,93]. In humans, the intranasal administration of vasopressin seems to narrow the focus of attention and influence cognitive processes, similar to the focused-obsessive thoughts and compulsive rituals of obsessive-compulsive patients[90].

Finally, structural neuroimaging studies observed dysfunctioning in OCD patients' anterior cingulated gyrus, which is known to be involved in the regulation of the HPA axis[94,95].

In conclusion, obsessive-compulsive disordered subjects show a hyperactivity of the HPA axis but the increased hormonal levels might be a consequence of stress[7] or, vice versa, they might be involved in the pathophysiology of OCD, sustaining clinical features like perseverative or grooming behaviors[86].

CHILDHOOD STRESSFUL EVENTS, HPA AXIS AND SP

Several authors hypothesized that early stressful life events (including separation from parents, parents' marital discord, sexual/physical/emotional abuse, familial violence, childhood diseases) and parental rearing styles (such as neglect and family history of psychiatric disorders, like anxiety disorders, depression and suicidality) have a role in the onset of SP and may increase the severity of social phobic symptoms[5,55,96-98].

Accordingly, sexual and/or physical abuse were most specifically associated with SP and childhood abuse seems to be an important risk factor for the development of this disorder[4,97,98].

Table 4 Hypothalamic pituitary adrenal axis functioning and its correlation with psychopathology and childhood traumata in social phobia patients

Author	Control group	Sample	Cortisol levels	CRH levels	Stress test	Correlations with childhood traumata and psychopathology
Potts *et al*[100], 1991	15 HC	10 SP	= Urinary	-	-	-
Levin *et al*[103], 1993	14 HC	36 (28 generalized SP + 8 specific SP)	= Plasma	-	Ten-minute talk	-
Uhde *et al*[101], 1994	-	54-64 SP patients	= Plasma and urinary	-	= DST (Dex 1 mg)	-
Martel *et al*[105], 1999	21 HC	27 SP	= Salivary basal and task-related	-	Modified TSST	Correlated to anticipatory anxiety in both groups
Furlan *et al*[104], 2001	17 HC	18 SP	After speech task: ↑ 90% increase in salivary levels in 7 SP; ↓ 32% in salivary LE in 11 SP. After exercise task: =	-	Public speaking task and physical exercise task	-
Condren *et al*[32], 2002	15 HC	15 SP	↑ Plasma cortisol after test; = plasma cortisol basal	= Basal and after test	Public mental arithmetic and short term memory test	-
van West *et al*[106], 2008	25 HC	25 SP	↑ Salivary cortisol after test	-	Public speaking test	Correlated to trait but not state anxiety levels
Roelofs *et al*[107], 2009	22 HC, 17 patients with PTSD	18 SP	↑ Salivary cortisol after test	-	Social approach-avoidance task in social stress condition (TSST)	Cortisol increase correlated to the social avoidance behavior
Elzinga *et al*[99], 2010	16 SAD w/o CA, 16 HC, 16 PTSD with CA	9 SAD with CA	↑ Salivary cortisol after test; = salivary cortisol basal	-	TSST	CA is associated with ↑ cortisol reactivity to TSST
Lanzenberger *et al*[102], 2010	18 HC	12 subjects with SP	↓ Plasma levels	-	-	Negative correlations with 5HT binding in brain regions and positive correlation with trait anxiety

HC: Healthy controls; DST: Dexamethasone suppression test; TSST: Trier social stress test; SAD: Separation anxiety disorder; CA: Childhood abuse; SP: Social phobia; PTSD: Posttraumatic stress disorder; Dex: Dexamethasone.

Moreover, in line with the hypothesis that SP is a stress-related condition, HPA axis hyperactivity can represent the linkage between stressful events and the onset and development of this disorder[4,11].

Elzinga *et al*[99] found a significant association between a history of childhood abuse (emotional, physical or sexual abuse) and enhanced cortisol reactivity to a psychosocial stress task in patients with SP, although any difference in baseline cortisol levels has been reported between SP patients, PTSD patients and healthy controls (Table 4).

Moreover, several authors reported normal basal HPA axis functioning in adult social phobics[100,101] (Table 4). Mean basal morning plasma cortisol levels were significantly lower in patients with SP, than in healthy control subjects, and a significant correlation between cortisol plasma levels and trait but non state anxiety scores seems to exist[102] (Table 4).

Conflicting results are reported after a stress test (Table 4). Levin *et al*[103] found decreased plasma cortisol levels in response to a public speaking task, both in adult patients with SP and normal controls. Furlan *et al*[104] found that SP patients display a bimodal salivary cortisol response and a larger increase in salivary cortisol levels following a speech task, but any difference from normal subjects has been reported, under physical stress or basal conditions (Table 4).

Martel *et al*[105] observed similar salivary cortisol levels in social phobic adolescent girls and controls, in response to a modified trier social stress test (TSST), even if cortisol levels appeared to be a sensitive measure of anticipatory anxiety prior to the performance task in both groups (Table 4). On the other hand, van West *et al*[106] reported that prepubertal subjects with social anxiety show elevated salivary cortisol response to a psychosocial stressor (Table 4).

The hyper-responsiveness of the adrenal cortex during the psychosocial stressor and the similar basal levels of cortisol with respect to controls were also confirmed by Condren *et al*[32] (Table 4).

Recently, Roelofs *et al*[107] provided the first evidence for a direct link between increased cortisol stress-responsiveness and social avoidance behavior in SP patients (Table 4). During a social approach avoidance task in a social stress condition (provided by the TSST), social phobics showed increased cortisol responses compared to healthy participants and PTSD patients. Moreover, social stress elicited increased avoidance tendencies towards

Table 5 Hypothalamic pituitary adrenal axis functioning and its correlations with psychopathology in generalized anxiety disordered patients

Author	Control group	Sample	Cortisol levels	DST	Correlations with psychopathology
Mantella *et al*[114], 2008	42 HC	71 GAD subjects	↑ Morning basal and peak salivary cortisol	-	↑ Psychopathology
Steudte *et al*[118], 2011	15 HC	15 GAD patients	↓ Cortisol in the first and second 3-cm hair segments; = salivary diurnal cortisol profiles	-	-
Schweizer *et al*[112], 1986	-	79 GAD subjects	-	27% non-suppression	-
Tiller *et al*[113], 1988	13 HC	30 GAD patients	-	27% non-suppression	Normalization of HPAA suppression after successful non drug behavioral treatment
Tafet *et al*[115], 2005	8 non treated GAD outpatients	17 treated GAD outpatients	= Morning plasma cortisol; ↑ evening plasma cortisol	-	↓ Evening plasma cortisol level after cognitive treatment
Pomara *et al*[116], 2005	90 HC	41 GAD patients	↑ Plasma cortisol levels	-	↓ Plasma cortisol after acute and chronic treatment with diazepam
Rosenbaum *et al*[117], 1983	22 HC	22 GAD subjects	= 24 h urinary cortisol levels	-	-

HC: Healthy controls; DST: Dexamethasone suppression test; GAD: Generalized anxiety disorder; HPAA: Hypothalamic pituitary adrenal axis.

social threat stimuli in SP patients and this behavior was predicted by cortisol responses[107].

Moreover, stating that shyness, separation anxiety disorder (SAD) and behavioral inhibition (BI) have been postulated to be precursors of SP[108], high cortisol levels have been reported in shy children and adults[29,109], in children suffering from SAD[110], and in children with BI[111]. Some authors have hypothesized that the increased CRH and cortisol levels of these children can exacerbate their fearfulness and predispose them to develop SP[109].

In conclusion, a hyper-responsiveness of the adrenal cortex has been reported in social phobics, mainly during a psychosocial stressor[32,104,106,107], while findings at baseline are similar to those of controls[32,107]. However, several authors have hypothesized that HPA axis hyperactivity may link early stressful events to the development of SP[11,40,99].

CHILDHOOD STRESSFUL EVENTS, HPA AXIS AND GAD

Few studies have examined HPA axis activity in GAD, even if the persistent excessive anxiety and uncontrollable worry about a variety of events and situations that characterize GAD patients[2] suggest that these subjects are exposed to repeated stressful experiences, which could consequently lead to an altered cortisol secretory pattern.

The first investigations on HPA axis functioning in GAD used the DST (Table 5). Non-suppression rates of 27% were reported[112,113], suggesting a reduced negative feedback sensitivity of the HPA axis.

More recently, Mantella *et al*[114] showed that elderly individuals with GAD exhibited a 40%-50% increase in basal salivary cortisol levels, with higher peak cortisol levels and larger areas under the curve, compared to matched control subjects (Table 5). Additionally, severity of GAD, as measured by psychometric instruments, was positively correlated with cortisol levels[114]. Also Tafet *et al*[115] and Pomara *et al*[116] observed that patients with GAD presented increased levels of circulating cortisol (Table 5). Tafet *et al*[115] reported that cognitive therapy (CT) was effective in improving distressful clinical symptoms of GAD and in recovering psychoneuroendocrinological functions of these subjects. In fact, after a maximum of 24 sessions of CT, a significant decrease in the Hamilton Anxiety Rating Scale and a significant decrease in previously increased levels of circulating cortisol were observed[115]. Pharmacological therapy also showed its efficacy in the treatment of GAD: reductions of anxiety symptoms and plasma cortisol levels were reported after acute and chronic diazepam treatment, even if independent of GAD status and drug dosage[116].

On the other hand, other studies failed to show aberrant adrenocortical activity in GAD: similar 24 h urinary cortisol levels[117] and plasma cortisol levels[118] were observed in GAD patients and healthy controls (Table 5).

Finally, Steudte *et al*[118] studied cortisol secretion using hair analysis, which provides a retrospective reflection of cortisol secretion for a period up to 6 mo. Results showed significantly lower (50%-60%) cortisol levels in the first and second 3 cm hair segments of GAD patients, compared to those of controls, while no group difference in salivary diurnal cortisol profiles was observed (Table 5). An attempt to explain this finding is that, under naturalistic conditions, GAD may be associated with hypocortisolism, similar to healthy individuals living under chronic stress conditions and to patients with several bodily disorders (like chronic fatigue syndrome, fibromyalgia, other somatoform disorders, rheumatoid arthritis and asthma)[119,120].

In conclusion, different studies suggest that GAD

is associated with hypercortisolism. A possible explanation of this finding is that chronic stress, along with the inadequacy to cope with it or the perceived loss of controllability, may lead to persistent HPA axis activation and the sustained increase of cortisol levels[121]. Moreover, the unremitting activation of the HPA axis is supposed to be mediated by changes in the sensitivity, or in the number, of CRH and/or glucocorticoid receptors of the hippocampus, limbic system and cortical levels (brain areas associated with anxiety disorders). Thus, it is possible that the autoregulatory feedback of GAD is not as efficient as in healthy subjects and cortisol hypersecretion is not downregulated[114].

Furthermore, GAD patients report a high rate of childhood physical or sexual abuse that can be associated with an alteration of the HPA axis and can contribute to the onset and maintenance of the disorder[5].

DISCUSSION

Data concerning the relationship between childhood stressful life events, HPA axis and anxiety disorders have been reviewed.

The vast majority of studies agreed on the hyperactivity of the HPA axis[40] and high rates of early stressful life events[3-5,12] in anxiety disorders. However, conflicting results on HPA axis functioning emerged from this review: patients with PTSD show baseline high CRH levels and low plasma cortisol levels; both normal and increased hormonal activity have been reported in PD patients[70,73]; OCD subjects show a hyperactivity of HPA axis[86,89-91]; a hyper-responsiveness of the adrenal cortex has been reported in social phobics after a psychosocial stressor[32,104,106,107], but normal levels have been observed at baseline[32,101]; and lastly, several studies suggest that GAD is associated with hypercortisolism[112-116].

Several hypotheses have been proposed in order to explain these discordant data. The first is the effect of comorbidity that might explain some of the differences in HPA axis activity among comorbid depressed patients[122].

Another explanation is based on the cognitive/emotional modulation, as some authors observed a normalization of the HPA axis of panic patients after treatment[36].

A third hypothesis develops from the habituation phenomena. In fact, individuals with high and persistent anxiety levels feel stressed regularly, showing a state of chronic adrenal stress hyper-reactivity and persistently elevated cortisol concentrations. These effects may influence HPA axis functioning, inducing a sort of counter-regulative adaptation and thus downregulating HPA axis stress responsivity[8,16]. Hence, high and persistent levels of anxiety could be associated with low cortisol concentrations[123,124], reflecting resilience rather than a risk for psychopathology[8,16].

On the other hand, elevations in cortisol levels that persist across time could also tune HPA axis activity to a higher level and could result in damage of the hippocampal glucocorticoid receptors or even a loss of hippocampal neurons[66], reducing the negative feedback of CRH secretion and resulting in higher CRH and cortisol concentrations[124].

Furthermore, the link between childhood adverse experiences, HPA axis abnormalities and anxiety disorders has not been studied carefully. A well accepted hypothesis is that stressful life events, not being specific of any psychiatric disorder, can act as triggers on HPA axis dysregulation, predicting a general vulnerability to anxiety and mood disorders[4,5,11].

In line with these observations, some authors have hypothesized that the neuroendocrine alterations after an early stress can result in a biological 'wound' that increases the individual's vulnerability to stressors later in life and, thus, predisposes an individual to develop mood or anxiety disorders that are known to manifest or worsen in relationship to acute or chronic life stress[3-5,7,11,96]. In fact, once the HPA axis is over-activated during the developmental processes, it remains permanently unstable, overdriven, vulnerable or dysfunctional[7,16,125], possibly due to transcriptional/epigenomic mechanisms[126,127].

However, a retrospective recall bias may influence the assessment of early events in several ways[11]. The poor reliability of the memories relevant to childhood[9,10], the "search for meaning", by which the subjects tend to search for reasons for the present distress in their past experiences, and the attitude of the interviewer, who may or may not encourage the patient, all affect the accurate retrieval of past events[11].

In conclusion, the review of the available literature supports an alteration of the HPA axis in anxiety disordered patients but the relationship with early stressful life events is still to be elucidated. Authors conclude that childhood life events and HPA abnormalities may be aspecifically and transnosographically related, not only to all anxiety disorders, but broadly to all psychiatric disorders. Thus, studying the role of early stressful life events in the later development of anxiety disorders may help clinicians in the prevention and treatment of these disorders.

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Online Submissions: http://www.wjgnet.com/esps/
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World J Psychiatr 2012 February 22; 2(1): I
ISSN 2220-3206 (online)

Acknowledgments to reviewers of *World Journal of Psychiatry*

We acknowledge our sincere thanks to our reviewers. Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of our World Series Journals. Both the editors of the journals and authors of the manuscripts submitted to the journals are grateful to the following reviewers for reviewing the articles (either published or rejected) over the past period of time.

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World J Psychiatr 2012 February 22; 2(1): I
ISSN 2220-3206 (online)

Events Calendar 2012

January 19-22, 2012
The 64th Annual National Congress of The Indian Psychiatric Society
Kochi, Kerala, India

January 20-21, 2012
AACAP 2012 Psychopharmacology Update Institute
Child and Adolescent Psychopharmacology: Integrating Current Data into Clinical Practice
Sheraton New York Hotel and Towers, New York, United States

Februrary 08-11, 2012
Thematic Conference of the World Psychiatric Association
Granada

Februrary 09-10, 2012
14th National Conference: Dementias 2012
London, United Kingdom

February 9-12, 2012
New Zealand Association of Psychotherapists Conference 2012
The Face of the Other
Victoria University, Wellington, New Zealand

February 18, 2012
Inaugural RANZCP Symposium on Youth Mental Health
Mantra on Russell, Melbourne, Australia

Februrary 23-24, 2012
Ⅱ Annual Meeting on Therapeutics in Psychiatry
Barcelona, Italy

February 23-24, 2012
Voices VIC 2012 Conference
Voices, Conversations & Transformations – Diverse Approaches to Recovery
Storey Hall, RMIT University, Melbourne, Australia

February 23-25, 2012
American Psychosocial Oncology Society 9th Annual Conference
Miami, FL, United States

February 29, 2012
Conjoint Medical Education Seminar
Hilton on the Park, Melbourne, Australia

March 3-6, 2012
20th European Congress of Psychiatry
Prague, Czech Republic

March 16-19, 2012
2012 American Association for Geriatric Psychiatry Annual Meeting
Washington, DC, United States

March 17, 2012
Body In Mind 2012
AMREP Centre, Alfred Hospital, Melbourne, Australia

March 21-24, 2012
American Neuropsychiatric Association 23rd Annual Meeting
New Orleans, LA, United States

March 21-25, 2012
American Counseling Association 2012 Annual Conference & Exposition
San Francisco, CA, United States

March 23-24, 2012
Psychiatric Society of Virginia 2012 Spring Meeting
Richmond, VA, United States

March 27-31, 2012
5th Annual Psychopharmacology Institute and ISPN Annual Conference - International Society Of Psychiatric-Mental Health Nurses
Atlanta, GA, United States

April 11-14, 2012
33rd Annual Meeting & Scientific Sessions of the Society of Behavioral Medicine
New Orleans, LA, United States

April 12-15, 2012
2012 Anxiety Disorders Association of America Annual Conference
Arlington, VA, United States

April 16-18, 2012
Australian & New Zealand Disaster and Emergency Management Conference
Brisbane Convention Centre, Australia

April 18-21, 2012
45th American Association of Suicidology Annual Conference
Baltimore, MD, United States

April 23-26
Freedom and Recovery: Integrated Mental Health and Addiction Treatment for Service Members
San Diego, CA, United States

May 2-4, 2012
ANZSGM Annual Scientific Meeting 2012
Dementia: Managing Not to Forget
Hilton Hotel, Sydney, Australia

May 5-9, 2012
2012 American Psychiatric Association Annual Meeting
Philadelphia, PA, United State

May 20-24, 2012
RANZCP 2012 Congress
Hobart, Tasmania, Australia

June 14-17, 2012
American Psychiatric Nurses Association 9th Annual Psychopharmacology Institute
Reston, VA, United States

July 6-8, 2012
RANZCP Queensland Branch Weekend Conference
Hyatt Regency Coolum, Australia

July 7-10, 2012
Society For Developmental and Behavioral Pediatrics 2012 Annual Meeting
Phoenix, AZ, United States

July 10-13, 2012
International Congress of the Royal College of Psychiatrists
BT Convention Centre, Liverpool, United Kingdom

August 6-8, 2012
13th International Mental Health Conference
Outrigger Inn, Gold Coast, Australia

September 4-7, 2012
Faculty of Forensic Psychiatry Conference
Hong Kong Academy of Medicine, Hong Kong, China

September 7-11, 2012
International Psychogeriatric Association International Meeting 2012 (Jointly Hosted By the RANZCP Faculty of Psychiatry of Old Age)
Cairns, Queensland, Australia

September 13-16, 2012
American Association For Marriage And Family Therapy Annual Conference 2012
Charlotte, NC, United States

September 27-29, 2012
2nd International Congress on Borderline Personality Disorder and Allied Disorders
Match research, need and demand to treatment and resources
RAI Amsterdam, The Netherlands

October 1-3, 2012
Ranzcp Section of Psychotherapy 2012 Conference
Monash University Centre, Prato, Italy

October 3-5, 2012
RANZCP Faculty of Child and Adolescent Psychiatry Annual Meeting
Novotel Manly Pacific, Sydney, Australia

October 4-7, 2012
64th Institute On Psychiatric Services
New York, NY, United States

October 13-14, 2012
RANZCP Victorian Branch Conference 2012
RACV Healesville Country Club, Australia

October 17-20, 2012
International Convention Of Pan-American Medical Women´s Alliance
Guadalajara, Mexico

October 21-24, 2012
ISQua 29th International Conference
Geneva, Switzerland

November 7-10, 2012
American Psychiatric Nurses Association 26th Annual Conference
Pittsburgh, PA, United States

November 8-11, 2012
International Conference on Clinical Practice in Alzheimer Disease
Budapest, Hungary

November 20-23, 2012
Silent Witnesses: The Place of Coronial System in A Civilised Society (Asia Pacific Coroners' Society)
Amora Hotel, Sydney, Australia

November 22-25, 2012
The 2nd International Multidisciplinary Forum on Palliative Care
Florence, Italy

November 10-12, 2012
CHADD 23rd Annual International Conference on ADHD - Children and Adults with Attention Deficit/Hyperactivity Disorder
Lake Buena Vista, FL, United States

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World J Psychiatr 2012 February 22; 2(1): I-V
ISSN 2220-3206 (online)

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Name of journal

World Journal of Psychiatry

ISSN

ISSN 2220-3206 (online)

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Indexed and Abstracted in
Digital Object Identifier.

Published by
Baishideng Publishing Group Co., Limited

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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