Psychiatry Research: Neuroimaging 234 (2015) 44–51

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Structural brain network analysis in families multiply affected with bipolar I disorder

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ARTICLE INFO

Article history:
Received 13 February 2015
Received in revised form
17 July 2015
Accepted 19 August 2015
Available online 20 August 2015

Keywords:
Familial bipolar disorder
Network analysis
Diffusion-weighted MRI
Endophenotype

ABSTRACT

Disrupted structural connectivity is associated with psychiatric illnesses including bipolar disorder (BP). Here we use structural brain network analysis to investigate connectivity abnormalities in multiply affected BP type I families, to assess the utility of dysconnectivity as a biomarker and its endophenotypic potential. Magnetic resonance diffusion images for 19 BP type I patients in remission, 21 of their first degree unaffected relatives, and 18 unrelated healthy controls underwent tractography. With the automated anatomical labelling atlas being used to define nodes, a connectivity matrix was generated for each subject. Network metrics were extracted with the Brain Connectivity Toolbox and then analysed for group differences, accounting for potential confounding effects of age, gender and familial association. Whole brain analysis revealed no differences between groups. Analysis of specific mainly frontal regions, previously implicated as potentially endophenotypic by functional magnetic resonance imaging analysis of the same cohort, revealed a significant effect of group in the right medial superior frontal gyrus and left middle frontal gyrus driven by reduced organisation in patients compared with controls. The organisation of whole brain networks of those affected with BP I does not differ from their unaffected relatives or healthy controls. In discreet frontal regions, however, anatomical connectivity is disrupted in patients but not in their unaffected relatives.

1. Introduction

The brain is an immensely complex system that is both highly specialised and integrated. Through recent advances in diffusion-weighted magnetic resonance imaging (MRI) and the application of graph theory, we can now model anatomical connectivity within the brain as a network. To date, multiple studies have used network analysis to investigate the organisation of the brain, determining it to be a vastly well-organised network displaying small world properties and a large degree of clustering, where communities of grey matter structures are more highly connected to each other than to regions in other clusters (Hagmann et al., 2007, 2008; Iturria-Medina et al., 2008; Gong et al., 2009; Bassett et al., 2011). This technique has also been successfully implemented in a few studies to examine anatomical network abnormalities in disease (Lo et al., 2010; van den Heuvel et al., 2010; Caeyenberghs et al., 2012, 2014; Leow et al., 2013; Reijmer et al., 2013a, 2013b). Most relevant of the network analysis literature for the current study is an investigation of bipolar disorder (BP) that revealed impaired connectivity between hemispheres for the BP patients compared with controls (Leow et al., 2013). Considering the recent consensus review of BP that determined two key emotional control networks are dysfunctional in BP (Strakowski et al., 2012), we decided to use network analysis to evaluate the structural networks of the brain and determine at a network rather than local level what is abnormal in BP. The rationale for this form of investigation has been further strengthened by the

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http://dx.doi.org/10.1016/j.pscychresns.2015.08.004
0925-4927/

Table 1
Subject demographics

	Bipolar I (19)	Relatives (21)	Controls (18)	Test statistic	*p*-value
Age (years), mean (SD)	43.26 (10.16)	42.52 (13.65)	41.72 (12.24)	$F_{(2)}=0.07$	0.93
Age (years), range	30–62	21–64	26–63		
Gender, M/F	9/10	12/9	10/8	$\chi^2=0.45$	0.80
Full-scale IQ, mean (SD)	114.6 (15.4)	118.8 (7.5)	114.9 (13.9)	$F_{(2,53)}=1.02$	0.47
Parental SES[a]	9	13	11	$\chi^2=1.03$	0.60
BDI, mean (SD)	7.9 (7.0)	5.0 (3.5)	3.4 (3.7)	$i_{(2,51)}=3.49$	0.038
ASRM, mean (SD)	3.5 (2.6)	1.8 (2.5)	1.0 (1.8)	$F_{(2,51)}=4.95$	0.011
Age at symptom onset (years)[b], mean (SD)	22.94 (5.67)				
Duration of illness (years)[b], mean (SD)	20.25 (10.84)				
Depressive episodes[b], mean (SD)	5.9 (6.3)				
Manic episodes[b], mean (SD)	7.0 (7.01)				
Hospitalisations[b], mean (SD)	3.3 (1.4)				
Current psychotropic medication[b], n					
None	3				
Lithium	9				
Mood stabilizers, other (e.g., valproate)	7				
Antidepressants	4	1			
Antipsychotics	4				

ASRM – Altman Self-Rating Mania scale, BDI – Beck Depression Inventory, M – male, F – female, SD – standard deviation, SES – socio-economic status.

[a] Class I or II (professional, managerial and technical occupations). Based on details of parental occupation at time of participants' birth.

[b] Data based on $n=16$ BP patients, data unavailable for the remaining 3.

findings of Wessa et al. (2014), whose review developed neurobiological models of BP that relate BP to abnormalities in neural networks, including networks involving the amygdala, prefrontal cortex and anterior cingulate gyrus. Here, we us network analysis techniques to investigate differences in structural connectivity in BP I patients, their first degree relatives and healthy controls, in order to further assess dysconnectivity between grey matter regions as a biomarker in BP and as a potential endophenotypic marker. This is the first attempt to do so in BP. Metrics derived from diffusion imaging have previously been shown to be highly heritable (Kochunov et al., 2010; Geng et al., 2012; Jahanshad et al., 2013) and thus have potential as endophenotypic markers for psychiatric disorders. Although these findings are not network-based, it is reasonable to assume the heritability also extends to network measures. These data have previously been analysed using tract-based spatial statistics (TBSS) and tractography, two complementary methods to investigate focal abnormalities (Chaddock et al., 2009; Emsell et al., 2014), whereas the novel approach used herein concerns itself with the network organisation of the brain rather than local abnormalities.

There is a vast array of network metrics available for investigation; herein we restricted our analysis to the following robust and commonly used metrics: clustering coefficient, global and local efficiency and characteristic path length. These, and many others, have been described in detail by Rubinov and Sporns (2010), but below is a brief introduction to network analysis and a description of each.

The network is a mathematical model of how the brain is organised; it is made up of nodes and edges. Nodes in this case are distinct anatomical grey matter areas whereas the edges are the white matter connections between them derived using diffusion-weighted MRI and tractography. Anatomical networks are simultaneously both highly segregated and integrated. In this study we investigate local and global measures of each.

Characteristic path length (CPL) is a global measure of integration within a network. The shortest path length is the fewest number of edges that must be travelled to go from one node to another (Bullmore and Sporns, 2009) and CPL is the average shortest path length between each pair of nodes in the network. Global efficiency (E_g) is related, as it is the average inverse of the shortest path length. These differ in that CPL is primarily affected by long paths while E_g as the inverse is primarily influenced by short paths. Local efficiency (E_l) is, as the name suggests, a local measure of efficiency or integration. The clustering coefficient (CC) is a measure of segregation within the network. It is the fraction of nodes' neighbours that are also neighbours of each other; it also quantifies the number of connections between the nearest neighbours of a node as a proportion of the maximum number of possible connections. Higher CC indicates higher segregation and clustering around that node. The CC for the whole brain is the average prevalence of clustered connectivity around individual nodes (Rubinov and Sporns, 2010).

Below we use network analysis to test the hypothesis that brain structural connectivity is disrupted in patients with BP and investigate the potential of network analysis measures as endophenotypic markers of BP by including unaffected first degree relatives in our analysis.

2. Methods

2.1. Participants

The majority of participants had previously taken part in structural (McDonald et al., 2004, 2005) and functional studies of BP (Drapier et al., 2008; Allin et al., 2010; Surguladze et al., 2010; Radua et al., 2013). All participated in our previous diffusion studies employing voxel-based analysis (Chaddock et al., 2009) and tractography (Emsell et al., 2013). Subject demographics have been described in detail elsewhere (Emsell et al., 2013) and are summarised in Table 1. Nineteen BP I patients in remission, 21 of their first degree relatives (4 parents, 10 siblings and 7 children) and 18 unrelated healthy volunteers took part in this study after giving written informed consent. Unaffected relatives did not fulfil criteria for bipolar disorder or psychotic disorder, but other non-psychotic lifetime diagnoses were not exclusion criteria for either relative or control groups. Three participants from the relatives group had a lifetime diagnosis of major depressive disorder