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Shared abnormality of white matter integrity in schizophrenia and bipolar disorder: A comparative voxel-based meta-analysis

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ABSTRACT

Patients with schizophrenia and bipolar disorder (BD) shared a significant overlap in genetic susceptibility, pharmacological treatment responses, neuropsychological deficits, and epidemiological features. However, it remains unknown whether these clinical overlaps are mediated by shared or disorder-specific abnormalities of white matter integrity. In this voxel-based meta-analytic comparison of whole-brain white matter integrity, we aimed to identify the shared or disorder-specific structural abnormalities between schizophrenia and BD. A comprehensive literature search was conducted up to February 2016 to identify studies that compared between patients and healthy controls (HC) by using whole-brain diffusion approach (schizophrenia: 24 datasets with 754 patients vs. 775 HC; BD: 23 datasets with 705 patients vs. 679 HC). Voxel-wise meta-analyses were conducted and restricted to unified template using seed-based d-Mapping. Abnormal white matter integrity was calculated within each condition and a direct comparison of effect size was performed of alterations between two conditions. Two regions with significant reductions of fractional anisotropy (FA) characterized abnormal water diffusion in both disorders: the genu of the corpus callosum (CC) and posterior cingulum fibers. There was no significant difference found between the two disorders. Our results highlighted shared impairments of FA at genu of the CC and left posterior cingulum fibers, which suggests that, phenotypic overlap between schizophrenia and BD could be related to common brain circuit dysfunction.

1. Introduction

The relationship between schizophrenia and bipolar disorder (BD) has been the focus of a growing number of studies: shared a significant overlap in genetic risk factors (Lichtenstein et al., 2009; Purcell et al., 2009), neuropsychological deficits (Hill et al., 2009; Kumar et al., 2015), pharmacological treatment responses (Maier et al., 2006; Murray et al., 2004) and epidemiological features, hence possibly leading to a common pathogenic mechanisms, and challenging Kraepelinian dichotomy (Craddock and Owen, 2005). The two illnesses continue to rank among the leading causes of disability worldwide, largely because the underlying neurobiological continuum linking the two psychotic disorders remains elusive and hence resulting in limited therapeutic and prognostic value (Frangou, 2014). Therefore, further exploration of the underlying neurobiology of both disorders would be valuable. Diffusion tensor imaging (DTI), a non-invasive MRI technology, is a powerful imaging method for characterizing the integrity of white matter circuitry because it links anatomical and functional neuroimaging together (Assaf and Pasternak, 2008). Although, a few studies have attempted to compare these two conditions, such as Kumar et al. (2015) and Lu et al. (2011), the consistency and replicability of findings in relation to white matter abnormalities in the two psychotic disorders remain uncertain usually due to small sample.

In light of these previous findings, this study therefore aims at conducting a quantitative, voxel-based meta-analytic comparison of all published whole-brain structural MRI studies of white matter abnormalities in patients with schizophrenia and BD to reliably identify shared or disorder-specific white matter abnormalities between two illnesses, which could aid the understanding of pathophysiological basis of the clinical continuum of psychosis. We integrated both widely used whole brain DTI approaches: voxel-based analysis (VBA) and tract-based spatial statistics (TBSS), by using a novel meta-analytic technique which allows us to comparing the effects size between two disorders. In addition, some necessary analyses were conducted to guarantee that our findings were robust and reliable.

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Based on current perspectives of dysconnectivity in psychosis (Nortje et al., 2013; Pettersson-Yeo et al., 2011), we hypothesized both schizophrenia and BD would show decreased white-matter integrity relative to controls and both disorders would show no significant differences in abnormalities of white matter (Cui et al., 2011; Kumar et al., 2015; McIntosh et al., 2008; Sussmann et al., 2009), whereas according to previous independent meta analyses we expected shared white matter abnormalities in frontal white matter to genu of the corpus callosum (CC) (Ellison-Wright and Bullmore, 2009; Wise et al., 2016).

2. Materials and methods

2.1. Study selection

Using PubMed, Web of Knowledge, and Scopus, we conducted a comprehensive literature search of studies published up to February 2016 that used whole-brain approach comparisons between individuals with schizophrenia or BD and healthy controls (HC). The selection of papers for the meta-analysis was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher et al., 2009). The search terms were "Schizophrenia" or "schizoaffective" or "Bipolar" and "Diffusion tensor imaging" or "DTI". Next, additional studies were collected by reviewing the reference list of the relevant papers and publications that cited those articles found in the first step, or through the 'related article' function of the PubMed database. Finally, the reference lists of those review articles were inspected for adding more relevant studies. Similar to previous meta study (Wise et al., 2016), exclusion criteria were as follows: (1) age below 18 or above 65, to minimize the effect of neurodevelopment and neurodegeneration as potential confounders on white matter diffusivity (Barnea-Goraly et al., 2005); (2) no HC group; (3) papers that used region of interest method; (4) did not use VBA or TBSS analysis (5) paper that did not report coordinates of effect in original paper and further could not be obtained through contracting the corresponding authors. To avoid sample overlaps, the following selection standard was followed (Wise et al., 2016): (1) the largest sample was included when multiple studies used the same dataset; (2) only the results from the whole group of participants were considered in case of multiple sub-groups analyses; (3) only pretreatment data were included in case of longitudinal studies. Literature Searches indicated forty-four studies (47 datasets) (Ambrosi et al., 2016; Benedetti et al., 2011; Bruno et al., 2008; Buchsbaum et al., 2006; Canales-Rodríguez et al., 2014; Chaddock et al., 2009; Chan et al., 2010; Chen et al., 2012; Cheung et al., 2008; Cui et al., 2011; Ebdrup et al., 2015; Guo et al., 2012; Ha et al., 2011; Hao et al., 2006; Hao et al., 2009; Hubl et al., 2004; Jeong et al., 2009; Jones et al., 2005; Kumar et al., 2015; Lagopoulos et al., 2013; Liu et al., 2010; Liu et al., 2014; Lu et al., 2011; Magioncalda et al., 2016; Mahon et al., 2012; Mahon et al., 2009; Mori et al., 2007; Nakamura et al., 2012; Oertel-Knöchel et al., 2014; Ozcelik-Eroglu et al., 2014; Reid et al., 2016; Schlösser et al., 2007; Seok et al., 2007; Shergill et al., 2007; Sprooten et al., 2013; Sussmann et al., 2009; Szeszko et al., 2005; Szeszko et al., 2008; Versace et al., 2008; Versace et al., 2010; Wang et al., 2011; Wessa et al., 2009; Zanetti et al., 2009; Zeng et al., 2016) meeting criteria for inclusion in the analysis (see Tables 1 and 2 for details). Four studies compared both schizophrenia and BD with control subjects (Cui et al., 2011; Kumar et al., 2015; Lu et al., 2011; Sussmann et al., 2009). A PRISMA flow chart of study selection is shown in Fig. S1 (see Supplementary material). Among the range of measures derived from DTI, fractional anisotropy (FA) was the only one consistently reported in all of studies and was therefore the only one examined in this meta-analysis. Importantly, reduction in FA provides a possible expression of demyelination (Beaulieu, 2002; Song et al., 2002), which existed in both disorders (Davis et al., 2003; Kempton et al., 2008).

2.2. Recorded variables and contrasts

Once the studies were selected, the following variables were recorded from each article: sample sizes, mean age of participants, sex (male, female), mean illness duration of patient, mean psychiatric symptoms scores on Positive and Negative Syndrome Scale (positive scale, PS and negative scale, NS) for schizophrenia, mean scores on Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale 17-Item (HAMD-17) for BD, proportion of medicated patients (antipsychotics for schizophrenia, lithium for BD) in each study, subtype for BD (BD-I,

Table 1
Characteristics of schizophrenia studies included in the meta-analysis.

Study	Analysis	Schizophrenia patients								Healthy controls		
		N	Mean age	Sex (F)	Illness Duration (years)	PS	NS	Antipsychotics (%)	State	N	Mean age	Sex (F)
Buchsbaum et al. (2006)	VBA	63	41.7	19	18.2	15	17.3	95.20%	Chronic	55	42.4	23
Cheung et al. (2008)	VBA	25	28.5	13	0.5	20.4	14.6	0	FE	26	28.2	13
Cui et al. (2011)	VBA	25	25.8	9	3.9	22.5	20.9	100%	Chronic	30	23.9	12
Ebdrup et al. (2016)	TBSS	38	25.9	10	6.25	20.7	22.1	0	FE	38	25.8	12
Eroglu et al. (2014)	TBSS	16	34.3	6	11.62	22.41	21.06	87.50%	Chronic	8	33.88	3
Guo et al. (2012)	TBSS	20	24	11	0.55	22.9	20.9	0	FE	26	23.6	12
Hao et al. (2006)	VBA	21	23.71	9	0.86	NA	NA	100%	FE	21	25.05	11
Hao et al. (2009)	VBA	34	25.44	14	1.69	21.3	22.03	100%	Chronic	34	25.77	14
Hubl et al. (2004)	VBA	26	32.2	10	8.1	20.45	21.95	92.30%	Chronic	13	32	5
Jeong et al. (2009)	TBSS	10	39.6	0	19	NA	NA	100%	Chronic	10	44.1	0
Jones et al. (2005)	VBA	14	34	0	8	NA	NA	100%	Chronic	14	34	0
Kumar et al. (2015)	TBSS	40	33.5	10	9.92	NA	NA	NA	Chronic	41	34.72	7
Liu et al. (2014)	TBSS	17	38.5	10	15.41	21.1	22.9	0	Chronic	17	34.1	11
Mori et al. (2007)	VBA	42	40	16	16.8	NA	NA	100%	Chronic	42	39.2	16
Nakamura et al. (2012)	VBA	58	27.6	20	4.27	NA	NA	100%	Chronic	58	26.4	20
Reid et al. (2016)	TBSS	29	33.8	9	13.4	(BPRS) 10.1	6.3	51.70%	Chronic	20	37.1	6
Schlösser et al. (2007)	VBA	18	29.6	4	NA	NA	NA	100%	Chronic	18	29	6
Seok et al. (2007)	VBA	30	29.6	15	7.5	NA	NA	100%	Chronic	22	30.3	11
Shergill et al. (2007)	VBA	33	32	3	7	NA	NA	93.90%	Chronic	40	34	5
Sussmann et al. (2009)	VBA	28	38	13	16.8	10.5	NA	100%	Chronic	38	37.2	19
Szeszko et al. (2005)	VBA	10	26.9	4	NA	NA	NA	60%	FE	13	28.9	6
Szeszko et al. (2008)	VBA	33	25.1	12	4.25	NA	NA	18.20%	Chronic	30	25.9	12
Wang et al. (2011)	VBA	68	24.13	36	0.75	26.31	19.61	56%	FE	100	25.6	48
Zeng et al. (2016)	TBSS	55	25	33	0.65	46 (BPRS)	NA	0	FE	61	25.33	33

BPRS, brief psychiatric rating scale; F, female; FE, first-episode; M, male; NA, not mentioned in original study; NS, Positive and Negative Syndrome Scale-negative scores; PS, Positive and Negative Syndrome Scale-positive scores; TBSS, tract-based spatial statistics; VBA, voxel-based analysis.

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