Shared intermediate phenotypes for schizophrenia and bipolar disorder: neuroanatomical features of subtypes distinguished by executive dysfunction

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Background: Shared genetic vulnerability for schizophrenia and bipolar disorder may be associated with common neuroanatomical features. In view of the evidence for working memory dysfunction as a candidate intermediate phenotype for both disorders, we explored neuroanatomical distinctions between subtypes defined according to working memory (n-back task) performance. **Methods:** We analyzed T_1 -weighted MRI scans for patients with schizophrenia-spectrum disorder, bipolar-I disorder (BD-I) and healthy controls. The VBM8 toolbox was used to assess differences in grey and white matter volume across traditional diagnostic groups (schizophrenia v. BD-I). Subsequently, groups were defined as “executively spared” (ES) based on the achievement of greater than 50% accuracy in the 2-back task performance (comparable to performance in the control group) or “executively deficit” (ED) based on the achievement of less than 50% accuracy. **Results:** Our study included 40 patients with schizophrenia-spectrum disorders, 30 patients with BD-I and 34 controls. Both the schizophrenia and BD-I groups showed grey matter volume reductions relative to the control group, but not relative to each other. The ED subtype ($n = 32$ [10 BD-I, 22 schizophrenia]) showed grey matter volume reductions in the bilateral superior and medial frontal gyri, right inferior opercular gyri and hippocampus relative to controls. The ES subtype ($n = 38$ [20 BD-I, 18 schizophrenia]) showed grey matter volume reductions in the right precuneus and left superior and medial orbital frontal gyri relative to controls. The ED subtype showed grey matter volume reduction in the right inferior frontal and precentral gyri relative to the ES subtype. There were no significant differences in white matter volume in any group comparisons. **Limitations:** This analysis was limited by small sample sizes. Further, insufficient numbers were available to assess a control-deficit comparison group. We were unable to assess the effects of mood stabilizer dose on brain structure. **Conclusion:** Neuroanatomical commonalities are evident among patients with schizophrenia-spectrum disorders and BD-I with working memory deficits. Reduced inferior frontal lobe volume may mediate cognitive deficits shared across the psychosis–mood spectrum.

Introduction

After more than a century of scientific inquiry into psychotic and mood disorders as separate diagnostic entities, recent epidemiological and molecular evidence supports the existence of shared genetic contributions to schizophrenia, schizoaffective disorder and bipolar-I disorder (BD-I).^{1–5} Generally, psychiatric disorders are also now recognized as disorders of brain networks⁶ that subserve a number of discrete cognitive domains (e.g., learning, memory, emotion processing), and it is plausible that aberration in any given brain network will be implicated in more than 1 disorder.⁷ This is especially so in the context of disorders on the psychosis–mood spectrum, for which evidence of both com-

mon cognitive deficits^{8,9} and shared brain abnormalities^{9–12} has emerged over the past decade.

Working memory impairment (and associated prefrontal-striatal network dysfunction) is among the most likely endophenotypic candidates for both schizophrenia^{13,14} and BD-I,¹⁵ with state-independent deficits reported in both affected probands and their unaffected relatives^{16,17} and with replicated genetic associations.^{18–20} These impairments are usually reported to be of greater magnitude in patients with schizophrenia.^{8,21–23} However, working memory deficits are not uniform — there is substantial interindividual variation among study samples, with some suggestion that clinical profile, particularly a lifetime history of psychosis, may modulate the severity of impairment.^{17,24} In view of the current focus on brain circuits

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rather than diagnoses^{6,25} and the high degree of concordance among the neuroanatomical profiles of both schizophrenia and BD-I,^{26,27} we set out to determine the neuroanatomical profile of subgroups of patients with either schizophrenia or BD-I, defined instead on the basis of working memory performance using a well-characterized working memory task (n-back).²⁸

Prior efforts to distinguish neuroanatomical underpinnings of schizophrenia and BD-I have implicated a range of overlapping brain regions. Both disorders have been associated with volume deficits of the frontal lobes, particularly precentral, inferior frontal, orbitofrontal and anterior cingulate gyri, and the insula.^{9–12} In addition to frontal lobe deficits, bipolar disorder has been uniquely associated with enlarged amygdala volume.^{29–31} Typically, schizophrenia is characterized by a larger magnitude and broader range of volume reductions,^{10,29,30} with grey matter volume deficits additionally encompassing superior, inferior and medial temporal lobe gyri, hippocampus/amygdala and thalamus, in addition to reduced global brain volume and ventricular enlargement.^{26,32} However, this literature is potentially confounded by a myriad of illness-related features (e.g., symptom profile, medication); not surprisingly, the structural imaging literature on both disorders shows high variability with generally poor levels of replication. Nonetheless, the overlap among reported neuroanatomical aberrations suggests that shared regional brain volume loss may underpin phenotypic commonalities (e.g., working memory impairments) among individuals with either disorder.

Previous studies have generally not observed consistent associations between domains of cognitive impairment and neuroanatomical alterations in either disorder. Some evidence suggests that regionally specific brain volumes, particularly prefrontal cortex and subcortical nuclei, may show a linear association with working memory and executive functioning performance in both disorders^{33–37} as well as an association between integrity of frontoparietal white matter tracts and working memory ability in patients with schizophrenia³⁸; however, other evidence suggests more complex associations may exist between neuroanatomy and task-specific domains of cognition.^{49,40} For example, a study found that people with schizophrenia showed a lack of the normal linear association between prefrontal cortex grey matter volume and spatial working memory ability.⁴¹ In the context of the inconsistent associations reported between neuroanatomy and cognitive ability among traditional samples of patients with schizophrenia and BD-I, novel approaches to patient classification based on working memory ability may be usefully applied to studies elucidating neurobiological mechanisms of shared cognitive dysfunctions among (some) individuals with either of these disorders.

The characterization of neuroanatomical features distinguishing patients with cognitive subtypes of psychosis or mood disorders, particularly those defined by working memory profile, may highlight regions of distinct neuropathology for targeted genetic and neurobiological interrogation. The goal of the present study was to quantify the grey and white matter volume differences associated with working memory performance in a pooled sample of patients with schizophrenia, schizoaffective disorder or BD-I. Dichotomous clinical subtypes were defined according to working memory perform-

ance accuracy: based on standard working memory task (2-back condition) performance, cross-disorder subtypes for comparison comprised an “executively deficit” (ED) group scoring less than 50% correct and an “executively spared” (ES) group scoring above 50% (i.e., comparable to healthy control performance). We hypothesized that, independent of diagnosis, patients with more severe working memory impairments would show more pronounced deficits of prefrontal grey and white matter volume relative to both healthy controls and to the subgroup of patients with intact cognitive ability.

Methods

Participants

We included participants meeting ICD-10 criteria for schizophrenia or schizoaffective disorder (collectively referred to as the schizophrenia group) or for BD-I; diagnoses were confirmed using the OPCRIT algorithm⁴² applied to interviewer ratings on the Diagnostic Interview for Psychosis (DIP).⁴³ Patients were recruited between 2010 and 2013 from outpatient services of South Eastern Sydney and St. Vincent’s Hospital health services and through local community advertisements. Additional participants with schizophrenia were recruited from the Australian Schizophrenia Research Bank (ASRB) volunteer database,⁴⁴ and patients with BD-I were recruited from the Black Dog Institute Bipolar Disorders Clinic.⁴⁵ We recruited healthy controls from the ASRB database and through advertisement in the local community. Controls were required to have no personal history of DSM-IV Axis 1 disorders and no history of psychosis in their first-degree biological relatives. General exclusion criteria applied to both patients and controls included inability to communicate sufficiently in English, current neurologic disorder, head injuries with loss of consciousness, a diagnosis of substance abuse or dependence in the 6 months preceding the study and/or electroconvulsive therapy within the 6 months preceding the study.

All volunteers provided informed consent according to procedures approved by the University of New South Wales Human Research Ethics committees (HC12384), the South East Sydney and Illawarra Area Health Service (HREC 09/081) and St. Vincent’s Hospital Sydney (HREC/10/SVH/9). In cases where clinical participants were recruited from hospital outpatient units, the ability to provide informed consent was confirmed by the treating medical staff.

Cognitive and clinical assessment

Current symptom severity was assessed in patients using the Positive and Negative Syndrome Scale (PANSS),⁴⁶ the DIP⁴³ and the Global Assessment of Functioning scale.⁴⁷ We used DIP items to identify a lifetime history of psychotic symptoms, including hallucinations or delusions. Data on psychiatric medications were collected via self-report and, when further clarification was required, via contact with the participants’ treating clinicians. Participants were also assessed using the Edinburgh Handedness Inventory⁴⁸ and the Depression, Anxiety and Stress Scale.⁴⁹ Comprehensive

neuropsychological assessment included the Wechsler Abbreviated Scale of Intelligence (WASI)⁵⁰ and Wechsler Test of Adult Reading⁵¹ to estimate current and premorbid IQ, respectively; the Repeatable Battery for the Assessment of Neuropsychological Symptoms to assess the subdomains of immediate memory, visuospatial construction, language, attention and delayed memory;⁵² the Letter-Number Sequencing test for working memory;⁵³ and the Controlled Oral Word Association Test for executive function.⁵⁴

Working memory subtypes

We administered an n-back task²⁸ during a functional imaging paradigm to assess working memory ability (see the study by Quidé and colleagues¹³). Participants were shown a pseudorandomized sequence of numbers (1–4) every 1800 ms and were asked to recall the number presented 2 stimulus trials previously (2-back, presented 3600 ms prior). Accuracy was recorded as percentage correct of the total possible number of responses (incorrect and missed trials). Prior to scanning, patients were trained to achieve at least 50% accuracy on the n-back task. Those who achieved less than 50% accuracy during the task composed the ED group, and those scoring above 50% composed the ES group. The 50% cut-off for distinction of clinical subgroups was used to create a subgroup of participants comparable to the controls, who achieved no lower than 50% accuracy. The number of recruits to the control group who recorded accuracy below the 50% criterion was insufficient to form a control-deficit comparison subgroup, so they were excluded from all analyses.

Image processing

High-resolution T_1 -weighted structural MRI scans (MPRAGE) were collected on a Philips Achieva 3 T scanner with the following parameters: repetition time 8.9 ms, echo time 4.1 ms, field of view 240 mm, matrix 268×268 , 200 contiguous 0.9 mm sagittal slices. All scans were screened for artifacts and manually reoriented to anterior–posterior commissure orientation. The VBM8 toolbox for SPM8 was used for image analysis (<http://dbm.neuro.uni-jena.de/vbm/>). We applied a unified segmentation approach combined with hidden Markov random fields to delineate grey and white matter and cerebrospinal fluid segments. Normalization using a nonlinear warp negated the need to further account for total individual brain volume in group-level analyses. Normalized images were additionally modulated with the Jacobian determinants of the deformation parameters, thus preserving the absolute tissue volumes. Finally, images were smoothed with an 8 mm full-width at half-maximum filter for inclusion in group-based analyses.

Statistical analysis

Two analysis approaches were undertaken. The first group of analyses aimed to assess any differences in grey and white matter volume in the schizophrenia and BD-I groups relative both to the control group and to each other. For this approach, we undertook an analysis of variance (ANOVA) to compare

images from 3 groups, using age and sex as covariates of no interest. We performed post hoc 2-sample t test analyses to test the significance and directionality of pairwise between-group differences. In a pooled group of all clinical participants (schizophrenia and BD-I), regression analyses explored any effects of medication dose on either grey or white matter volume (imipramine- and chlorpromazine-equivalent doses).

The second set of analyses compared volume differences of grey and white matter among the subtypes defined according to working memory ability relative to the control group and to each other. We performed an ANOVA to compare images from the 3 groups, using age and sex as covariates of no interest, further quantifying between-group differences using post hoc 2-sample t tests. In addition, full factorial analyses were used to examine any statistical interactions between diagnostic groups (control, schizophrenia, BD-I) and performance accuracy (score) on the 2-back condition.

Statistical significance in all analyses was inferred at the cluster level with family-wise error correction (FWE) at $p < 0.05$ (after applying an uncorrected voxel-wise threshold of $p < 0.005$). This method allows for nonisotropic smoothness in the data, taking into account both the peak height and spatial extent of significant clusters, and is sensitive to the spatial distribution of significant voxels. Regions showing significant differences in grey matter volume between groups were localized using the WFU PickAtlas toolbox for SPM8, incorporating the Montreal Neurological Institute atlas labels (v3.0.3; <http://fmri.wfubmc.edu/software/PickAtlas>). Statistical analyses of sociodemographic, clinical and cognitive data were conducted using PASW Statistics version 21 (SPSS Inc.). We used 1-way ANOVA with Tukey honestly significant difference post hoc tests, 2-sample t tests, χ^2 analyses and independent-samples median tests, as appropriate, to investigate differences among both clinical and cognitive groups of patients relative to controls (significance threshold for each test was set at $\alpha = 0.05$).

Results

Sample

We included 40 patients in the schizophrenia group (28 with schizophrenia and 12 with schizoaffective disorder), 30 patients in the BD-I group and 34 participants in the control group. The ED subgroup comprised 32 participants: 10 patients with BD-I and 22 with schizophrenia. The ES subgroup comprised 38 participants: 20 patients with BD-I and 18 with schizophrenia.

Comparison of cross-disorder subtypes defined by executive function

Participant characteristics

Tables 1 and 2 report detailed characteristics of the cognitively derived (ED, ES) subgroups. The ED group was significantly older than the control and ES groups (both $p < 0.05$); there was no difference in age between the control and ES groups. Both patient groups showed significant WASI-IQ impairments compared with controls, but the ES group had a significantly higher IQ than the ED group ($p = 0.027$). The ED group

showed substantially more severe symptoms across all PANSS subdomains, particularly negative symptoms, as well as poorer global functioning than the ES group; however, there was no difference between these 2 groups in the frequency of a lifetime history of psychotic symptoms. There were no differences between the ES and ED groups in frequency or dose of antipsychotic or antidepressant medications, but the ES group received more mood stabilizers (Table 1).

Whole brain volume differences between cross-disorder subtypes

We observed grey matter volume reductions for each cross-disorder performance subtype (ED, ES) relative to controls (Fig. 1). An overall ANOVA (controlling for age and sex) re-

vealed a main effect across the 3 groups ($F_{2,99} = 10.12$, $p < 0.001$, uncorrected) in the right precuneus and superior parietal (angular) gyrus, right rolandic operculum, left superior and orbital frontal gyri and cerebellar vermis.

Pairwise comparison of patients grouped according to working memory ability showed that, relative to controls, patients in the ED group showed grey matter volume reductions of the bilateral superior, middle, medial frontal and anterior cingulate gyri; right rolandic and inferior opercular gyri; and hippocampus (all $p < 0.05$, FWE-corrected). In the ES group relative to controls, grey matter volume differences were located in the right precuneus and angular gyrus and in the left superior and medial orbital frontal gyri. Neither the ED nor the ES group showed any regions of increased grey matter volume relative to

Table 1: Demographic, clinical and cognitive data for working memory performance-based groups and controls

Characteristic	Group; mean $\pm$ SD*			Statistic	p value	Tukey HSD $p < 0.05$
	Control, $n = 34$	ES, $n = 38$	ED, $n = 32$			
No. BD-I/schizoaffective/schizophrenia		20/7/11	10/5/17			
Age, yr	32.6 $\pm$ 10.6	38.2 $\pm$ 10.8	44.9 $\pm$ 11.8	$F_{2,101} = 10.3$	< 0.001	ED > control/ES†
Sex, male/female	16/18	17/21	19/13	$\chi^2_2 = 1.66$	0.44	NS
Right/left/both	29/1/4	35/1/2	27/1/4	$\chi^2_4 = 1.35$	0.85	NS
Years of education	16.91 $\pm$ 2.2	15.41 $\pm$ 2.8	14.23 $\pm$ 2.9	$F_{2,100} = 8.35$	< 0.001	Control > ED‡
2-back score %	0.81 $\pm$ 0.14	0.72 $\pm$ 0.14	0.30 $\pm$ 0.13	$F_{2,101} = 128.6$	< 0.001	Control > ES† > ED‡
WASI-IQ	119 $\pm$ 10.3	110.9 $\pm$ 12.5	102.8 $\pm$ 14.8	$F_{2,98} = 12.5$	< 0.001	Control > ES† > ED‡
WTAR	112.4 $\pm$ 7.4	107.5 $\pm$ 12.0	97.97 $\pm$ 16.0	$F_{2,98} = 11.2$	< 0.001	Control/ES > ED‡
IED total errors	-0.01 $\pm$ 1.5	0.19 $\pm$ 1.6	1.13 $\pm$ 1.9	$F_{2,98} = 4.24$	0.017	Control > ES†
RBANS-immediate memory	100.1 $\pm$ 17.4	87.76 $\pm$ 17.5	80.9 $\pm$ 19.9	$F_{2,99} = 9.16$	< 0.001	Control > ES/ED†
RBANS-visuospatial	111.5 $\pm$ 74.9	87.1 $\pm$ 18.4	92.4 $\pm$ 66.9	$F_{2,99} = 1.68$	0.19	NS
RBANS-language	105.3 $\pm$ 11.4	98.8 $\pm$ 16.8	94.5 $\pm$ 14.6	$F_{2,99} = 4.40$	0.015	Control > ED
RBANS-attention	100.3 $\pm$ 21.8	93.97 $\pm$ 17.1	85.5 $\pm$ 16.6	$F_{2,99} = 5.14$	0.007	Control > ED†
RBANS-delayed memory	98.3 $\pm$ 9.8	88.3 $\pm$ 16.6	81.9 $\pm$ 15.7	$F_{2,99} = 10.25$	< 0.001	Control > ES/ED†
RBANS-total	507.2 $\pm$ 41.7	445.0 $\pm$ 85.8	409.8 $\pm$ 81.0	$F_{2,99} = 14.57$	< 0.001	Control > ES/ED‡
DASS-total	10.2 $\pm$ 12.5	32.9 $\pm$ 25.3	34.5 $\pm$ 31.8	$F_{2,101} = 10.62$	< 0.001	Control > ES/ED‡
Age at onset, yr	—	24.3 $\pm$ 7.8	26.6 $\pm$ 10.3	$t_{99} = 1.0$	0.32	NS
GAF	—	59.2 $\pm$ 15.8	49.5 $\pm$ 11.5	$t_{98} = -2.86$	0.006	ES > ED‡
YMRS	—	8.2 $\pm$ 10.5	7.5 $\pm$ 7.9	$t_{99} = -0.338$	0.74	NS
Lifetime history of psychosis, yes/no	—	31/38	27/32	$\chi^2_1 = 0.96$	> 0.99	NS
Lifetime history of psychosis, BD/ schizophrenia	—	15 BD/16 schizophrenia	6 BD/ 21 schizophrenia	$\chi^2_1 = 4.23$	0.06	NS
PANSS-Positive	—	11.8 $\pm$ 5.1	15.1 $\pm$ 6.3	$t_{98} = 2.4$	0.019	ED > ES
PANSS-Negative	—	11.9 $\pm$ 5.2	16.2 $\pm$ 6.2	$t_{98} = 3.1$	0.003	ED > ES‡
PANSS-General	—	27.2 $\pm$ 8.0	32.4 $\pm$ 8.3	$t_{98} = 2.65$	0.010	ED > ES
IMI, yes/no	—	12/26	12/20	$\chi^2_1 = 0.27$	0.62	NS
IMI	—	153.58 $\pm$ 178.9	96.03 $\pm$ 71.5	$t_{22} = -1.03$	0.31	NS
IMI, median	—	83.2	107.8		0.68	NS
CPZ, yes/no	—	26/12	26/6	$\chi^2_1 = 1.49$	0.28	NS
CPZ	—	481.9 $\pm$ 425.6	953.1 $\pm$ 1750.9	$t_{51} = 1.33$	0.19	NS
CPZ, median	—	400.0	220.0		0.41	NS
Mood stabilizer, yes/no	—	23/15	10/22	$\chi^2_1 = 5.97$	0.018	ES > ED

BD-I = bipolar I disorder; COWAT = Controlled Oral Word Association Task; CPZ = Chlorpromazine equivalent antipsychotic dose; DASS = Depression, Anxiety and Stress Scale; ED = executive deficit clinical subgroup; ES = executive spared clinical subgroup; DASS = Depression Anxiety Stress Scale; GAF = Global Assessment of Functioning; HSD = Tukey honestly significant difference post hoc test; IED = Intra/Extradimensional Set Shift Test (CANTAB); IMI = Imipramine equivalent antidepressant dose; NS = not statistically significant; PANSS = Positive and Negative Syndrome Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SD = standard deviation; SZ = schizophrenia; SZA = schizoaffective disorder; WASI-IQ = Wechsler Abbreviated Scale of Intelligence — Intelligence Quotient; WTAR = Wechsler Test of Adult Reading, YMRS = Young Mania Rating Scale.

*Unless otherwise indicated.

† $p < 0.05$.

‡ $p < 0.001$.

the control group. Table 3 provides detailed results of these comparisons.

Comparing the patient subgroups directly, the ED group showed grey matter volume reductions relative to the ES group in a large cluster encompassing the right rolandic operculum (inferior frontal), precentral and postcentral gyri (all $p < 0.05$, FWE-corrected), controlling for age and sex.

Assessment of white matter volume among the 3 groups identified no significant differences in any comparison (Fig. 1 and Table 3).

Comparison of traditional diagnostic groups

Participant characteristics

Table 2 outlines detailed participant characteristics according to clinical diagnoses. Both diagnostic groups (schizophrenia, BD-I) were significantly older than the control group, but did not dif-

fer from each other (Tukey honestly significant difference test, $p = 0.34$). There were no differences in sex distribution across groups. Participants with schizophrenia had significantly lower mean WASI-IQ equivalent scores than controls ($p < 0.001$), whereas those with BD-I showed only a nonsignificant trend toward lower mean WASI-IQ scores relative to controls ($p = 0.06$; Table 2). Compared with patients in the BD-I group, patients in the schizophrenia group had significantly more severe symptoms across all PANSS subdomains, lower global functioning and more frequent lifetime history of psychosis. Most patients (96%) were medicated at the time of scanning; patients with schizophrenia more frequently received antipsychotics, and those with BD-I more frequently received mood stabilizers.

Whole-brain volume differences between clinical groups

Characteristic reductions of grey matter volumes were observed in each disorder relative to controls. An overall

Table 2: Demographic, clinical and cognitive data for clinical groups and controls

Characteristic	Group; mean (SD)*			Statistic	p value	Tukey HSD $p < 0.05$
	Control, $n = 34$	BD-I, $n = 30$	SZ, $n = 40$ (12 SZA)			
Age, yr	32.6 (10.6)	39.06 (12.8)	42.93 (10.6)	$F_{2,101} = 7.73$	0.001	SZ > control†
Sex, male/female	16/18	12/18	24/16	$\chi^2_2 = 2.92$	0.23	NS
Right/left/both	29/1/4	27/1/2	35/1/4	$\chi^2_4 = 0.523$	0.97	NS
Years education	16.91 (2.2)	15.5 (3.0)	14.37 (2.8)	$F_{2,100} = 8.19$	0.001	Control > SZ‡
2-back score %	0.81 (0.14)	0.59 (0.22)	0.49 (0.27)	$F_{2,101} = 20.19$	< 0.001	Control > BD-I > SZ‡
WASI-IQ	119 (10.3)	111.3 (10.9)	104.5 (15.5)	$F_{2,96} = 11.14$	< 0.001	Control > SZ‡
WTAR	112.4 (7.4)	109.1 (12.9)	98.6 (14.5)	$F_{2,98} = 12.62$	< 0.001	Control/BD-I > SZ‡
RBANS-immediate memory	100.1 (17.4)	89.6 (16.2)	80.9 (19.9)	$F_{2,99} = 9.99$	< 0.001	Control > SZ‡
RBANS-visuospatial	111.5 (74.9)	82.4 (17.1)	94.9 (60.0)	$F_{2,99} = 2.03$	0.14	NS
RBANS-language	105.3 (11.4)	100.1 (19.0)	94.5 (12.8)	$F_{2,99} = 4.98$	0.009	Control > SZ‡
RBANS-attention	100.3 (21.8)	94.9 (18.1)	86.5 (15.9)	$F_{2,99} = 5.08$	0.008	Control > SZ‡
RBANS-delayed memory	98.3 (9.8)	86.1 (16.6)	84.9 (16.4)	$F_{2,99} = 8.36$	< 0.001	Control > BD-I/SZ‡
RBANS-total	507.2 (41.7)	435.8 (90.8)	423.8 (81.0)	$F_{2,99} = 12.35$	< 0.001	Control > BD-I/SZ‡
DASS-total	10.2 (12.5)	29.3 (25.7)	36.9 (29.8)	$F_{2,101} = 11.58$	< 0.001	Control > BD-I/SZ‡
Age onset	—	25.59 (11.2)	25.09 (6.5)	$t_{99} = 0.212$	0.83	NS
Lifetime history of psychosis, yes/no	—	21/9	37/3	$\chi^2_1 = 6.11$	0.023	SZ > BD†
PANSS-Positive	—	10.57 (4.2)	15.33 (6.1)	$t_{88} = -3.65$	< 0.001	SZ > BD-I‡
PANSS-Negative	—	10.77 (4.1)	16.23 (6.3)	$t_{88} = -4.15$	< 0.001	SZ > BD-I‡
PANSS-General	—	26.4 (6.9)	31.98 (8.9)	$t_{88} = -2.85$	0.006	SZ > BD-I‡
GAF	—	61.5 (14.5)	49.7 (12.8)	$t_{88} = 3.59$	0.001	BD-I > SZ‡
YMRS	—	6.7 (8.4)	8.83 (10.0)	$t_{88} = -0.94$	0.35	NS
IMI, yes/no	—	8/22	16/24	$\chi^2_1 = 1.35$	0.31	NS
IMI	—	91.41 (82.9)	141.5 (156.4)	$t_{22} = -0.84$	0.41	NS
IMI, median	—	67.5	132.8		0.67	NS
CPZ	—	15/15	37/3	$\chi^2_1 = 16.2$	< 0.001	SZ > BD-I‡
CPZ	—	380.5 (327.9)	854.1 (1492.2)	$t_{50} = -1.21$	0.23	NS
CPZ, median	—	300.0	266.7		> 0.99	NS
Mood stabilizer, yes/no	—	26/4	7/33	$\chi^2_1 = 32.9$	< 0.001	BD-I > SZ‡

BD-I = bipolar I disorder; COWAT = Controlled Oral Word Association Task; CPZ = Chlorpromazine equivalent antipsychotic dose; DASS = Depression, Anxiety and Stress Scale; ED = executive deficit clinical subgroup; ES = executively spared clinical subgroup; DASS = Depression Anxiety Stress Scale; GAF = Global Assessment of Functioning; HC = healthy controls; HSD = Tukey's Honestly Significant Difference post hoc test; IED = Intra/Extradimensional Set Shift Test (CANTAB); IMI = Imipramine equivalent antidepressant dose; NS = not statistically significant; PANSS = Positive and Negative Syndrome Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SD = standard deviation; SZ = schizophrenia; SZA = schizoaffective disorder; WASI-IQ = Wechsler Abbreviated Scale of Intelligence — Intelligence Quotient; WTAR = Wechsler Test of Adult Reading; YMRS = Young Mania Rating Scale.

*Unless otherwise indicated.

† $p < 0.05$.

‡ $p < 0.001$.

ANOVA, including age and sex as covariates, revealed a main effect across 3 groups ($F_{2,99} = 10.12$, $p < 0.001$, uncorrected) in the right precuneus, left superior orbital frontal gyrus, parahippocampus and cerebellar vermis.

We assessed directionality of effect using post-hoc t tests; after controlling for age and sex, we inferred significant whole brain differences at the cluster level with FWE correction ($p < 0.05$). Full details of the 2-sample comparisons are reported in Table 4. Relative to controls, patients with schizophrenia showed significant reductions of grey matter volume in the left hippocampus and parahippocampus; left medial, superior and middle orbital frontal gyri; and right middle frontal gyrus. Relative to controls, patients with BD-I showed robust grey matter volume reductions in the right precuneus and superior parietal (angular) and postcentral gyri and the left superior and medial orbital frontal gyri (Fig. 2). Neither clinical group showed any regions of increased grey matter volume relative to the control group that survived correction for multiple comparisons. Direct comparison of the schizophrenia and BD-I groups revealed no regional clusters surviving the significance threshold. Additional analysis identified no regional interaction between clinical group and n-back performance score. Within the pooled clinical group, we found no significant associations between grey matter volume and mean doses of antipsychotics (chlorpromazine equivalents) or antidepressants (imipramine equivalents). Assessment of white matter volume among the 3 groups revealed no differences in any comparison.

Fig. 1: Regions of significant grey matter volume reduction in working memory-derived subgroups. Volume reductions in executive deficit (ED) relative to controls are shown in orange. Reductions in the executive spared (ES) group are shown in green. Direct comparison between clinical subgroups (ES > ED) is shown in purple. Analysis was corrected at the cluster level ($p < 0.05$, family-wise error-corrected); $p < 0.005$, voxelwise uncorrected. Data are presented in Montreal Neurological Institute space on an average template brain in the neurological convention. Axial slices at $z = -14, -4, 10, 22, 32$ and 50 , respectively.

In addition, we identified no significant associations between white matter volume and doses of imipramine or chlorpromazine equivalents (Fig. 2 and Table 4).

Discussion

This study provides evidence for distinct neuroanatomical profiles differentiating cross-disorder subtypes of patients (with schizophrenia or BD-I) who show pronounced working memory deficits from their nondeficit counterparts. To our knowledge, these results are among the first to demonstrate the utility of the Research Domain Criteria project (RDoC)⁶ approach to identifying shared intermediate phenotypes across the psychosis–mood diagnostic spectrum. In a subgroup of individuals characterized by severe impairments in working memory (regardless of diagnosis), diffuse grey matter volume reductions of the right anterior cingulate; superior, middle and

Table 3: Regions of brain volume reductions in working memory–based subtypes of psychosis compared with controls ($p < 0.05$, cluster corrected, family-wise error)

Comparison; region	k, no. of voxels	Peak	T
Control > ES			
Right	1966		
Precuneus		8, -70, 49	5.87
Angular gyrus (superior parietal)		28, -60, 43	3.22
Precuneus		16, -57, 48	3.13
Left	2301		
Superior orbital frontal gyrus		-20, 60, -14	4.52
Medial orbital frontal gyrus		-9, 56, -15	4.1
Medial orbital frontal gyrus		-3, 68, -9	3.85
Control > ED			
Left	5620		
Superior frontal gyrus		-18, 48, 4	4.5
Anterior cingulate gyrus		0, 44, 9	4.48
Medial frontal gyrus		-15, 46, 18	3.99
Right	3003		
Rolandic operculum		57, -6, 15	4.48
Inferior opercular frontal gyrus		56, 14, 33	3.91
Rolandic operculum		51, -4, 6	3.87
Right	2245		
Superior frontal gyrus		32, 54, 7	4.31
Middle frontal gyrus		42, 42, 16	3.95
Middle frontal gyrus		44, 52, 19	3.79
Left	1928		
Hippocampus		-27, -39, -5	4.1
Hippocampus		-39, -27, -6	3.85
Hippocampus		-42, -18, -14	3.79
ES > ED			
Right	3193		
Rolandic operculum		58, -3, 12	5.58
Precentral gyrus		63, 9, 21	3.72
Postcentral gyrus		62, 2, 33	3.45

ED = executive deficit subtype of psychosis; ES = executive spared subtype of psychosis.

inferior frontal gyri; and left hippocampus were revealed relative to healthy controls. In contrast, the group of patients with relatively spared working memory performance showed more circumscribed grey matter volume loss within the left orbital frontal gyri and the right precuneus. Notably, the pattern of neuroanatomical aberrations for the group with relatively spared working memory performance overlapped with volume reductions in the BD-I group (in traditional diagnostic comparisons); however, it is notable that patients with schizophrenia made up almost half the ES subgroup. Direct comparison of the ES and ED subgroups showed substantial reductions of grey matter volume in the ED group localized around the right rolandic operculum (right inferior frontal gyrus; rIFG) and pre- and postcentral gyri, with clusters extending toward the insular cortex. Surprisingly, there were no significant differences in white matter volume among the ES or ED groups relative to controls. The lack of white matter volume differences may represent an issue of insufficient power, but in the context of significant grey matter volume findings, these results imply greater severity of, or less interindividual variability in, grey matter volume aberrations in patients with subtypes of psychosis and mood disorders characterized by working memory impairment. The patients with greater impairments in working memory ability may thus represent a neuroanatomically distinct subtype that spans traditional diagnostic categories of schizophrenia-spectrum disorders and BD-I.

These results were revealed in the context of a lack of grey matter volume differences between the traditional diagnostic categories of BD-I and schizophrenia (including schizoaffective disorder). Substantial evidence has highlighted common brain aberrations, including both global and regional deficits,^{10,12,29,30} in addition to selected diagnosis-specific findings^{9,11} among patients with these disorders relative to controls. However, the regions identified as “distinguishing” the diagnoses vary across studies, and our results appear consistent with those of recent investigations demonstrating a lack of substantial diagnostic specificity in neuroanatomical profile.^{12,55} This variability across studies may be attributable, in part, to variation in the significance thresholds applied, statistical power, or to many other factors intrinsic to the acquisition or analysis techniques involved. However, the variability is likely also a consequence of the inherent variability

across and within patient samples, which hampers the generalizability of any imaging analyses according to traditional diagnostic categories.

While our analytic approach represents an attempt to reduce the phenotypic heterogeneity inherent in traditional diagnostic categories of schizophrenia and BD, we cannot presume to have attenuated all within-group variability with the use of cognitively derived subtypes. However, the utility of this approach is in delineating a cross-disorder subgroup of patients with severe working memory deficit and characterized by extensive grey matter volume loss in frontal cortices

Table 4: Regions of brain volume reductions in schizophrenia spectrum and bipolar-I disorders compared with controls ($p < 0.05$, cluster corrected, family-wise error)

Comparison; region	k, no. of voxels	Peak	<i>T</i>
Control > BD-I			
Right	4756		
Precuneus		9, -73, 45	5.84
Superior parietal lobule		24, -58, 48	4.21
Postcentral gyrus		20, -33, 57	3.933
Left	2911		
Superior orbital frontal gyrus		-20, 60, -15	5.15
Medial orbital frontal gyrus		-10, 58, -11	3.99
Medial orbital frontal gyrus		-2, 68, -8	3.5
Control > SZ			
Left	2714		
Parahippocampus		-27, -37, -8	4.69
Hippocampus		-36, -19, -18	3.92
Brainstem		-18, -15, -11	3.6
Left	2224		
Superior medial orbital frontal gyrus		-18, 47, 3	3.88
Superior orbital frontal gyrus		-12, 56, -9	3.68
Middle orbital frontal gyrus		-20, 62, -12	3.68
Right	1967		
Middle frontal gyrus		40, 42, 16	3.84
Middle frontal gyrus		33, 52, 7	3.76
Middle frontal gyrus		46, 39, 25	3.51

BD = bipolar-I disorder; SZ = schizophrenia.

Fig. 2: Regions of significant grey matter volume reduction in the schizophrenia (red-yellow) and bipolar disorder (blue-green) groups relative to controls. Analysis was corrected at the cluster level ($p < 0.05$, family-wise error-corrected); $p < 0.005$, voxelwise uncorrected. Axial slices at $z = -14, -5, 11, 48$ and 60 , respectively.

and hippocampal regions, greater functional impairment and more severe symptomatology. The distribution of the cognitive phenotype across disorders is consistent with previous evidence of more severe working memory deficits in patients with schizophrenia⁸ and suggests that these cross-disorder cases with severe cognitive deficit may share some genetic underpinnings. This proposal is supported by evidence that many of the shared risk genotypes (notably evident only in subsets of both schizophrenia and BD-I populations), have been shown to modulate neurocognitive functioning and brain morphometry in clinical and nonclinical populations. For example, multiple polymorphisms within the catechol-O-methyltransferase (*COMT*) and disrupted in schizophrenia (*DISC1*) genes have been associated with differential cognitive ability in people with both disorders^{56–58} across a range of domains, including n-back performance,¹⁹ as well as modulating cortical^{58–60} and subcortical^{61,62} brain volumes. The complex phenotypes of these cognitively derived subgroups imply potential for multiple genes of small effect to confer susceptibility collectively, both to cognitive capacity and illness risk.⁶³

The specific finding of more pronounced rIFG volume loss in the ED group is consistent with findings of previous structural and functional imaging studies of working memory function;^{64,65} however, differential rIFG volume might also be more broadly relevant for modulating global cognitive and clinical features. In the current analysis, the ED subgroup demonstrated significant impairments across multiple cognitive measures, including general intelligence (IQ), immediate and delayed memory, language, attention and global functioning (Table 1). Previous evidence supports the association between volume of the inferior frontal regions and the regulation of cognitive control, attention and salience detection;^{66,67} notably, rIFG lesions are associated with impairments in cognitive control,⁶⁸ while positive associations between IFG morphometry and verbal cognitive function have also been reported in patients with psychosis⁶⁹ and healthy controls.⁶⁵ Complementary findings from functional imaging studies have frequently reported that heightened IFG activation during working memory tasks may reflect compensatory mechanisms among high-functioning patients performing the task equivalently to controls.^{70,71} The specific rIFG volume loss observed here may also contribute to the differential clinical profiles of these cross-disorder subtypes, as the ED patients demonstrate greater symptom severity across all domains of positive, negative and general symptoms and poorer global functioning. Previous studies have found associations between rIFG volume and severity of both positive^{72–74} and negative symptoms,⁷⁵ while a recent meta-analysis also identified that rIFG volume may differentiate high-risk individuals who transition to psychosis from those who do not transition.⁷⁶ Notably, an association has been reported between increasing age and reduced volume of the rIFG and superior temporal gyrus in a subsample of patients with schizophrenia who have prominent symptoms of paranoia.⁷⁷ This may have particular relevance to growing literature documenting an apparent “accelerated” aging trajec-

tory in several psychotic and mood disorders.^{78,79} Despite a statistical control for age in all analyses, it is possible that the significant age differences among the groups in the present study may also contribute to the observed results.

Limitations

Limitations of the present study include those inherent to structural imaging studies, particularly those using the voxel-based analysis technique, which relies on predominantly automated segmentation and labelling to identify key regions of significant group difference. Voxel-based analyses are useful as they provide an unbiased, whole brain comparison, but they are susceptible to normalization error and misregistration,⁸⁰ also limiting the accuracy of regional localization with relatively coarse atlas labelling. However, the present data analysis involved a nonlinear warp, which reduces reliance on global brain shape during registration and increases registration accuracy. In addition, these novel findings should be considered with caution given the relatively small size of the patient groups, who were recruited predominantly from outpatient sources. Future studies of larger samples, including inpatients, will be required to determine the generalizability of the present results. A further limitation lies in the restriction of included controls to only those whose performance exceeded the criterion of greater than 50% accuracy. This restriction was undertaken to ensure comparable performance accuracy between the ES and control groups. The small number of controls that exhibited poorer working memory function ($n = 8$, excluded from all analyses) was deemed insufficient to permit examination of an additional, control-deficit, comparison group.

In addition, these analyses have not assessed associations of brain volume with dosages of mood stabilizer medications, which were more frequently prescribed for the BD-I group (Table 2). All analyses have assessed the effects of both imipramine and chlorpromazine equivalent standardized doses on grey and white matter volumes; however, an equivalent standardized dose index is not available for mood stabilizers. Our participants were receiving a variety of agents, including lithium, valproate, carbamazepine and lamotrigine; lithium in particular has been associated previously with increased subcortical volume.⁸¹ However, in the present analysis, none of the clinical groups showed any significant increases of grey matter volume relative to the control group. Furthermore, a meta-analysis comparing treated and untreated first-episode patients with schizophrenia⁸² has suggested an effect of antipsychotic treatments on the grey matter volume of regions including the insula, medial and inferior frontal cortices, superior temporal gyrus, amygdala and precentral gyrus. In the present study, direct investigation of any correlative associations between imipramine and chlorpromazine mean doses and brain volumes did not identify significant associations. Importantly, the cognitively defined subgroups showed no differences in the frequency or dose of antipsychotics or antidepressants (Table 1).

Conclusion

The present findings of more pronounced volume loss in frontal cortices and hippocampal regions in a cross-disorder subtype of patients defined by severe working memory impairment, in concert with their greater functional disability and more severe symptomatology, highlights the utility of considering working memory ability as a “shared” intermediate phenotype for some patients with schizophrenia and BD-I. We have demonstrated neuroanatomical commonalities among patients with schizophrenia and BD-I with pronounced working memory deficits, while patients with spared working memory capacity showed less severe grey matter loss relative to controls; aberrations of rIFG volume may mediate some of the phenotypic differences among cognitively derived subtypes that span the traditional diagnostic categories of schizophrenia and BD.

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References

- Lichtenstein P, Yip BH, Björk C, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* 2009;373:234-9.
- Ivleva EI, Morris DW, Moates AF, et al. Genetics and intermediate phenotypes of the schizophrenia-bipolar disorder boundary. *Neurosci Biobehav Rev* 2010;34:897-921.
- Cross-Disorder Group of the Psychiatric Genomics Consortium. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet* 2013;45:984-94.
- Purcell SM, Wray NR, Stone JL, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 2009;460:748-52.
- Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. *Nat Genet* 2011;43:969-76.
- Insel T, Cuthbert B, Garvey M, et al. Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry* 2010;167:748-51.
- Buckholtz JW, Meyer-Lindenberg A. Psychopathology and the human connectome: toward a transdiagnostic model of risk for mental illness. *Neuron* 2012;74:990-1004.
- Bora E, Yucel M, Pantelis C. Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: meta-analytic study. *Br J Psychiatry* 2009;195:475-82.
- Ivleva EI, Morris DW, Osuji J, et al. Cognitive endophenotypes of psychosis within dimension and diagnosis. *Psychiatry Res* 2012;196:38-44.
- De Peri L, Crescini A, Deste G, et al. Brain structural abnormalities at the onset of schizophrenia and bipolar disorder: a meta-analysis of controlled magnetic resonance imaging studies. *Curr Pharm Des* 2012;18:486-94.
- Molina V, Galindo G, Cortés B, et al. Different gray matter patterns in chronic schizophrenia and chronic bipolar disorder patients identified using voxel-based morphometry. *Eur Arch Psychiatry Clin Neurosci* 2011;261:313-22.
- Rimol LM, Hartberg CB, Nesvag R, et al. Cortical Thickness and subcortical volumes in schizophrenia and bipolar disorder. *Biol Psychiatry* 2010;68:41-50.
- Quidé Y, Morris RW, Shepherd AM, et al. Task-related frontostriatal functional connectivity during working memory performance in schizophrenia. *Schizophr Res* 2013;150:468-75.
- Gur RE, Calkins ME, Gur RC, et al. The consortium on the genetics of schizophrenia: neurocognitive endophenotypes. *Schizophr Bull* 2007;33:49-68.
- Glahn DC, Almasy L, Barguil M, et al. Neurocognitive endophenotypes for bipolar disorder identified in multiplex multigenerational families. *Arch Gen Psychiatry* 2010;67:168-77.
- Krabbendam L, Arts B, van Os J, et al. Cognitive functioning in patients with schizophrenia and bipolar disorder: a quantitative review. *Schizophr Res* 2005;80:137-49.
- Glahn DC, Bearden CE, Cakir S, et al. Differential working memory impairment in bipolar disorder and schizophrenia: effects of lifetime history of psychosis. *Bipolar Disord* 2006;8:117-23.
- Glahn DC, Almasy L, Blangero J, et al. Adjudicating neurocognitive endophenotypes for schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 2007;144B:242-9.
- Goldberg TE, Egan MF, Gscheidle T, et al. Executive subprocesses in working memory: relationship to catechol-O-methyltransferase val158met genotype and schizophrenia. *Arch Gen Psychiatry* 2003;60:889-96.
- Egan MF, Goldberg TE, Kolachana BS, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A* 2001;98:6917-22.
- Badcock JC, Michie PT, Rock D. Spatial working memory and planning ability: contrasts between schizophrenia and bipolar I disorder. *Cortex* 2005;41:753-63.
- Vohringer PA, Barroilhet SA, Amerio A, et al. Cognitive impairment in bipolar disorder and schizophrenia: a systematic review. *Front Psychiatry* 2013;4:87. 4.

23. Bora E, Yucel M, Pantelis C. Cognitive impairment in schizophrenia and affective psychoses: implications for DSM-V criteria and beyond. *Schizophr Bull* 2010;36:36-42.
24. Simonsen C, Sundet K, Vaskinn A, et al. Neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders depends on history of psychosis rather than diagnostic group. *Schizophr Bull* 2011;37:73-83.
25. Cuthbert BN, Insel TR. Toward new approaches to psychotic disorders: the NIMH Research Domain Criteria project. *Schizophr Bull* 2010;36:1061-2.
26. Shepherd AM, Laurens KR, Matheson SL, et al. Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. *Neurosci Biobehav Rev* 2012;36:1342-56.
27. Strakowski SM, DelBello MP, Adler C. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Mol Psychiatry* 2005;10:105-16.
28. Callicott JH, Ramsey NF, Tallent K, et al. Functional magnetic resonance imaging brain mapping in psychiatry: methodological issues illustrated in a study of working memory in schizophrenia. *Neuropsychopharmacology* 1998;18:186-96.
29. Arnone D, Cavanagh J, Gerber D, et al. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. *Br J Psychiatry* 2009;195:194-201.
30. Ellison-Wright I, Bullmore E. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. *Schizophr Res* 2010;117:1-12.
31. Strakowski SM, Delbello M, Adler C. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Mol Psychiatry* 2005;10:105-16.
32. Bora E, et al. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophr Res* 2011;127:46-57.
33. Killgore W, Rosso IM, Gruber SA, et al. Amygdala volume and verbal memory performance in schizophrenia and bipolar disorder. *Cogn Behav Neurol* 2009;22:28-37.
34. Garlinghouse MA, Roth RM, Isquith PK, et al. Subjective rating of working memory is associated with frontal lobe volume in schizophrenia. *Schizophr Res* 2010;120:71-5.
35. Harms MP, Wang L, Csernansky JG, et al. Structure-function relationship of working memory activity with hippocampal and prefrontal cortex volumes. *Brain Struct Funct* 2013;218:173-86.
36. Hartberg CB, Sundet K, Rimol LM, et al. Brain cortical thickness and surface area correlates of neurocognitive performance in patients with schizophrenia, bipolar disorder, and healthy adults. *J Int Neuropsychol Soc* 2011;17:1080-93.
37. Hartberg CB, Sundet K, Rimol LM, et al. Subcortical brain volumes relate to neurocognition in schizophrenia and bipolar disorder and healthy controls. *Prog Neuropsychopharmacol Biol Psychiatry* 2011;35:1122-30.
38. Karlsgodt KH, van Erp TG, Poldrack RA, et al. Diffusion tensor imaging of the superior longitudinal fasciculus and working memory in recent-onset schizophrenia. *Biol Psychiatry* 2008;63:512-8.
39. Antonova E, Sharma T, Morris R, et al. The relationship between brain structure and neurocognition in schizophrenia: a selective review. *Schizophr Res* 2004;70:117-45.
40. Crespo-Facorro B, Barbadillo L, Pelayo-Terán JM, et al. Neuropsychological functioning and brain structure in schizophrenia. *Int Rev Psychiatry* 2007;19:325-36.
41. Cocchi L, Walterfang M, Testa R, et al. Grey and white matter abnormalities are associated with impaired spatial working memory ability in first-episode schizophrenia. *Schizophr Res* 2009;115:163-72.
42. McGuffin P, Farmer A. A polydiagnostic application of operational criteria in studies of psychotic illness: development and validation of the OPCRIT system. *Arch Gen Psychiatry* 1991;48:764-70.
43. Castle DJ, Jablensky A, McGrath JJ, et al. The diagnostic interview for psychoses (DIP): development, reliability and applications. *Psychol Med* 2006;36:69-80.
44. Loughland C, Draganic D, McCabe K, et al. Australian Schizophrenia Research Bank: a database of comprehensive clinical, endophenotypic and genetic data for aetiological studies of schizophrenia. *Aust N Z J Psychiatry* 2010;44:1029-35.
45. Mitchell PB, Johnston AK, Corry J, et al. Characteristics of bipolar disorder in an Australian specialist outpatient clinic: comparison across large datasets. *Aust N Z J Psychiatry* 2009;43:109-17.
46. Kay SR, Flszbein A, Opfer LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophr Bull* 1987;13:261-76.
47. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington (DC): The Association; 1994.
48. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;9:97-113.
49. Lovibond SH, Lovibond PF. *Manual for the Depression Anxiety Stress Scales*. 2nd edition. Sydney (AU): Psychology Foundation of Australia; 1995.
50. Wechsler D. Wechsler Abbreviated Scale of Intelligence (WASI). New York (NY): The Psychological Corporation; 1999.
51. Wechsler D. Wechsler Test of Adult Reading (WTAR). New York (NY): The Psychological Corporation; 2001.
52. Randolph C. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). San Antonio (TX): The Psychological Corporation; 1998.
53. Wechsler D. Wechsler Adult Intelligence Scales. 3rd edition. New York (NY): The Psychological Corporation; 1997.
54. Spreen O, Strauss E. *A compendium of neuropsychological tests: administration, norms, and commentary*. New York (NY): Oxford University Press; 1998.
55. Ivleva EI, Bidesi AS, Keshavan MS, et al. Gray matter volume as an intermediate phenotype for psychosis: bipolar-schizophrenia network on intermediate phenotypes (B-SNIP). *Am J Psychiatry* 2013;170:1285-96.
56. Bilder RM, Volavka J, Czobor P, et al. Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. *Biol Psychiatry* 2002;52:701-7.
57. Burdick KE, Funke B, Goldberg JF, et al. COMT genotype increases risk for bipolar I disorder and influences neurocognitive performance. *Bipolar Disord* 2007;9:370-6.
58. Carless MA, Glahn DC, Johnson MP, et al. Impact of DISC1 variation on neuroanatomical and neurocognitive phenotypes. *Mol Psychiatry* 2011;16:1096-104.
59. Lawrie SM, Hall J, McIntosh AM, et al. Neuroimaging and molecular genetics of schizophrenia: pathophysiological advances and therapeutic potential. *Br J Pharmacol* 2008;153(Suppl 1):S120-4.
60. Ohnishi T, Hashimoto R, Mori T, et al. The association between the Val158Met polymorphism of the catechol-O-methyl transferase gene and morphological abnormalities of the brain in chronic schizophrenia. *Brain* 2006;129:399-410.
61. Ehrlich S, Morrow EM, Roffman JL, et al. The COMT Val108/158Met polymorphism and medial temporal lobe volumetry in patients with schizophrenia and healthy adults. *Neuroimage* 2010;53:992-1000.
62. Callicott JH, Straub RE, Pezawas L, et al. Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. *Proc Natl Acad Sci U S A* 2005;102:8627-32.
63. Owen MJ, Craddock N, Jablensky A. The genetic deconstruction of psychosis. *Schizophr Bull* 2007;33:905-11.
64. Wager TD, Smith E. Neuroimaging studies of working memory: a meta-analysis. *Cogn Affect Behav Neurosci* 2003;3:255-74.
65. Antonova E, Kumari V, Morris R, et al. The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. *Biol Psychiatry* 2005;58:457-67.
66. Brass M, Derrfuss J, Forstmann B, et al. The role of the inferior frontal junction area in cognitive control. *Trends Cogn Sci* 2005;9:314-6.

67. Derrfuss J, Brass M, Neumann J, et al. Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. *Hum Brain Mapp* 2005;25:22-34.
68. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. *Trends Cogn Sci* 2004;8:170-7.
69. Ehrlich S, Brauns S, Yendiki A, et al. Associations of cortical thickness and cognition in patients with schizophrenia and healthy controls. *Schizophr Bull* 2012;38:1050-62.
70. Tan H-Y, Choo WC, Fones CS, et al. fMRI study of maintenance and manipulation processes within working memory in first-episode schizophrenia. *Am J Psychiatry* 2005;162:1849-58.
71. Townsend J, Bookheimer SY, Foland-Ross LC, et al. fMRI abnormalities in dorsolateral prefrontal cortex during a working memory task in manic, euthymic and depressed bipolar subjects. *Psychiatry Res* 2010;182:22-9.
72. Suga M, Yamasue H, Abe O, et al. Reduced gray matter volume of Brodmann's area 45 is associated with severe psychotic symptoms in patients with schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2010;260:465-73.
73. Iwashiro N, Suga M, Takano Y, et al. Localized gray matter volume reductions in the pars triangularis of the inferior frontal gyrus in individuals at clinical high-risk for psychosis and first episode for schizophrenia. *Schizophr Res* 2012;137:124-31.
74. Gaser C, Nenadic I, Volz HP, et al. Neuroanatomy of "hearing voices": a frontotemporal brain structural abnormality associated with auditory hallucinations in schizophrenia. *Cereb Cortex* 2004;14:91-6.
75. Bergé D, Carmona S, Rovira M, et al. Gray matter volume deficits and correlation with insight and negative symptoms in first-psychotic-episode subjects. *Acta Psychiatr Scand* 2011;123:431-9.
76. Fusar-Poli P, Borgwardt S, Crescini A, et al. Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. *Neurosci Biobehav Rev* 2011;35:1175-85.
77. Nenadic I, Sauer H, Smesny S, et al. Aging effects on regional brain structural changes in schizophrenia. *Schizophr Bull* 2012;38:838-44.
78. Kirkpatrick B, Messias E, Harvey PD, et al. Is schizophrenia a syndrome of accelerated aging? *Schizophr Bull* 2008;34:1024-32.
79. Koutsouleris N, Davatzikos C, Borgwardt S, et al. Accelerated brain aging in schizophrenia and beyond: a neuroanatomical marker of psychiatric disorders. *Schizophr Bull* 2013 Oct. 13 [Epub ahead of print].
80. Mechelli A, Price CJ, Friston KJ, et al. Voxel-based morphometry of the human brain: methods and applications. *Current Medical Imaging Reviews* 2005;1:105-13.
81. Hallahan B, Newell J, Soares JC, et al. Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. *Biol Psychiatry* 2011;69:326-35.
82. Leung M, Cheung C, Yu K, et al. Gray matter in first-episode schizophrenia before and after antipsychotic drug treatment. Anatomical likelihood estimation meta-analyses with sample size weighting. *Schizophr Bull* 2011;37:199-211.