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ORIGINAL ARTICLE

The effect of *COMT*, *BDNF*, *5-HTT*, *NRG1* and *DTNBP1* genes on hippocampal and lateral ventricular volume in psychosis

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Background. Morphometric endophenotypes which have been proposed for psychotic disorders include lateral ventricular enlargement and hippocampal volume reductions. Genetic epidemiological studies support an overlap between schizophrenia and bipolar disorder, and *COMT*, *BDNF*, *5-HTT*, *NRG1* and *DTNBP1* genes have been implicated in the aetiology of both these disorders. This study examined associations between these candidate genes and morphometric endophenotypes for psychosis.

Method. A total of 383 subjects (128 patients with psychosis, 194 of their unaffected relatives and 61 healthy controls) from the Maudsley Family Psychosis Study underwent structural magnetic resonance imaging and genotyping. The effect of candidate genes on brain morphometry was examined using linear regression models adjusting for clinical group, age, sex and correlations between members of the same family.

Results. The results showed no evidence of association between variation in *COMT* genotype and lateral ventricular, and left or right hippocampal volumes. Neither was there any effect of the *BDNF*, *5-HTTLPR*, *NRG1* and *DTNBP1* genotypes on these regional brain volumes.

Conclusions. Abnormal hippocampal and lateral ventricular volumes are among the most replicated endophenotypes for psychosis; however, the influences of *COMT*, *BDNF*, *5-HTT*, *NRG1* and *DTNBP1* genes on these key brain regions must be very subtle if at all present.

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Introduction

Endophenotypes are quantitative, heritable traits that are characteristic of a disorder, and are typically assessed by laboratory-based methods rather than clinical observation (Gottesman & Gould, 2003). They are likely to be useful in dissecting the pathophysiology of disorders with complex genetics and multi-factorial causal pathways such as schizophrenia and bipolar disorder (Wickham & Murray, 1997; Canon & Keller, 2006; Braff *et al*. 2007*b*).

Endophenotypes are presumed closer to genetic variation than are clinical symptoms of psychotic disorders, and include abnormalities of neurophysiology, cognitive function and brain morphometry (Braff *et al*. 2007*a*). Brain volume measurements show high heritability, with estimates ranging from 66% to 97% for overall brain size and 40% to 69% for the hippocampus (Peper *et al*. 2007), and therefore morphometric endophenotypes of psychosis have been proposed including hippocampal volume deficits and lateral ventricular enlargement (Seidman *et al*. 2002; McDonald *et al*. 2004, 2006). Although several studies have reported high heritability (79–85%) for lateral ventricular volume (Reveley *et al*. 1984; Pfefferbaum *et al*. 2000) and shape (Styner *et al*. 2005), some recent studies have also found evidence for common environmental effects on lateral ventricle volume in schizophrenia (Rijsdijk *et al*. 2005). Both increased lateral ventricular volume and reduced hippocampal volume are amongst the most robustly demonstrated structural deficits in psychosis (Lawrie & Abukmeil, 1998; Wright *et al*. 2000; Walterfang *et al*. 2006). These

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deficits are not only associated with the illness, but have also been consistently described in the unaffected relatives of patients, and they also co-segregate in families (Cannon, 2005; Styner *et al*. 2005; McDonald *et al*. 2006; Prasad & Keshavan, 2008). Studies have shown that lateral ventricular and hippocampal volumes tend to be stable over time and can be measured reliably and non-invasively in large samples, thus fulfilling the criteria for promising endophenotypes (Wood *et al*. 2001; Whitworth *et al*. 2005).

A range of genes involved in plasticity and cortical microcircuitry has been proposed to be implicated in the development of psychotic disorders (Harrison & Weinberger, 2005). Among such genes are those coding for catechol-*O*-methyl transferase (*COMT*) (Egan *et al*. 2001; Chen *et al*. 2004; Craddock *et al*. 2006; Riley & Kendler, 2006; Tunbridge *et al*. 2006) and brain-derived neurotrophic factor (*BDNF*) (Sklar *et al*. 2002; Neves-Pereira *et al*. 2005). *COMT* is considered to be a candidate gene for schizophrenia because of its role in the metabolic clearance of dopamine, and also because the region of chromosome 22q11.2 containing *COMT* is the location of a relatively common microdeletion called velocardiofacial syndrome, which is associated with very high rates of psychosis (Williams *et al*. 2007). Some but not all studies have implicated *BDNF* in the pathogenesis and morphological abnormalities of schizophrenia and bipolar disorder (Neves-Pereira *et al*. 2002; Rosa *et al*. 2006). Genes associated with neurodevelopment such as neuregulin (*NRG1*) and dysbindin (*DTNBP1*) have also been associated with both schizophrenia and bipolar disorder (Stefansson *et al*. 2002; Li *et al*. 2006; Burdick *et al*. 2007; Joo *et al*. 2007; Georgieva *et al*. 2008). These genes are believed to regulate different neurodevelopmental processes including neuronal and glial cell survival, proliferation, migration and differentiation (Law, 2003; Weickert *et al*. 2004; Kwon *et al*. 2005). A role for the serotonin transporter (*5-HTT*) gene has also been proposed (Mata *et al*. 2004; Cho *et al*. 2005; Dubertret *et al*. 2005; Mansour *et al*. 2005; Farmer *et al*. 2007), especially for the development of affective psychosis. In addition to acting as a neurotransmitter, serotonin is a regulator of brain development, which may influence neurogenesis, neuronal apoptosis, cell migration and synaptic plasticity, and *5-HTT* may also mediate brain abnormalities in psychosis (Seidman & Wencel, 2003).

The concept of a dichotomy of 'functional psychosis' between schizophrenia and bipolar disorder continues to form the basis for diagnostic and clinical practice. However, the pattern of findings from epidemiological and molecular genetic studies increasingly supports an overlap of genetic susceptibility for these illnesses (Bramon & Sham, 2001; Badner & Gershon, 2002; Cardno *et al*. 2002; Murray *et al*. 2004; Funke *et al*. 2005; Craddock *et al*. 2006; Rosa *et al*. 2006; Maier, 2008). Such notions are compatible with the arguments of Craddock & Owen (2007), highlighting the disadvantages of a dichotomous classification, and emphasising on 'rethinking psychosis'.

It remains unclear whether specific genetic polymorphisms, which have been putatively implicated in schizophrenic or affective psychoses, are associated with regional morphometric endophenotypes. Hence, in the present study we examined for associations between either lateral ventricular or hippocampal volumes and variation in the *COMT*, *BDNF*, *5-HTT*, *NRG1* and *DTNBP1* genes in a large sample of patients with psychosis, their unaffected first-degree relatives and healthy volunteers.

Method

Sample

A total of 383 subjects (128 patients with psychosis, 194 of their unaffected relatives and 61 unrelated healthy controls) of white European ethnicity who had undergone structural magnetic resonance imaging (MRI) scanning as part of the Maudsley Family Study of Psychosis were included. Patients and relatives were nationally recruited by requests to clinical teams and appeal through voluntary organizations. Controls were mainly recruited on their responses to advertisements in the local media. Subjects were excluded from the study if they had a diagnosis of alcohol or substance dependence in the last 12 months, neurological disorders, or head injury with loss of consciousness longer than a few min. This study has been described in detail elsewhere (Bramon *et al*. 2004). All participants were clinically interviewed with the Schedule for Affective Disorders and Schizophrenia Lifetime Version (Endicott & Spitzer, 1978) which was supplemented with information from case-notes and other relatives to assign or rule out a lifetime Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnosis. Although never psychotic, some of the relatives and controls had experienced Axis I disorders at some point in their lives.

Genotyping

DNA was obtained from all subjects and the rs4680 and the rs6265 single nucleotide polymorphisms (SNPs), which encode the *COMT* Val^{158}Met and the *BDNF* Val^{66}Met polymorphisms respectively, were genotyped by primer extension assay using SNuPe technology (Amersham International, UK). The methods have been described in detail elsewhere (Hoda *et al*. 1996; Dempster *et al*. 2005; Bramon *et al*. 2006). The 44-base pair (bp) insertion/deletion within the

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promoter region of the serotonin transporter gene (*5-HTTLPR*) was amplified by standard polymerase chain reaction (PCR) with primers described in Gelernter *et al*. (1997) and short and long alleles for each participant were identified under UV light after electrophoretic separation in a 3% agarose gel. As defined by Stefansson *et al*. (2002, 2003), the core neuregulin-1 (*NRG1*) at-risk haplotype consists of one single nucleotide polymorphism marker (SNP8NGR22153) and two microsatellites (478 B14-848 and 420 M9-1395). As described in Williams *et al*. (2003), SNP8NRG221533 was genotyped using the primer extension SNuPe and the genotyping platform Megabace (Amersham Biosciences, UK), and the microsatellites were genotyped using a fluorescently labelled primer PCR assay, and were analysed by the ABI 3100 genetic analyser (Applied Biosystems, USA). The single nucleotide polymorphisms, dysbindin-P1578 (rs1018381) and dysbindin-P1325 (rs1011313) as described in Breen *et al*. (2006), were genotyped using KBiosciences (http://www.kbioscience.co.uk), with a competitive allele-specific PCR system.

Structural MRI

1.5-mm-thick contiguous coronal T1-weighted three-dimensional spoiled gradient recall echo sequence MRI images covering the entire brain were acquired on a 1.5 T GE Signa System Scanner (General Electric, USA) using one of the following protocols: repetition time (TR) = 13.1 ms; inversion time (TI) = 450 ms; echo time (TE) = 5.8 ms; number of excitations = 1; flip angle = 20°; acquisition matrix = 256 × 256 × 128 or TR = 35 ms, TE = 5 ms, number of excitations = 1, flip angle = 30°, acquisition matrix = 256 × 256 × 128. Each MRI was rated blind to group affiliation and the acquired images were analysed using MEASURE (Johns Hopkins University, USA), an image analysis program that uses stereologically unbiased estimation of volume (Frangou *et al*. 1997). Before making any measurements, head tilt was corrected by aligning each brain along the anterior commissure–posterior commissure axis in the sagittal plane and along the interhemispheric fissure in the coronal and axial planes. These methods have been described in detail elsewhere (McDonald *et al*. 2002, 2006; Schulze *et al*. 2003). Measurements of left hippocampal volume, right hippocampal volume and total lateral ventricular volume were included in the analysis.

Analysis

The effect of candidate genes on brain morphometry was examined using linear mixed models fitted with maximum likelihood methods. Correlations between members of the same family were accounted for by including random intercepts for families, which is needed to maintain correct type 1 error rates. Total lateral ventricular volume, and left and right hippocampal volumes were the dependent variables, and genotypes of *COMT*, *BDNF*, *5-HTT*, *DTNBP1* and *NRG1* were the main independent variables. In addition, all analyses were adjusted by the fixed effects of clinical group (patient, relative or control), age and sex. The statistical software packages used were Stata version 9 (StataCorp LP, USA) and SPSS version 15 for Microsoft Windows (SPSS Inc., USA).

Results

The sample included 128 patients with a psychotic disorder, 194 of their unaffected relatives and 61 unrelated healthy controls. Relatives consisted of 74 siblings, 104 parents, 15 offspring and one nephew of individuals with psychosis. A diagnostic breakdown and demographic characteristics are provided in Table 1. There was a significant sex difference between the subgroups, with a higher proportion of males amongst patients compared with the controls [$\chi^2(1) = 5.60$, $p = 0.02$]. However, relatives and controls were well matched in sex [$\chi^2(1) = 0.33$, $p = 0.57$]. Patients and controls were dissimilar in their mean ages [$t = 2.16$, 95% confidence interval (CI) = 0.37 to 8.89, $p = 0.03$], and the relatives were significantly older than the controls ($t = -3.39$, 95% CI = –11.7 to −3.1, $p = 0.001$) and the patients ($t = 8.56$, 95% CI = 9.27–14.79, $p < 0.001$). Dissimilarities in age were predictable given the study design because the relatives often included parents who were considerably older than the probands. As in previous studies on endophenotypes all analyses were adjusted by age and sex (McDonald *et al*. 2006).

Genotype frequencies for patients [*COMT*: $\chi^2(1) = 0.37$, $p = 0.54$; *BDNF*: $\chi^2(1) = 0.71$, $p = 0.39$; *5-HTTLPR*: $\chi^2(1) = 1.08$, $p = 0.29$; *NRG1*: $\chi^2(1) = 1.92$, $p = 0.17$; dysbindin-P1578: $\chi^2(1) = 0.01$, $p = 0.92$; dysbindin-P1325: $\chi^2(1) = 0.67$, $p = 0.41$], relatives [*COMT*: $\chi^2(1) = 0.88$, $p = 0.35$; *BDNF*: $\chi^2(1) = 1.47$, $p = 0.23$; *5-HTTLPR*: $\chi^2(1) = 0.82$, $p = 0.37$; *NRG1*: $\chi^2(1) = 0.43$, $p = 0.51$; dysbindin-P1578: $\chi^2(1) = 0.11$, $p = 0.74$; dysbindin-P1325: $\chi^2(1) = 0.41$, $p = 0.52$] and controls [*COMT*: $\chi^2(1) = 3.81$, $p = 0.051$; *BDNF*: $\chi^2(1) = 0.26$, $p = 0.61$; *5-HTTLPR*: $\chi^2(1) = 0.01$, $p = 0.92$; *NRG1*: $\chi^2(1) = 0.64$, $p = 0.42$; dysbindin-P1578: $\chi^2(1) = 0.23$, $p = 0.63$; dysbindin-P1325: $\chi^2(1) = 0.9$, $p = 0.34$] did not deviate from the Hardy–Weinberg equilibrium. Tables 2, 3 and 4 give a description of the distribution of the genotypes against mean morphometric measures.

There was no association between variation in the *COMT* genotype and lateral ventricular, left hippocampal or right hippocampal volumes. Neither did we

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Table 1. *Demographic and clinical characteristics of the sample*

	Patients	Relatives	Controls
Subjects, *n*	128	194	61
Male, *n* (%)	82 (64)	81 (42)	28 (46)
Mean age, years (S.D.)	36.16 (10.38)	48.19 (14.81)	40.79 (15.12)
Age range, years	17–70	16–78	19–77
Handedness Right, *n* (%)	113 (88)	166 (86)	56 (92)
DSM-IV diagnosis, *n*	Schizophrenia (83) Psychotic bipolar disorder (36) Schizo-affective disorder (7) Psychotic disorder NOS (2)	No illness (151) Major depressive disorder without psychosis (36) Panic disorder (4) Social phobia (1) Bulimia nervosa (1) Dysthymia (1)	No illness (57) Major depressive disorder without psychosis (4)

S.D., Standard deviation; DSM, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; NOS, not otherwise specified.

observe any effect of the *BDNF* or *5-HTTLPR* or *DTNBP1* or *NRG1* genotypes on these regional brain volumes. Because of multiple testing in our analysis, significance was adjusted at $p<0.01$. Detailed results are displayed in Table 5.

In order to ensure that combining the diagnoses of schizophrenia and bipolar disorder did not obscure an effect on the individual illness, we repeated the linear regression analysis separately for the two diagnoses (adjusting for the confounders as previously stated). Again, we found no evidence of association between the key candidate genes and endophenotypes. We also carried out further analysis, excluding all DSM-IV non-psychotic Axis I diagnoses from the relatives and controls group to rule out any possible obscurity of findings because of heterogeneity of diagnoses in the sample. Even then we did not find any evidence of association between the genes and morphometry. When compared with the controls, the patients and relatives in this sample showed significant deficits in ventricular and hippocampal volumes; these have been reported in detail by McDonald *et al*. (2006).

Discussion

We found no associations between variation in five candidate genes for psychotic illness and measurements of lateral ventricular and hippocampal volumes in a large sample of patients with psychotic disorders, their relatives and controls.

Several previous studies have suggested that polymorphisms within the *COMT* and the *BDNF* genes might contribute to morphological abnormalities in psychosis (Szeszko *et al*. 2005; Agartz *et al*. 2006; Ho *et al*. 2006, 2007; Lawrie *et al*. 2008). Lawrie *et al*. (2008) reported that subjects with a *COMT* Val allele had reduced grey matter density in the anterior cingulate cortex. Some smaller studies (Ohnishi *et al*. 2006; Crespo-Facorro *et al*. 2007) have claimed that variation in the *COMT* Val^{158}Met genotype is associated with changes in volumes of several regions such as reductions of the limbic, paralimbic and neocortical areas and enlargement of the lateral ventricles in both acute and chronic psychoses. Taylor *et al*. (2007) reported an association between *COMT* Val^{158} homozygote individuals and reduction of hippocampal volumes in a sample of 31 healthy individuals. Ho *et al*. (2007) in their study on 119 patients with 'recent-onset schizophrenia spectrum disorders' measured changes in brain volumes over an average of 3 years, and concluded that the *BDNF* Met^{66} variant may be one of several factors affecting progressive brain volume changes in schizophrenia. Of the brain structures measured were the lateral ventricles, which were found to be increased in Met^{66} allele carriers when compared with Val^{66} homozygous patients. Ho *et al*. (2006) reported that *BDNF* Met^{66} allele carriers had smaller temporal lobe volumes when they looked at 80 healthy controls and 183 patients with 'schizophrenia spectrum disorder'. Gruber *et al*. (2008) in their study on 30 patients with schizophrenia and 52 non-affected family members found that the *NRG1* haplotype HAP_{ICE} was associated with lower hippocampal volumes in patients and family members. Mata *et al*. (2009) also demonstrated in a sample of 95 subjects that a variant of the *NRG1* gene contributed to lateral ventricular enlargement in the early stages of schizophrenia. To the best of our knowledge, no studies have found significant associations between these regional brain volumes and variations in *DTNBP1* genes or

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Table 2. *Distribution of* COMT, BDNF *and* 5-HTTLPR *genotypes* versus *regional brain volumes*

	Lateral ventricles			Hippocampus				
	n	Mean lateral ventricular volume, ml (S.D.)		*n*	Mean left hippocampal volume, ml (S.D.)		Mean right hippocampal volume, ml (S.D.)	
COMT								
Patients								
Met/Met	36	18.95	(7.73)	36	2.40	(0.40)	2.48	(0.36)
Val/Met	61	20.27	(10.10)	61	2.41	(0.35)	2.48	(0.33)
Val/Val	32	20.80	(12.49)	32	2.42	(0.37)	2.46	(0.34)
Relatives								
Met/Met	53	20.56	(13.38)	53	2.42	(0.37)	2.44	(0.36)
Val/Met	88	19.30	(11.97)	88	2.47	(0.40)	2.47	(0.39)
Val/Val	48	18.88	(7.66)	47	2.43	(0.42)	2.49	(0.35)
Controls								
Met/Met	18	15.22	(6.47)	18	2.49	(0.34)	2.54	(0.33)
Val/Met	22	14.91	(8.08)	21	2.43	(0.23)	2.56	(0.22)
Val/Val	19	21.51	(17.42)	19	2.43	(0.31)	2.54	(0.33)
Total								
Met/Met	107	19.12	(10.86)	107	2.43	(0.37)	2.47	(0.35)
Val/Met	171	19.08	(10.96)	170	2.44	(0.37)	2.48	(0.36)
Val/Val	99	20.01	(11.59)	98	2.43	(0.38)	2.49	(0.34)
COMT total	377	19.34	(11.08)	375	2.43	(0.37)	2.48	(0.35)
BDNF[a]								
Patients								
Val/Val	89	18.55	(7.50)	89	2.44	(0.38)	2.48	(0.34)
Val/Met + Met/Met	39	22.67	(14.43)	39	2.39	(0.32)	2.48	(0.34)
Relatives								
Val/Val	136	19.11	(11.39)	135	2.43	(0.39)	2.46	(0.36)
Val/Met + Met/Met	58	20.45	(11.21)	58	2.48	(0.42)	2.47	(0.42)
Controls								
Val/Val	44	16.01	(10.02)	43	2.48	(0.30)	2.56	(0.28)
Val/Met + Met/Met	17	19.97	(15.12)	17	2.38	(0.26)	2.52	(0.31)
Total								
Val/Val	269	18.42	(10.06)	267	2.44	(0.37)	2.48	(0.34)
Val/Met + Met/Met	114	21.14	(12.92)	114	2.43	(0.37)	2.48	(0.37)
BDNF total	383	19.23	(11.04)	381	2.44	(0.37)	2.48	(0.35)
5-HTTLPR								
Patients								
S/S	17	19.92	(9.46)	17	2.57	(0.28)	2.54	(0.28)
S/L	43	19.41	(10.51)	43	2.55	(0.36)	2.59	(0.32)
L/L	42	20.77	(10.42)	42	2.41	(0.31)	2.53	(0.29)
Relatives								
S/S	26	18.41	(9.09)	26	2.48	(0.40)	2.46	(0.38)
S/L	66	19.87	(13.34)	66	2.53	(0.37)	2.52	(0.37)
L/L	57	21.41	(11.92)	56	2.56	(0.37)	2.57	(0.36)
Controls								
S/S	13	19.32	(15.69)	13	2.44	(0.17)	2.51	(0.15)
S/L	28	17.35	(10.39)	28	2.43	(0.32)	2.53	(0.29)
L/L	16	16.20	(11.60)	16	2.60	(0.25)	2.72	(0.27)
Total								
S/S	56	19.08	(10.85)	56	2.50	(0.32)	2.50	(0.31)
S/L	137	19.21	(11.90)	137	2.52	(0.36)	2.54	(0.34)
L/L	115	20.45	(11.38)	114	2.51	(0.34)	2.57	(0.33)
5-HTTLPR total	308	(19.65)	(11.50)	307	2.51	(0.34)	2.55	(0.33)

S.D., Standard deviation; *COMT*, catechol-*O*-methyl transferase; *BDNF*, brain-derived neurotrophic factor; *5-HTTLPR*, serotonin transporter promoter region; Met, methionine; Val, valine; S, short; L, long.

[a] *BDNF* (Val^{66}/Met^{66} and Met^{66}/Met^{66}) was collapsed under single headings because of the relatively few numbers of Met^{66}/Met^{66} in our sample.

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Table 3. *Distribution of dysbindin SNPs* versus *regional brain volumes*

	Lateral ventricles			Hippocampus				
	n	Mean lateral ventricular volume, ml (S.D.)		*n*	Mean left hippocampal volume, ml (S.D.)		Mean right hippocampal volume, ml (S.D.)	
Dysbindin-P1578[a]								
Patients								
C/C	101	19.49	(10.74)	101	2.42	(0.36)	2.49	(0.33)
C/T+T/T	22	20.31	(8.14)	22	2.51	(0.33)	2.55	(0.32)
Relatives								
C/C	146	18.98	(11.24)	146	2.44	(0.38)	2.46	(0.36)
C/T+T/T	32	21.59	(12.74)	31	2.54	(0.46)	2.52	(0.42)
Controls								
C/C	52	17.72	(12.42)	51	2.45	(0.30)	2.55	(0.29)
C/T+T/T	7	14.69	(4.62)	7	2.53	(0.29)	2.66	(0.20)
Total								
C/C	299	18.93	(11.27)	298	2.43	(0.36)	2.49	(0.34)
C/T+T/T	61	20.34	(10.66)	60	2.53	(0.39)	2.55	(0.37)
Dysbindin-P1578 total	360	19.17	(11.17)	358	2.45	(0.37)	2.50	(0.35)
Dysbindin-P1325[a]								
Patients								
G/G	108	20.11	(10.49)	108	2.43	(0.34)	2.49	(0.33)
G/A+A/A	17	16.38	(7.80)	17	2.45	(0.45)	2.52	(0.39)
Relatives								
G/G	148	19.67	(11.64)	147	2.43	(0.41)	2.45	(0.38)
G/A+A/A	35	19.84	(10.75)	35	2.51	(0.36)	2.52	(0.34)
Controls								
G/G	49	16.71	(10.57)	48	2.47	(0.29)	2.56	(0.30)
G/A+A/A	9	21.14	(17.82)	9	2.42	(0.32)	2.52	(0.23)
Total								
G/G	305	19.35	(11.10)	303	2.43	(0.37)	2.48	(0.35)
G/A+A/A	61	19.07	(11.28)	61	2.48	(0.38)	2.52	(0.34)
Dysbindin-P1325 total	366	19.30	(11.12)	364	2.44	(0.37)	2.49	(0.35)

SNPs, Single nucleotide polymorphisms; S.D., standard deviation.

[a] Dysbindin-P1578 (C/T and T/T) and dysbindin-P1325 (G/A and A/A) genotypes were collapsed under single headings because of the relatively few numbers of T/T and A/A genotypes in the sample.

5-HTTLPR insertion/deletion polymorphisms in psychotic disorders.

We combined patient, relatives and control groups in our study in order to maximize statistical power. The rationale for combining the traditional diagnoses of psychosis in our study has already been explained (Murray *et al*. 2004; Craddock & Owen, 2007). In our subjects, the psychoses group was pragmatic in that it consisted of a combination of schizophrenia and bipolar disorder with a history of psychotic symptoms, mostly from multiply affected families and relatively stable in symptomatology at the time of assessment.

Volumetric abnormalities are often seen at the time of illness onset (Morgan *et al*. 2007) of both bipolar disorder and schizophrenia but there are conflicting views about the time of onset of such changes, as some structures such as hippocampal volumes have been suggested to be the result of non-illness-specific events such as obstetric complications or transition to psychosis (Stefanis *et al*. 1999; Wood *et al*. 2008). A meta-analysis comparing first-episode psychosis with healthy controls has shown evidence of decreased hippocampal volumes and enlarged lateral ventricles (Steen *et al*. 2006). These abnormalities have been demonstrated in never-medicated '1st episode schizophrenia' patients (Chua *et al*. 2007), but it has been suggested that although most deficits in schizophrenia are found at symptom onset, some may become more pronounced with illness progression (Kumari &

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Table 4. *Distribution of* NRG1 *haplotype* versus *regional brain volumes*

	Lateral ventricles			Hippocampus				
	n	Mean lateral ventricular volume, ml (S.D.)		*n*	Mean left hippocampal volume, ml (S.D.)		Mean right hippocampal volume, ml (S.D.)	
NRG1								
Patients								
C/C	19	21.92	(10.95)	19	2.31	(0.28)	2.39	(0.26)
C/T	66	19.59	(11.35)	66	2.44	(0.39)	2.51	(0.34)
T/T	33	19.45	(8.23)	33	2.46	(0.30)	2.48	(0.35)
Relatives								
C/C	26	19.74	(11.06)	26	2.49	(0.34)	2.51	(0.32)
C/T	86	18.43	(9.02)	86	2.47	(0.40)	2.47	(0.37)
T/T	58	21.69	(14.92)	57	2.49	(0.39)	2.50	(0.39)
Controls								
C/C	11	12.76	(8.13)	11	2.65	(0.27)	2.71	(0.26)
C/T	21	16.02	(8.51)	21	2.49	(0.27)	2.58	(0.29)
T/T	16	18.72	(14.55)	16	2.32	(0.26)	2.44	(0.21)
Total								
C/C	56	19.11	(10.86)	56	2.46	(0.33)	2.51	(0.31)
C/T	173	18.58	(9.93)	173	2.46	(0.38)	2.50	(0.35)
T/T	107	20.55	(13.10)	106	2.46	(0.35)	2.48	(0.35)
NRG1 total	336	19.30	(11.18)	335	2.46	(0.36)	2.50	(0.34)
***NRG1*microsatellite 478 B14-848**[a]								
Patients								
No 216	66	20.37	(10.34)	66	2.44	(0.35)	2.49	(0.31)
One 216	46	19.35	(10.73)	46	2.40	(0.39)	2.47	(0.37)
Two 216	12	17.93	(9.01)	12	2.43	(0.36)	2.51	(0.35)
Relatives								
No 216	86	19.23	(10.85)	86	2.47	(0.41)	2.50	(0.41)
One 216	77	20.82	(12.91)	76	2.43	(0.40)	2.43	(0.34)
Two 216	18	16.90	(7.07)	18	2.33	(0.35)	2.39	(0.33)
Controls								
No 216	25	16.44	(13.72)	25	2.46	(0.29)	2.52	(0.21)
One 216	19	16.11	(7.10)	19	2.49	(0.28)	2.59	(0.29)
Two 216	11	16.11	(5.94)	11	2.45	(0.35)	2.62	(0.40)
Total								
No 216	177	19.26	(11.12)	177	2.46	(0.37)	2.50	(0.35)
One 216	142	19.72	(11.64)	141	2.43	(0.38)	2.47	(0.35)
Two 216	41	16.99	(7.27)	41	2.39	(0.35)	2.48	(0.36)
NRG1 microsatellite 478 B14-848 total	360	19.18	(10.97)	359	2.44	(0.37)	2.49	(0.35)
***NRG1* microsatellite 420 M9-1395**[a]								
Patients								
No 319	44	18.71	(8.75)	44	2.41	(0.33)	2.45	(0.31)
One 319	57	20.23	(11.44)	57	2.49	(0.37)	2.55	(0.34)
Two 319	21	20.43	(10.82)	21	2.29	(0.37)	2.43	(0.34)
Relatives								
No 319	62	18.30	(9.32)	61	2.46	(0.41)	2.45	(0.38)
One 319	86	20.76	(13.17)	86	2.45	(0.41)	2.49	(0.39)
Two 319	30	20.09	(10.74)	30	2.40	(0.37)	2.41	(0.32)
Controls								
No 319	14	18.57	(17.13)	14	2.44	(0.33)	2.55	(0.23)
One 319	25	15.89	(7.56)	25	2.48	(0.28)	2.54	(0.23)
Two 319	15	14.85	(5.87)	15	2.50	(0.31)	2.64	(0.38)

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Table 4 (*cont.*)

	Lateral ventricles			Hippocampus				
	n	Mean lateral ventricular volume, ml (S.D.)		*n*	Mean left hippocampal volume, ml (S.D.)		Mean right hippocampal volume, ml (S.D.)	
Total								
No 319	120	18.48	(10.21)	119	2.44	(0.37)	2.47	(0.34)
One 319	168	19.86	(11.97)	168	2.47	(0.38)	2.52	(0.35)
Two 319	66	19.01	(10.01)	66	2.39	(0.36)	2.47	(0.35)
NRG1 microsatellite 420 M9-1395 total	354	19.23	(11.03)	353	2.44	(0.37)	2.49	(0.35)

NRG1, Neuregulin-1; S.D., standard deviation.

[a] For the first microsatellite, the 216 base-pair (bp) product was the allele conveying risk, and individuals were coded as alleles with no risk (no 216 bp) or alleles with risk (one or two copies of 216 bp). Accordingly, the subjects were coded on the number of copies of the 216 bp they inherited. The same principle was applied to the second microsatellite, for which the 319 bp product was the allele conveying risk.

Cooke, 2006). However, these psychotic disorders are largely considered to be neurodevelopmental in origin, although there have been some suggestions that there may be progressive neurodegenerative pathology (Lieberman, 1999; Halliday, 2001; Church *et al*. 2002; Malaspina, 2006; DeLisi, 2008). The effects of medication, particularly anti-psychotics, on brain volumes have generated much interest but results so far have neither been fully conclusive nor consistent (Chakos *et al*. 2005; Lieberman *et al*. 2005; Massana *et al*. 2005; Scherk & Falkai, 2006; Molina *et al*. 2007). Hence, the underlying assumption with regards to our design and sample characteristics was that any regional brain changes in our medicated psychoses group would have already manifested at the time of assessment. Most of the unaffected relatives had lived through the major risk period of psychosis. The younger relatives accounted for a very small fraction of this group, and any brain abnormalities in these hypothetically at-risk subjects on a future pathway to psychosis were unlikely to alter the overall results. One of the main advantages of this study was that it examined variation in relatives and controls as well as patients, thus including participants in whom illness and medication could not account for brain structural variation.

Although lateral ventricular enlargement and hippocampal volume deficits are amongst the relatively common and consistent deficits in schizophrenia, other structures are also consistently involved, such as prefrontal and superior temporal grey matter loss (Shenton *et al*. 2001). Lateral ventricular and hippocampal abnormalities are reported in both affective and non-affective psychotic disorders. Meta-analysis and individual studies of regional morphometry have shown lateral ventricular enlargement and hippocampal volume reductions in bipolar disorders (McDonald *et al*. 2004; Hajek *et al*. 2005; Strasser *et al*. 2005; Bearden *et al*. 2008; Kempton *et al*. 2008). We failed to find gene–morphometry associations even within Kraepelinian distinctions and, increasingly, recent studies suggest that the phenotypic classifications are arbitrary distinctions that have been forced on a continuum of risk factors, neurobiology and course of illness (Boks *et al*. 2007; Dutta *et al*. 2007; Peralta & Cuesta, 2007). Our study, which was constructed on the basis of current concepts of genetic overlap and shared biological deficits across a heterogeneous psychoses phenotype, also has its limitations. In spite of growing arguments in favour of shared symptomatology, shared genes and shared structural deficits in the brain, there are dissimilarities between schizophrenia and bipolar disorders. In comparison with non-affective psychotic disorders, structural changes in affective disorders are believed to be less pronounced (Wang & Ketter, 2000), hence associations between structural deficits in the brain and affective disorders tend to be less consistent. In spite of the common genetic basis across the psychotic spectrum, the aetiology of schizophrenia is believed to differ from affective disorders on aspects of environmental factors, neurodevelopment and neurobiological progression (Ketter *et al*. 2004). Hence, it is possible that phenotypic heterogeneity may potentially dilute gene–morphometry associations, which would further constrict the notion of finding consistent levels of identical morphometric abnormalities across these disorders.

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Table 5. *Association between key genotypes and morphometric endophenotypes*

	Estimated mean difference, ml (95% CI)		p^a
***COMT* Val^{158}Met SNP**			
Total lateral ventricular volume			
Met/Met *versus*			
Val/Met	0.15	(−2.37 to 2.68)	0.91
Val/Val	1.43	(−1.52 to 4.39)	0.34
Left hippocampal volume			
Met/Met *versus*			
Val/Met	0.01	(−0.07 to 0.09)	0.89
Val/Val	0.03	(−0.07 to 0.13)	0.58
Right hippocampal volume			
Met/Met *versus*			
Val/Met	0.001	(−0.08 to 0.08)	0.99
Val/Val	0.04	(−0.06 to 0.13)	0.43
***BDNF* Val^{66} Met SNP**			
Total lateral ventricular volume			
Val/Val *versus* Val/Met + Met/Met	1.25	(−1.00 to 3.50)	0.28
Left hippocampal volume			
Val/Val *versus* Val/Met + Met/Met	0.03	(−0.05 to 0.10)	0.46
Right hippocampal volume			
Val/Val *versus* Val/Met + Met/Met	0.03	(−0.04 to 0.10)	0.45
***5-HTTLPR* 44 base pair insertion/deletion polymorphism**			
Total lateral ventricular volume			
S/S *versus*			
S/L	−0.27	(−3.40 to 2.86)	0.87
L/L	−0.84	(−4.37 to 2.69)	0.64
Left hippocampal volume			
S/S *versus*			
S/L	0.004	(−0.09 to 0.10)	0.93
L/L	0.02	(−0.09 to 0.13)	0.68
Right hippocampal volume			
S/S *versus*			
S/L	0.03	(−0.06 to 0.12)	0.56
L/L	0.07	(−0.03 to 0.17)	0.16
***NRG1* C/T SNP**			
Total lateral ventricular volume			
TT *versus*			
C/T	−2.62	(−5.11 to −0.13)	0.04
C/C	−0.85	(−4.22 to 2.52)	0.62
Left hippocampal volume			
TT *versus*			
C/T	−0.003	(−0.09 to 0.08)	0.94
C/C	0.06	(−0.06 to 0.17)	0.33
Right hippocampal volume			
TT *versus*			
C/T	−0.01	(−0.08 to 0.07)	0.88
C/C	0.05	(−0.05 to 0.16)	0.34
***NRG1* microsatellite 478 B14-848 (at-risk allele 216)**			
Total lateral ventricular volume			
No copy of 216 *versus*			
One copy of 216	0.06	(−2.16 to 2.28)	0.96
Two copies of 216	−2.19	(−5.82 to 1.44)	0.24

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Table 5 (*cont.*)

	Estimated mean difference, ml (95% CI)		p^a
Left hippocampal volume			
No copy of 216 *versus*			
One copy of 216	−0.08	(−0.15 to −0.003)	0.04
Two copies of 216	−0.04	(−0.16 to 0.08)	0.53
Right hippocampal volume			
No copy of 216 *versus*			
One copy of 216	−0.05	(−0.12 to 0.02)	0.15
Two copies of 216	−0.01	(−0.13 to 0.11)	0.88
***NRG1* microsatellite 420 M9-1395 (at-risk allele 319)**			
Total lateral ventricular volume			
No copy of 319 *versus*			
One copy of 319	0.68	(−1.75 to 3.10)	0.59
Two copies of 319	−0.87	(−4.15 to 2.42)	0.61
Left hippocampal volume			
No copy of 319 *versus*			
One copy of 319	−0.06	(−0.14 to 0.02)	0.17
Two copies of 319	−0.11	(−0.22 to 0.004)	0.06
Right hippocampal volume			
No copy of 319 *versus*			
One copy of 319	−0.002	(−0.08 to 0.07)	0.96
Two copies of 319	−0.06	(−0.17 to 0.04)	0.24
Dysbindin-P1578 C/T SNP			
Total lateral ventricular volume			
C/C *versus* C/T+T/T	0.002	(−2.99 to 2.99)	0.99
Left hippocampal volume			
C/C *versus* C/T+T/T	0.03	(−0.07 to 0.13)	0.55
Right hippocampal volume			
C/C *versus* C/T+T/T	0.001	(−0.09 to 0.09)	0.98
Dysbindin-P1325 G/A SNP			
Total lateral ventricular volume			
G/G *versus* G/A+A/A	−0.09	(−3.12 to 2.93)	0.95
Left hippocampal volume			
G/G *versus* G/A+A/A	0.01	(−0.09 to 0.11)	0.85
Right hippocampal volume			
G/G *versus* G/A+A/A	0.02	(−0.08 to 0.11)	0.69

CI, Confidence interval; *COMT*, catechol-*O*-methyl transferase; Val, valine; Met, methionine; SNP, single nucleotide polymorphism; *BDNF*, brain-derived neurotrophic factor; *5-HTTLPR*, serotonin transporter promoter region; S, short; L, long; *NRG1*, neuregulin-1.

[a] Because of multiple testing, significance was set at the threshold of $p < 0.01$.

Candidate genes for psychosis have very modest to modest associations with clinical phenotypes, and sample sizes numbering in thousands would be needed to replicate results (Fan & Sklar, 2005; Li *et al*. 2006; Sand *et al*. 2006; Kanazawa *et al*. 2007; Shi *et al*. 2008). Hence, our study with a total of 383 individuals does not have the statistical power to replicate direct association between genes and clinical diagnoses. However, one of the advantages of an endophenotype approach is that fewer subject numbers are usually required to observe for significant associations between genotypes and intermediate phenotypes in comparison with studies on direct associations between candidate genes and clinical phenotypes. Based on several studies (Ho *et al*. 2006; Crespo-Facorro *et al*. 2007; Taylor *et al*. 2007; Mata *et al*. 2009) the influence of candidate genes on regional brain volumes has very modest to moderate effect sizes. In comparison with the existing literature, our study is relatively large and it has sufficient statistical power to detect similar effects of genes on regional brain volumes.

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It is plausible that individual genes alone do not and cannot predict regional volumetric changes, and that other distinct neurodevelopmental processes, which might be more specific for individual disorders, work in tandem to affect outcomes in brain structures (Dean *et al*. 2003; Murray *et al*. 2004; Broome *et al*. 2005; Isohanni *et al*. 2005). There is a large body of evidence demonstrating the inconsistency of associations between polymorphisms in *COMT*, *BDNF*, *5-HTT*, *NRG1* and *DTNBP1* genes and psychotic disorders in samples across the globe (Saleem *et al*. 2000; Munafò *et al*. 2005; Williams *et al*. 2005; Ikeda *et al*. 2006, 2008; Joo *et al*. 2006; Prata *et al*. 2006; Kanazawa *et al*. 2007; Nunokawa *et al*. 2007; Martorell *et al*. 2008; Sanders *et al*. 2008). In this context, our failure to replicate an association between these candidate genes and morphometric endophenotypes for psychosis is not so surprising.

In conclusion, abnormalities in hippocampal and lateral ventricular volumes are among the most replicated endophenotypes for psychosis but we believe that the influences of *COMT*, *BDNF*, *5-HTT*, *NRG1* and *DTNBP1* genes on these key brain regions must be very subtle if at all present. Psychosis endophenotypes are likely to be polygenic traits themselves and we would argue in favour of more extensive genotyping, ideally genome-wide association, to investigate their genetic basis.

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Declaration of Interest

None.

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