

## Original Article

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# Associations between psychosis endophenotypes across brain functional, structural, and cognitive domains

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**Abstract**

**Background.** A range of endophenotypes characterise psychosis, however there has been limited work understanding if and how they are inter-related.

**Methods.** This multi-centre study includes 8754 participants: 2212 people with a psychotic disorder, 1487 unaffected relatives of probands, and 5055 healthy controls. We investigated cognition [digit span ( $N = 3127$ ), block design ( $N = 5491$ ), and the Rey Auditory Verbal Learning Test ( $N = 3543$ )], electrophysiology [P300 amplitude and latency ( $N = 1102$ )], and neuroanatomy [lateral ventricular volume ( $N = 1721$ )]. We used linear regression to assess the interrelationships between endophenotypes.

**Results.** The P300 amplitude and latency were not associated (regression coef.  $-0.06$ , 95% CI  $-0.12$  to  $0.01$ ,  $p = 0.060$ ), and P300 amplitude was positively associated with block design (coef.  $0.19$ , 95% CI  $0.10$ – $0.28$ ,  $p < 0.001$ ). There was no evidence of associations between lateral ventricular volume and the other measures (all  $p > 0.38$ ). All the cognitive endophenotypes were associated with each other in the expected directions (all  $p < 0.001$ ). Lastly, the relationships between pairs of endophenotypes were consistent in all three participant groups, differing for some of the cognitive pairings only in the strengths of the relationships.

**Conclusions.** The P300 amplitude and latency are independent endophenotypes; the former indexing spatial visualisation and working memory, and the latter is hypothesised to index basic processing speed. Individuals with psychotic illnesses, their unaffected relatives, and healthy controls all show similar patterns of associations between endophenotypes, endorsing the theory of a continuum of psychosis liability across the population.

## Introduction

Psychotic disorders, including schizophrenia and bipolar disorder, have considerable heritability with estimates ranging between 60 and 85% (Cardno *et al.* 1999; Smoller & Finn, 2003; Sullivan *et al.* 2012), and there is evidence of significant genetic overlap between these disorders (Lee *et al.* 2013). Psychoses are complex genetic disorders where many common variants contribute small increments of risk, and rare variants contribute greater risks (Gratten *et al.* 2014; Geschwind & Flint, 2015). While many common loci and some rare variants have now been identified (Stefansson *et al.* 2008; Stone *et al.* 2008; Walsh *et al.* 2008; Xu *et al.* 2008; Purcell *et al.* 2009; Grozeva *et al.* 2011; Sklar *et al.* 2011; Lee *et al.* 2013; Ripke *et al.* 2013, 2014; Green *et al.* 2015), little is known about their functional roles and the mechanisms through which they lead to the disease (Geschwind & Flint, 2015; Harrison, 2015).

Endophenotypes could help us gain a better understanding of the underlying neurobiology (Gottesman & Gould, 2003; Cannon & Keller, 2006; Gur *et al.* 2007). These are biological markers which are heritable, co-segregate with a disorder within families, are observed in unaffected family members at a higher rate than in the general population, and are expressed in an individual whether or not the illness is active (Gottesman & Gould, 2003). Endophenotypes could thus be used to better understand the mechanisms underlying the associations between genetic variants and the disorder (Hall & Smoller, 2010; Braff, 2015).

Although there is an extensive literature identifying and validating endophenotypes for psychosis, fewer studies have examined the relationships between different endophenotypes. Studies conducted so far have mainly analysed the associations between different cognitive measures (Toomey *et al.* 1998; Dickinson *et al.* 2002, 2006; Sullivan *et al.* 2003; Gladsjo *et al.* 2004; Sheffield *et al.* 2014; Seidman *et al.* 2015), but there is a lack of literature examining brain structural-cognitive and electrophysiological-cognitive pairings. Moreover, the inclusion of unaffected relatives in these studies has been rare, yet examining relatives – who carry increased genetic risk but have no illness or treatment confounding factors – is crucial for establishing the utility of these markers for genetic research.

This study seeks to investigate the relationships between the following electrophysiological, neurocognitive, and neuroanatomical endophenotypes for psychosis:

- P300 event-related potential: Reduced amplitude and prolonged latency of the P300 wave have consistently been found in patients with psychotic illnesses as well as in unaffected relatives, compared with controls (Blackwood *et al.* 1991; Weisbrod *et al.* 1999; Pierson *et al.* 2000; Winterer *et al.* 2003; Bramon *et al.* 2005; Price *et al.* 2006; Schulze *et al.* 2008; Bestelmeyer *et al.* 2009; Díez *et al.* 2013; Light *et al.* 2015; Turetsky *et al.* 2015). The P300 amplitude is thought to be a correlate of attention and working memory (Näätänen, 1990; Ford, 2014). Although the latency has been less precisely characterized, it is thought to index classification speed (Polich, 2007, 2011).
- Cognitive performance: Deficits on cognitive tests such as digit span (measuring working memory), block design (measuring working memory and spatial visualisation), and the Rey Auditory Verbal Learning Task (RAVLT) immediate and delayed recall (measuring short- and long-term verbal memory, respectively) are common and persistent across psychotic

disorders (Heinrichs & Zakzanis, 1998; Gur *et al.* 2007; Bora *et al.* 2009; Stone *et al.* 2011; Bora & Pantelis, 2015; Kim *et al.* 2015b; Lee *et al.* 2015). Abnormalities are often observed before the onset of the illness as well as in unaffected relatives (Glahn *et al.* 2006; Saperstein *et al.* 2006; Snitz *et al.* 2006; Birkett *et al.* 2008; Horan *et al.* 2008; Forbes *et al.* 2009; Reichenberg *et al.* 2010; Ivleva *et al.* 2012; Park & Gooding, 2014; Gur *et al.* 2015).

- Lateral ventricular volume: Increased ventricular volume is a highly replicated finding in patients with psychosis compared with controls (Sharma *et al.* 1998; Fannon *et al.* 2000; Wright *et al.* 2000; Shenton *et al.* 2001; McDonald *et al.* 2002, 2006; Strasser *et al.* 2005; Boos *et al.* 2007; Crespo-Facorro *et al.* 2009; Kempton *et al.* 2010; Fusar-Poli *et al.* 2013; Haijma *et al.* 2013; Kumra *et al.* 2014). This enlargement has been attributed to neurodevelopmental difficulties, disease progression, and/or the effects of antipsychotic medications (Pilowsky *et al.* 1993; Gogtay *et al.* 2003; McDonald *et al.* 2006).

This multi-centre study, seeking to investigate the relationships between multi-modal endophenotypes, includes the largest sample yet of individuals with psychosis, their unaffected first-degree relatives, and controls. The main objective is to facilitate the use of endophenotypes for genetic research into psychosis, which requires well defined and characterised measures. The aim of this study was therefore to examine the relationships between different endophenotype pairs, and in particular, to characterise the P300 event related potential in the context of well-defined cognitive markers.

## Methods and materials

### Sample and clinical assessments

The total sample included 8754 participants: 2212 individuals with a diagnosis of a psychotic disorder (see Table 1 for a breakdown of diagnoses), 1487 of their unaffected first-degree relatives (with no personal history of psychosis), and 5055 healthy controls (with no personal or family history of psychosis). Relatives and controls were not excluded if they had a personal history of non-psychotic disorders (such as depression or anxiety), provided they were well and off psychotropic medication at the time of testing and for the preceding 12 months.

To confirm or rule out a DSM-IV (APA, 1994) diagnosis, all participants underwent a structured clinical interview with either the Comprehensive Assessment of Symptoms and History (Andreasen *et al.* 1992), the Structured Clinical Interview for DSM Disorders (Spitzer *et al.* 1992), the Schedule for Affective Disorders and Schizophrenia (Endicott & Spitzer, 1978) or the Schedule for Clinical Assessment in Neuropsychiatry, Version 2.0 (Wing *et al.* 1990). Participants were excluded if they had a history of neurologic disease or a loss of consciousness due to a head injury.

Recruitment took place across 11 locations in Australia and Europe (Germany, Holland, Spain, and the UK) (see online Supplementary Table S1 in the supplement). Participants provided written informed consent, and the study was approved by the respective ethical committees at each of the 11 participating centres.

The main focus of this paper is an analysis of the associations between different endophenotype domains, which represents new and unpublished data. Some centres have previously published comparisons in endophenotype performance between groups (patients, relatives, and controls) (Weisbrod *et al.* 1999;

**Table 1.** Sample characteristics (N = 8754)

	Patients with psychosis	Unaffected relatives	Controls	Total sample
Sample size, N (%)	2212 (25.3%)	1487 (17.0%)	5055 (57.7%)	8754
Age, mean years (s.d.) <sup>a</sup>	33.6 (10.6)	46.0 (15.8)	45.5 (16.2)	42.6 (15.8)
Age range (years)	16–79	16–85	16–89	16–89
Gender (% female) <sup>a</sup>	32.1%	58.0%	51.5%	47.7%
Diagnoses; N (%)				
Schizophrenia	1396 (63.1%)	–	–	1396 (15.9%)
Bipolar I disorder	135 (6.1%)	–	–	135 (1.5%)
Psychosis NOS	168 (7.6%)	–	–	168 (1.9%)
Schizophreniform disorder	158 (7.1%)	–	–	158 (1.8%)
Schizoaffective disorder	124 (5.6%)	–	–	124 (1.4%)
Brief psychotic disorder	56 (2.5%)	–	–	56 (0.6%)
Other psychotic illness	175 (7.9%)	–	–	175 (2.0%)
Depression		246 (16.5%)	232 (4.6%)	478 (5.5%)
Anxiety		47 (3.2%)	24 (0.5%)	71 (0.8%)
Other non-psychotic illness		62 (4.2%)	106 (2.1%)	168 (1.9%)
No psychiatric illness		1132 (76.1%)	4693 (92.8%)	5825 (66.5%)
Endophenotypes N=sample size, Mean (SD) of raw scores unadjusted for covariates				
P300 amplitude ( $\mu$ V)	N = 397 10.5 (6.1)	N = 379 11.0 (6.7)	N = 313 13.7 (7.0)	N = 1089 11.6 (6.7)
P300 latency (ms)	N = 401 382.6 (55.3)	N = 386 390.8 (56.1)	N = 315 356.9 (39.1)	N = 1102 378.2 (53.3)
Lateral ventricular volume (cm <sup>3</sup> )	N = 700 17.9 (9.9)	N = 337 18.7 (11.2)	N = 684 15.8 (8.8)	N = 1721 17.1 (9.8)
Block Design (% of max. score)	N = 850 49.9 (27.9)	N = 895 47.4 (25.6)	N = 3746 60.4 (21.2)	N = 5491 56.6 (23.8)
Digit Span (% of max. score)	N = 460 47.4 (15.9)	N = 136 40.0 (4.5)	N = 2531 51.5 (14.5)	N = 3127 50.4 (14.9)
RAVLT immediate recall (no. of words recalled)	N = 1232 7.6 (2.2)	N = 934 8.4 (2.1)	N = 1377 8.7 (2.0)	N = 3543 8.2 (2.2)
RAVLT delayed recall (no. of words recalled)	N = 1224 2.1 (1.0)	N = 927 2.9 (1.0)	N = 1358 2.9 (0.9)	N = 3509 2.6 (1.0)

s.d., standard deviation; NOS, not otherwise specified; RAVLT, Rey auditory verbal learning task.

<sup>a</sup>Missing data for age (717 subjects) and gender (6 subjects).

The group differences in endophenotype performance adjusted by covariates are reported in Table 2.

Hulshoff Pol *et al.* 2002; McDonald *et al.* 2002; Steel *et al.* 2002; Bramon *et al.* 2005; Johnstone *et al.* 2005; Hall *et al.* 2006b; Price *et al.* 2006; Schulze *et al.* 2006; González-Blanch *et al.* 2007; Crespo-Facorro *et al.* 2009; Waters *et al.* 2009; Wobrock *et al.* 2009; Touloupoulou *et al.* 2010; Collip *et al.* 2013). Here we also present results of a mega-analysis of the combined multi-centre sample.

### Neuropsychological assessments

The Wechsler Adult Intelligence Scale, revised version (Wechsler, 1981) or third edition (Wechsler, 1997), were

administered to participants. Performance on two subtests was used for analyses: the combined forward and backward digit span (measuring attention and working memory) and block design (measuring spatial visualisation). The Rey Auditory Verbal Learning Test (Rey, 1964), including both immediate and delayed recall (assessing short- and long-term verbal memory, respectively), was also administered. Higher scores on the cognitive tasks indicate better performance. Full methodology for each contributing site is reported elsewhere (Johnstone *et al.* 2005; Crespo-Facorro *et al.* 2007; González-Blanch *et al.* 2007; Waters *et al.* 2009; Touloupoulou *et al.* 2010; Walters *et al.* 2010; Korver *et al.* 2012).

**Table 2.** Endophenotype performance comparison across clinical groups

	Total sample	Patients – controls	Patients – relatives	Relatives – controls
Endophenotype	Global, <i>p</i> value*	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)
P300 amplitude	<0.001	−0.50 (−0.71 to −0.29) <i>p</i> < 0.001	−0.16 (−0.32 to −0.01) <i>p</i> = 0.061	−0.34 (−0.54 to −0.14) <i>p</i> = 0.001
P300 latency	<0.001	0.47 (0.33–0.61) <i>p</i> < 0.001	0.03 (−0.14–0.19) <i>p</i> = 0.749	0.44 (0.29–0.60) <i>p</i> < 0.001
Lateral ventricular volume		0.20 (0.08–0.32)	0.09 (−0.06 to 0.23)	0.11 (−0.04 to 0.25)
Digit span	<0.001	−0.72 (−0.88 to −0.55) <i>p</i> < 0.001	−0.14 (−0.32 to 0.05) <i>p</i> = 0.141	−0.58 (−0.77 to −0.39) <i>p</i> < 0.001
Block design	<0.001	−0.91 (−1.07 to −0.75) <i>p</i> < 0.001	−0.08 (−0.21 to 0.04) <i>p</i> = 0.190	−0.83 (−0.97 to −0.69) <i>p</i> < 0.001
RAVLT immediate recall	<0.001	−1.32 (−2.29 to −0.37) <i>p</i> = 0.007	−1.24 (−2.22 to −0.27) <i>p</i> = 0.012	−0.08 (−0.24 to 0.07) <i>p</i> = 0.286
RAVLT delayed recall	=0.123	−0.98 (−2.21 to 0.25) <i>p</i> = 0.118	−0.94 (−2.18 to 0.30) <i>p</i> = 0.136	−0.03 (−0.20 to 0.13) <i>p</i> = 0.669

Linear regression models investigating group differences on endophenotype performance. Endophenotype data were standardised for each site using the mean and standard deviation within each site. The main predictor was clinical group (patients, relatives, and controls). All models included age, gender, study site and, where significant, group × centre interactions. We used robust standard errors to account for correlations within families in all models.

\**P* value for the overall test of a group effect; Note that *p* values were not produced for the models that include lateral ventricular volume since we used bootstrapping, which is a percentile-based method; therefore we looked at the bias-corrected confidence intervals to check for significance.  
RAVLT, Rey auditory verbal learning task; CI, confidence interval.

### EEG data collection and processing

Electrophysiological data were obtained from three sites (online Supplementary Table S1). EEG data acquisition and processing methods varied slightly between sites as summarised below. The full methods for each site are reported elsewhere (Weisbrod *et al.* 1999; Bramon *et al.* 2005; Hall *et al.* 2006b; Price *et al.* 2006; Waters *et al.* 2009).

In summary, EEG was collected from 17 to 20 electrodes placed according to the International 10/20 system (Jasper, 1958). The P300 event related potential was obtained using a standard two-tone frequency deviant auditory oddball paradigm, with standard ('non target') tones of 1000 Hz and rare ('target') tones of 1500 Hz. The number of tones presented varied from 150 to 800, the tones were 80 dB or 97 dB, lasted for 20–50 ms, and the inter-stimulus interval was between 1 and 2 s. The majority of participants (93.4%) were asked to press a button in response to 'target' stimuli, but a subset were asked to close their eyes and count 'target' stimuli in their head.

The data were continuously recorded in one of three ways: 500 Hz sampling rate and 0.03–120 Hz band pass filter; 200 Hz sampling rate and 0.05–30 Hz band pass filter; or 400 Hz sampling rate and 70 Hz low-pass filter. Linked earlobes or mastoids were used as reference and vertical, and in most cases also horizontal, electro-oculographs were recorded at each site and used to correct for eye-blink artefacts using regression based weighting coefficients (Semlitsch *et al.* 1986). After additional manual checks, artefact-free epochs were included and baseline corrected before averaging. The averaged waveforms to correctly detected targets were then filtered using 0.03 or 0.05 Hz high-pass and 30 or 45 Hz low-pass filters. The peak amplitude and latency of the P300 were measured at electrode location PZ (parietal midline), within the range of 250–550 ms post-stimulus.

### MRI data collection and processing

MRI data acquisition and image processing varied between sites; see previous publications and the supplementary materials for an outline of the methods used for each centre (Barta *et al.* 1997; Frangou *et al.* 1997; Hulshoff Pol *et al.* 2002; McDonald *et al.*

2002, 2006; McIntosh *et al.* 2004, 2005a, b; Schulze *et al.* 2006; Crespo-Facorro *et al.* 2009; Dutt *et al.* 2009; Mata *et al.* 2009; Wobrock *et al.* 2009; Habets *et al.* 2011; Collip *et al.* 2013). Field strengths included 1, 1.5 or 3 Tesla. Lateral ventricular volumes were measured using automatic or semi-automatic region of interest analyses, and included the body, frontal, occipital, and temporal horns.

### Statistical methods

#### Mega-analysis of group comparisons

Endophenotype measures were first standardised for each site separately using the mean and standard deviation within each site. Linear regression analyses for each measure were used to establish whether endophenotype performance differed according to group (patients, relatives, and controls). The outcome in each regression model was the endophenotype measure and the main predictor was group. These analyses were adjusted for age, gender, clinical group, study site and, where significant, group × site interactions.

#### Associations between endophenotypes

Linear regression models were used to investigate associations between each pair of endophenotypes. Potential effect modification by group membership was assessed by specifying in the statistical model a term for the interaction between the predictor of the endophenotype pair and group (patient, relative, control). Where we found evidence that the relationship between a pair of endophenotypes differed according to group, associations are reported separately for patients, relatives, and controls. Where there was no evidence of effect modification, the interaction term was dropped from the model, and associations are reported for the whole sample adjusted for group. These analyses were adjusted for age, gender, clinical group, and study site.

In all analyses, we accounted for correlations between individuals within families using robust standard errors. 63% of the participants had no other family member taking part, but the study also included 1056 families of 2–11 members each (85% of the families had only two members included in the sample). This

family clustering violates the independence of observations assumption in linear regression. To account for this clustered structure in the dataset we created a new variable ‘family ID’ that was shared by all individuals in each family. Then we used the variance estimator with the robust cluster option in all the linear regression models. This allowed us to account for the within-family correlations and maintain correct type-1 error rates. This is a standard approach in family studies (Shaikh *et al.* 2013; Bramon *et al.* 2014; Ramlund *et al.* 2014).

We examined the distribution of residuals and plots of residuals *v.* fitted values for all models and were able to rule out departures from normality and heteroscedasticity. Lateral ventricular volume showed a positively skewed distribution and to account for this we used bootstrap methods for analyses where this is the outcome variable. Heteroscedasticity was not found to be a concern for ventricular volumes. *P* values are not presented for the models which used bootstrapping; instead, we examined the 95% bias-corrected confidence intervals to check for statistical significance at the 5% level ( $p = 0.05$ ).

Although we tested seven endophenotypes, we expect measurements within domains to be correlated and thus a correction of *p* values by seven tests through Bonferroni or other methods was deemed too stringent for a hypothesis-driven study such as this (Rothman, 1990; Savitz & Olshan, 1995; Perneger, 1998). We therefore corrected for associations between three domains (EEG, MRI, cognition), with a corrected significance threshold of  $0.05/3 = 0.0167$ , that we rounded to the slightly more stringent cut-off of  $p < 0.01$ . Statistical analyses were conducted using STATA version 13.

## Results

### Sample characteristics

The sample characteristics are summarised in Table 1. Patients were on average 12.4 years younger than relatives (95% CI: 11.4–13.4;  $p < 0.001$ ) and 11.9 years younger than controls (95% CI: 11.1–12.7;  $p < 0.001$ ). There was no evidence of any age difference between relatives and controls. There was a lower proportion of females than males among patients than among relatives and controls (32.1%, 58.0%, and 51.5% respectively; global  $p < 0.001$ ).

### Group comparisons on endophenotype performance

As shown in Fig. 1 and Table 2, differences between the three participant groups on the endophenotypes followed the expected pattern with performance improving from patients through to relatives and controls. We found evidence that patients’ scores differed significantly from those of controls with smaller P300 amplitudes, delayed P300 latency, larger lateral ventricular volumes and deficits in digit span, block design and RVLIT immediate recall. When compared with controls, the unaffected relatives showed reduced P300 amplitude, delayed P300 latency and poorer performance in digit span and block design.

### Associations between endophenotype pairs

#### Associations which do not differ according to clinical group

Associations between endophenotype pairs where there was no evidence of effect modification by group are reported in Table 3. There was no evidence of an association between the P300 amplitude and latency at the 1% level of statistical

significance (coef.  $-0.06$ , 95% CI  $-0.12$  to  $0.01$ ,  $p = 0.06$ ). The P300 amplitude was positively associated with digit span (coef.  $0.15$ , 95% CI  $0.04$ – $0.26$ ,  $p = 0.009$ ) and block design (coef.  $0.19$ , 95% CI  $0.10$ – $0.28$ ,  $p < 0.001$ ) performances, but not with either of the RAVLT measures. The P300 latency showed weak evidence of a negative association with digit span (coef.  $-0.15$ , 95% CI  $-0.28$  to  $-0.03$ ,  $p = 0.017$ ). Lateral ventricular volume showed no evidence of an association with any of the other measures. All cognitive pairings were significantly positively associated (all  $p < 0.001$ ).

#### Associations which differ according to clinical group

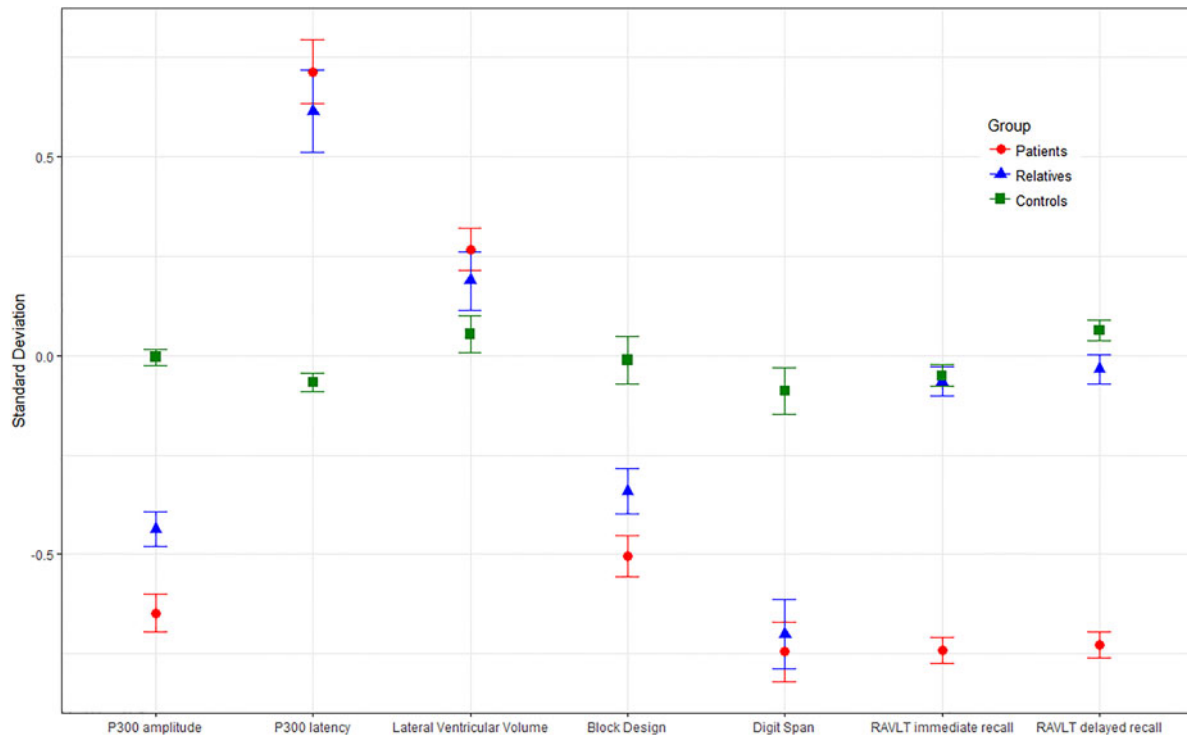
For three pairs of cognitive endophenotypes, we found evidence of an interaction with group. This indicates that the association between these endophenotype pairs differs between patients, relatives, and controls, as reported in Fig. 2 (and online Supplementary Table S3 in the Supplement). In all three cases, the relationship between endophenotype pairs was in the same direction for the three groups, differing only in magnitude.

There was strong evidence that digit span and RAVLT immediate and delayed recall were positively associated with scores on the block design task in all three groups (patients, relatives, and controls). The magnitude of each association was greater among patients than controls (all  $p < 0.01$ ), but there was no evidence that the strength of the relationship among relatives was different from that among controls (all  $p > 0.03$ ). See online supplementary Table S3 for full results.

## Discussion

This study examined the relationships between different multimodal psychosis endophenotypes in a large multi-centre sample of patients, their unaffected first-degree relatives, and controls.

Our mega-analysis confirms that both patients and relatives showed reduced amplitudes and prolonged latencies of the P300, compared with controls, replicating past findings and providing further evidence that these are endophenotypes for psychosis (Turetsky *et al.* 2000; Bramon *et al.* 2005; Price *et al.* 2006; Schulze *et al.* 2008; Thaker, 2008; Bestelmeyer *et al.* 2009; Díez *et al.* 2013). We found no evidence of association between the P300 amplitude and latency, indicating that these are independent measures. To examine whether variability on P300 amplitude and latency could potentially affect the correlations between these, we tested for heteroscedasticity between clinical groups. The standard deviations between the patient, relative, and control groups did not vary significantly and are thus unlikely to explain the lack of correlation between P300 amplitude and latency performance. In contrast to our results, Hall *et al.* (Hall *et al.* 2006a) and Polich *et al.* (Polich, 1992; Polich *et al.* 1997) found a negative correlation between the amplitude and latency. Notably however, these past studies included only small samples (up to 128 participants) compared with our study ( $N = 1083$ ), and they did not take into account covariates such as age and gender that are known to influence both P300 parameters (Goodin *et al.* 1978; Polich *et al.* 1985; Conroy & Polich, 2007; Chen *et al.* 2013). Furthermore, in the studies by Polich *et al.* (Polich, 1992; Polich *et al.* 1997) the amplitude – latency correlation was strongest over frontal electrodes, and not parietal as investigated in our current study. More recently, Hall *et al.* (2014) found a negative correlation between the amplitude and latency in a sample of 274 patients with psychosis and controls after controlling for age and gender effects. Further research is thus needed to clarify the



**Fig. 1.** Estimated marginal means (adjusted for average age, gender, and study site) of standardised endophenotype scores by group (patients, relatives, and controls). Error bars represent standard errors of the means. RAVLT, Rey auditory verbal learning task.

relationship between the P300 amplitude and latency. However, our findings in this large sample suggest that the measures are independent, indexing separate brain functions.

We found associations between the P300 amplitude and both digit span and block design, as in previous smaller studies (Souza *et al.* 1995; Polich *et al.* 1997; Fjell & Walhovd, 2001; Hermens *et al.* 2010; Kaur *et al.* 2011; Dong *et al.* 2015*b*). According to the context-updating theory (Heslenfeld, 2003; Kujala & Naatanen, 2003), the P300 amplitude is an attention-driven, context-updating mechanism, which subsequently feeds into memory stores (Polich, 2007, 2011). Hence, one would expect the amplitude to be associated with cognitive tasks that require attention and working memory, such as digit span and block design (Näätänen, 1990; Baddeley, 1992; Ford, 2014). The context-updating theory provides a possible explanation for the association between P300 amplitude and block design, since this task requires a constant update of the mental representation of the blocks, in order to complete the target pattern (Polich, 2007, 2011). The lack of evidence for associations between P300 amplitude and the RAVLT tests support the idea that the neurobiology of verbal memory is distinct from the attentional and working memory processes linked to the P300 amplitude (Polich, 2011).

The P300 latency showed evidence of a trend-level association with digit span, and no evidence of an association with the other measures. Previous studies have provided conflicting results, with some reporting associations with attention and working memory (Polich *et al.* 1983), while others have not (Fjell & Walhovd, 2001; Walhovd & Fjell, 2003; Dong *et al.* 2015*b*). The P300 latency has been conceptualised as a measure of classification speed (Polich, 2011; van Dinteren *et al.* 2014). Investigating the relationship between behavioural reaction times (i.e. the speed of button

press in the task) and the P300 latency, some have found associations (Bashore *et al.* 2014) while others have not (Ramchurn *et al.* 2014). Furthermore, there is a substantial body of research showing that the P300 latency as well as reaction times increase (that is they slow down) with ageing in healthy participants (Polich, 1996; Chen *et al.* 2013). Based on our findings we hypothesise that the P300 latency is a specific measure of processing speed at a basic neuronal level. In contrast, block design and the RAVLT task – while influenced by processing speed – reflect wider cognition including spatial abilities and verbal memory. The more complex elements to these tasks may therefore obscure effects of a simple processing speed, and hence explain the lack of association with P300 latency. The trend-level association with digit span performance – a task dependent on attention and short-term working memory – is in line with this interpretation too.

In terms of lateral ventricular volume, there was no evidence of a relationship with any other endophenotype investigated. Enlargement of cerebral ventricles remains the best replicated biological marker in schizophrenia and bipolar disorder, according to several meta-analyses (Kempton *et al.* 2010; Olabi *et al.* 2011; De Peri *et al.* 2012; Fusar-Poli *et al.* 2013; Fraguas *et al.* 2016; van Erp *et al.* 2016; Huhtaniska *et al.* 2017; Moberget *et al.* 2017). Our hypothesis that ventricular volumes would correlate with other endophenotypes of a functional nature was not confirmed by our data. Of course for such analyses our sample size was modest ranging 428–1001 and lack of statistical power could be a potential reason. Keilp *et al.* (Keilp *et al.* 1988) found an association with verbal memory and others have found enlarged lateral ventricles to be associated with poorer motor speed (Antonova *et al.* 2004; Hartberg *et al.* 2011; Dong *et al.* 2015*a*). A limitation of our study is the heterogeneity of the MRI methodology between study sites, which might have obscured any true associations. We

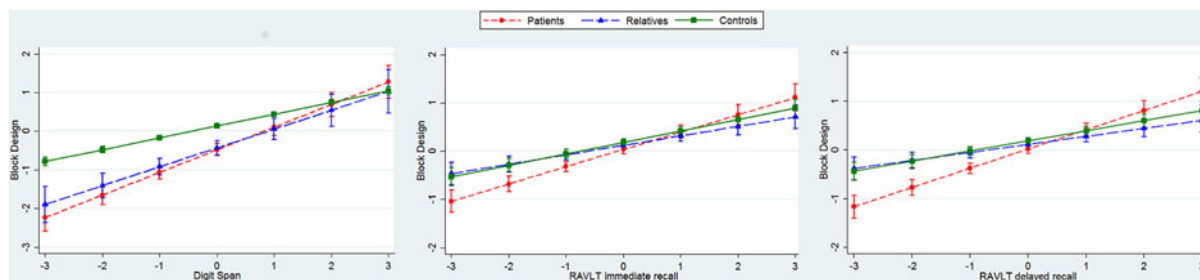
**Table 3.** Adjusted associations between endophenotypes in the whole sample

	P300 latency	Lateral ventricular volume	Digit span	Block design	RAVLT immediate recall	RAVLT delayed recall
P300 amplitude	<i>N</i> = 1083	<i>N</i> = 428	<i>N</i> = 340	<i>N</i> = 426	<i>N</i> = 255	<i>N</i> = 255
	−0.06 (−0.12 to 0.01)	0.05 (−0.07 to 0.15)	0.15 (0.04–0.26)	0.19 (0.10–0.28)	0.11 (−0.02 to 0.25)	0.08 (−0.06 to 0.22)
	<i>p</i> = 0.060		<i>p</i> = 0.009	<i>p</i> < 0.001	<i>p</i> = 0.102	<i>p</i> = 0.281
P300 latency	–	<i>N</i> = 434	<i>N</i> = 346	<i>N</i> = 437	<i>N</i> = 254	<i>N</i> = 254
		0.02 (−0.08 to 0.15)	−0.15 (−0.28 to −0.03)	−0.04 (−0.12 to 0.04)	0.03 (−0.09 to 0.15)	0.03 (−0.07 to 0.14)
			<i>p</i> = 0.017	<i>p</i> = 0.333	<i>p</i> = 0.699	<i>p</i> = 0.501
Lateral ventricular volume		–	<i>N</i> = 468	<i>N</i> = 1001	<i>N</i> = 498	<i>N</i> = 492
			−0.01 (−0.09 to 0.09)	0.02 (−0.04 to 0.09)	−0.04 (−0.14 to 0.06)	−0.02 (−0.11 to 0.09)
Digit Span			–	<i>N</i> = 2754	<i>N</i> = 291	<i>N</i> = 291
				0.33 (0.30–0.36)	0.39 (0.28–0.49)	0.31 (0.20–0.42)
				<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> < 0.001
Block Design				–	<i>N</i> = 2169	<i>N</i> = 2137
					0.26 (0.21–0.30)	0.24 (0.20–0.29)
					<i>p</i> < 0.001	<i>p</i> < 0.001
RAVLT immediate recall					–	<i>N</i> = 3505
						0.76 (0.74–0.78)
						<i>p</i> < 0.001

RAVLT, Rey auditory verbal learning task.

Regression models using standardised scores, adjusted for age, gender, study site and group using robust standard errors to account for correlations within families and, where significant, group × by centre interactions.

Statistics reported are sample sizes, regression coefficients (95% confidence intervals), and *p* values. Note that *p* values were not produced for the models that include lateral ventricular volume since we used bootstrapping, which is a percentile-based method; therefore we looked at the bias-corrected confidence intervals to check for significance.



**Fig. 2.** Interactions between group (patient, relative, and control) and endophenotype pairs (standardised scores). Graphs are adjusted for covariates (age, gender, and study site), and include 95% confidence intervals. RAVLT, Rey auditory verbal learning task.

conclude that ventricular volumes do not seem to exert a detectable influence on brain function in terms of cognition or cortical neurophysiology, however association studies of structural-functional biomarkers in larger samples are needed.

With regard to group comparisons, although patients showed enlarged lateral ventricles compared with controls, a very well supported finding (Wright *et al.* 2000; Steen *et al.* 2006; Cahn *et al.* 2009; Kempton *et al.* 2010), having adjusted by age and sex we observed no volume differences between relatives and controls. This is consistent with the latest meta-analysis of brain structure in relatives of patients with schizophrenia (Boos *et al.* 2007), and suggests that enlarged ventricles in patients are less heritable than previously thought. Instead, they might be related to illness progression, or to environmental effects or antipsychotic medication, as seen in both animal models of antipsychotic exposure (Dorph-Petersen *et al.* 2005; Konopaske *et al.* 2007), and in human studies (Ho *et al.* 2011; Fusar-Poli *et al.* 2013; Van Haren *et al.* 2013).

For all cognitive measures, patients performed less well than controls, consistent with extensive literature (Ayres *et al.* 2007; Horan *et al.* 2008; Bora *et al.* 2010, 2014; Fusar-Poli *et al.* 2012; Bora & Murray, 2014; Fatouros-Bergman *et al.* 2014; Stone *et al.* 2015). For the digit span and block design, there were also statistically significant differences between relatives and controls, suggesting a possible effect of increased genetic risk for psychosis. However, this was not seen for the immediate or delayed recall of the RAVLT task, where controls and relatives had similar performance. While some have reported verbal memory impairments in relatives of patients (Sitskoorn *et al.* 2004; Wittorf *et al.* 2004; Massuda *et al.* 2013), other studies have not (Üçök *et al.* 2013; Kim *et al.* 2015a). These findings suggest that working memory and spatial visualisation might represent more promising endophenotypes for genetic research into psychosis than verbal memory.

The associations between pairs of cognitive measures were strong and in the expected directions, as per previous findings (Dickinson *et al.* 2002; Sullivan *et al.* 2003; Gladsjo *et al.* 2004; Sheffield *et al.* 2014; Seidman *et al.* 2015). It is interesting to note that for some cognitive measures, the relationships interacted with group; however, the direction of the effect remained the same across patients, relatives, and controls. The interaction effects with group were found exclusively amongst the cognitive measures, and not in any of the other domains. This is possibly due to the larger sample sizes for the cognitive measures, yielding greater statistical power and enabling the detection of subtle interaction effects.

Both the lack of interaction effects for most associations investigated, and the gradient effects identified (where there was an

interaction), are consistent with the notion that endophenotype impairments characterising psychosis represent a continuum that includes both relatives and the general population. Ultimately this continuum reflects the underlying variation in genetic liability of developing the disease (Johns & van Os, 2001; Wiles *et al.* 2006; Allardyce *et al.* 2007; Esterberg & Compton, 2009; Ian *et al.* 2010; DeRosse & Karlsgodt, 2015).

This study has several limitations: Firstly, association analyses could only be done for those participants with data available for pairs of endophenotypes and this led to relatively smaller samples for some of the associations. Secondly, there was a mismatch in age and gender between patients and relatives. The group of relatives has older individuals and more females compared with the group of patients who are younger and include more males. This is a common occurrence in psychosis family studies because the onset of psychosis is typically in youth. Most of the families who participated in the study include unaffected parents (with greater participation of mothers) and their affected and unaffected offspring. Family studies in psychosis are less likely to recruit affected parents. Because of this, we recruited a control group with a wider age range than either the other groups and with a balanced gender distribution so as to improve the age and sex matching across the two key comparisons (controls *v.* patients, controls *v.* relatives). Furthermore, since age and sex remains a potential confounder, we included age and sex as co-variates in the models throughout the study. As shown in online Supplementary Table S4 in the supplement, there was no evidence of model instability based on the estimates and confidence interval width between the models with and without age and sex.

Another limitation of this study is that we were unable to account for potential moderators such as tobacco, other drug use and medication. Also, information about participants' socio-economic status was not available. These clinical and demographic variables could have a potentially important influence on how the three clinical groups perform on endophenotypes. However, the main analyses, which was to investigate associations between endophenotypes are all done within-individuals and are thus less likely to be influenced by exposure to drugs and medication. As for clinical variables such as depression, the sample included 5.5% of individuals with a history of depression. Depression did not constitute an exclusion criterion for our study because it is such a prevalent disorder that if excluded it would probably make our findings hard to generalize. We have re-analysed the group comparisons excluding all participants with a history of depression and the overall findings are unchanged.

A further potential limitation was the heterogeneity of methods between study sites; differences in cognitive test versions



and variation on the EEG and MRI protocols all introduced greater variability into the data. All measures were standardised within centres to minimise this variability. Despite this challenge, it is precisely through this multi-centre effort that we were able to achieve a very large sample, the key strength of this study. As the Psychiatric Genomics Consortium's work shows, large international collaborations are essential in genetic studies of common diseases and traits (Sklar *et al.* 2011; Lee *et al.* 2013; Smoller *et al.* 2013; Ripke *et al.* 2014). A further strength of this study is the use of regression models as opposed to the correlation approach frequently seen in the literature (Brewer *et al.* 1970; Polich *et al.* 1983, 1997; Breteler *et al.* 1994; Brillinger, 2001; Kim *et al.* 2003), which allowed us to account for some important confounding factors, such as ageing effects. Not only did this approach reduce vulnerability to spurious correlations, but it allowed the examination of interesting interaction effects across groups.

In summary, this study has investigated the relationships between endophenotypes for psychosis, including measures of cognition, electrophysiology, and brain structure. We have shown that cognitive measures are associated with each other as expected, and we have provided support for the notion that the amplitude and latency of the P300 are independent endophenotypes. The P300 amplitude is an index of spatial visualisation and working memory, while the latency is hypothesised to be a correlate of basic speed of processing. Individuals with psychotic illnesses, their unaffected relatives, and healthy controls all have similar patterns of associations between all pairs of endophenotypes, endorsing the theory of a continuum of liability of developing psychosis across the population.

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## References

Allardyce J, Suppes T, van Os J (2007) Dimensions and the psychosis phenotype. *International Journal of Methods in Psychiatric Research* **16**, S34–S40.

Andreasen NC, Flaum M, Arndt S (1992) The Comprehensive Assessment of Symptoms and History (CASH) An instrument for assessing diagnosis and psychopathology. *Archives of General Psychiatry* **49**, 615.

Antonova E, Sharma T, Morris R, Kumari V (2004) The relationship between brain structure and neurocognition in schizophrenia: a selective review. *Schizophrenia Research* **70**, 117–145.

APA (1994) *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association: Washington.

Ayres AM, Busatto GF, Menezes PR, Schaufelberger MS, Coutinho L, Murray RM, McGuire PK, Rushe T, Sczufca M (2007) Cognitive deficits

in first-episode psychosis: a population-based study in São Paulo, Brazil. *Schizophrenia Research* **90**, 338–343.

Baddeley A (1992) Working memory. *Science (New York, N.Y.)* **255**, 556–559.

Barta PE, Dhinra L, Royall R, Schwartz E (1997) Improving stereological estimates for the volume of structures identified in three-dimensional arrays of spatial data. *Journal of Neuroscience Methods* **75**, 111–118.

Bashore TR, Wylie SA, Ridderinkhof KR, Martinerie JM (2014) Response-specific slowing in older age revealed through differential stimulus and response effects on P300 latency and reaction time. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition* **21**, 633–673.

Bestelmeyer PEG, Phillips LH, Crombie C, Benson P, Clair DS (2009) The P300 as a possible endophenotype for schizophrenia and bipolar disorder: evidence from twin and patient studies. Elsevier Ireland Ltd. *Psychiatry Research* **169**, 212–219.

Birkett P, Sigmundsson T, Sharma T, Touloupoulou T, Griffiths TD, Reveley A, Murray R (2008) Executive function and genetic predisposition to schizophrenia – the Maudsley family study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **147B**, 285–293.

Blackwood DH, St Clair DM, Muir WJ, Duffy JC (1991) Auditory P300 and eye tracking dysfunction in schizophrenic pedigrees. *Archives of General Psychiatry* **48**, 899–909.

Boos HBM, Aleman A, Cahn W, Hulshoff Pol H, Kahn RS (2007) Brain volumes in relatives of patients with schizophrenia: a meta-analysis. *Archives of General Psychiatry* **64**, 297–304.

Bora E, Lin A, Wood SJ, Yung AR, McGorry PD, Pantelis C (2014) Cognitive deficits in youth with familial and clinical high risk to psychosis: a systematic review and meta-analysis. *Acta Psychiatrica Scandinavica* **130**, 1–15.

Bora E, Murray RM (2014) Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: do the cognitive deficits progress over, or after, the onset of psychosis? *Schizophrenia Bulletin* **40**, 744–755.

Bora E, Pantelis C (2015) Meta-analysis of cognitive impairment in first-episode bipolar disorder: comparison with first-episode schizophrenia and healthy controls. *Schizophrenia Bulletin* **41**, 1095–1104.

Bora E, Yücel M, Pantelis C (2009) Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: meta-analytic study. *The British Journal of Psychiatry: The Journal of Mental Science* **195**, 475–482.

Bora E, Yücel M, Pantelis C (2010) Cognitive impairment in affective psychoses: a meta-analysis. *Schizophrenia Bulletin* **36**, 112–125.

Braff DL (2015) The importance of endophenotypes in schizophrenia research. Elsevier B.V. *Schizophrenia Research* **163**, 1–8.

Bramon E, McDonald C, Croft RJ, Landau S, Filbey F, Gruzelić JH, Sham PC, Frangou S, Murray RM (2005) Is the P300 wave an endophenotype for schizophrenia? A meta-analysis and a family study. *NeuroImage* **27**, 960–968.

Breteler MM, van Amerongen NM, van Swieten JC, Claus JJ, Grobbee DE, van Gijn J, Hofman A, van Harskamp F (1994) Cognitive correlates of ventricular enlargement and cerebral white matter lesions on magnetic resonance imaging. The Rotterdam Study. *Stroke; A Journal of Cerebral Circulation* **25**, 1109–1115.

Brewer MB, Campbell DT, Crano WD (1970) Testing a single-factor model as an alternative to the misuse of partial correlations in hypothesis-testing research. *Sociometry* **33**, 1.

Brillinger DR (2001) Does anyone know when the correlation coefficient is useful? A study of the times of extreme river flows. *Technometrics* **43**, 266–273.

Cahn W, Rais M, Stigter FP, van Haren NEM, Caspers E, Hulshoff Pol HE, Xu Z, Schnack HG, Kahn RS (2009) Psychosis and brain volume changes during the first five years of schizophrenia. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* **19**, 147–151.

Cannon TD, Keller MC (2006) Endophenotypes in the genetic analyses of mental disorders. *Annual Review of Clinical Psychology* **2**, 267–290.

Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, Venturi P, Jones LA, Lewis SW, Sham PC, Gottesman II, Farmer AE, McGuffin P, Reveley AM, Murray RM (1999) Heritability estimates for psychotic disorders: the Maudsley Twin psychosis series. *Archives of General Psychiatry* **56**, 162–168.

- Chen KC, Lee IH, Yang YK, Landau S, Chang WH, Chen PS, Lu RB, David AS, Bramon E (2013) P300 waveform and dopamine transporter availability: a controlled EEG and SPECT study in medication-naïve patients with schizophrenia and a meta-analysis. *Psychological Medicine* **44**, 1–12.
- Collip D, Habets P, Marcelis M, Gronenschild E, Lataster T, Lardinois M, Nicolson NA, Myin-Germeys I (2013) Hippocampal volume as marker of daily life stress sensitivity in psychosis. *Psychological Medicine* **43**, 1377–1387.
- Conroy MA, Polich J (2007) Normative variation of P3a and P3b from a large sample. *Journal of Psychophysiology* **21**, 22–32.
- Crespo-Facorro B, Roiz-Santiañez R, Pelayo-Terán JM, Rodríguez-Sánchez JM, Pérez-Iglesias R, González-Blanch C, Tordesillas-Gutiérrez D, González-Mandly A, Díez C, Magnotta VA, Andreasen NC, Vázquez-Barquero JL (2007) Reduced thalamic volume in first-episode non-affective psychosis: correlations with clinical variables, symptomatology and cognitive functioning. *NeuroImage* **35**, 1613–1623.
- Crespo-Facorro B, Roiz-Santiañez R, Pérez-Iglesias R, Tordesillas-Gutiérrez D, Mata I, Rodríguez-Sánchez JM, de Lucas EM, Vázquez-Barquero JL (2009) Specific brain structural abnormalities in first-episode schizophrenia. A comparative study with patients with schizophreniform disorder, non-schizophrenic non-affective psychoses and healthy volunteers. *Schizophrenia Research* **115**, 191–201.
- De Peri L, Crescini A, Deste G, Fusar-Poli P, Sacchetti E, Vita A (2012) Brain structural abnormalities at the onset of schizophrenia and bipolar disorder: a meta-analysis of controlled magnetic resonance imaging studies. *Current Pharmaceutical Design* **18**, 486–494.
- DeRosse P, Karlsgodt KH (2015) Examining the psychosis continuum. *Current Behavioral Neuroscience Reports* **2**, 80–89.
- Dickinson D, Iannone VN, Gold JM (2002) Factor structure of the Wechsler Adult Intelligence Scale-III in schizophrenia. *Assessment* **9**, 171–180.
- Dickinson D, Ragland JD, Calkins ME, Gold JM, Gur RC (2006) A comparison of cognitive structure in schizophrenia patients and healthy controls using confirmatory factor analysis. *Schizophrenia Research* **85**, 20–29.
- Díez Á, Suazo V, Casado P, Martín-Loeches M, Molina V, Díez A, Suazo V, Casado P, Martín-Loeches M, Molina V (2013) Spatial distribution and cognitive correlates of gamma noise power in schizophrenia. *Psychological Medicine* **43**, 1175–1185.
- Dong C, Nabizadeh N, Caunca M, Cheung YK, Rundek T, Elkind MSV, DeCarli C, Sacco RL, Stern Y, Wright CB (2015a). Cognitive correlates of white matter lesion load and brain atrophy: the Northern Manhattan Study. *Neurology* **85**, 441–449.
- Dong S, Reder LM, Yao Y, Liu Y, Chen F (2015b). Individual differences in working memory capacity are reflected in different ERP and EEG patterns to task difficulty. *Brain Research* **1616**, 146–156.
- Dorph-Petersen K-A, Pierri JN, Perel JM, Sun Z, Sampson AR, Lewis DA (2005) The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* **30**, 1649–1661.
- Dutt A, McDonald C, Dempster E, Prata D, Shaikh M, Williams I, Schulze K, Marshall N, Walshe M, Allin M, Collier D, Murray R, Bramon E (2009) The effect of COMT, BDNF, 5-HTT, NRG1 and DTNBP1 genes on hippocampal and lateral ventricular volume in psychosis. *Psychological Medicine* **39**, 1783–1797.
- Endicott J, Spitzer RL (1978) A diagnostic interview. The schedule for affective disorders and schizophrenia. *Archives of General Psychiatry* **35**, 837–844.
- Esterberg ML, Compton MT (2009) The psychosis continuum and categorical versus dimensional diagnostic approaches. *Current Psychiatry Reports* **11**, 179–184.
- Fannon D, Tennakoon L, Sumich A, O’Ceallaigh S, Doku V, Chitnis X, Lowe J, Soni W, Sharma T (2000) Third ventricle enlargement and developmental delay in first-episode psychosis: preliminary findings. *The British Journal of Psychiatry* **177**, 354–359.
- Fatouros-Bergman H, Cervenka S, Flyckt L, Edman G, Farde L (2014) Meta-analysis of cognitive performance in drug-naïve patients with schizophrenia. *Schizophrenia Research* **158**, 156–162.
- Fjell AM, Walhovd KB (2001) P300 and neuropsychological tests as measures of aging: scalp topography and cognitive changes. *Brain Topography* **14**, 25–40.
- Forbes NF, Carrick LA, McIntosh AM, Lawrie SM (2009) Working memory in schizophrenia: a meta-analysis. *Psychological Medicine* **39**, 889–905.
- Ford JM (2014) Decomposing P300 to identify its genetic basis. *Psychophysiology* **51**, 1325–1326.
- Fraguas D, Díaz-Caneja CM, Pina-Camacho L, Janssen J, Arango C (2016) Progressive brain changes in children and adolescents with early-onset psychosis: a meta-analysis of longitudinal MRI studies. *Schizophrenia Research* **173**, 132–139.
- Frangou S, Sharma T, Sigmundsson T, Barta P, Pearson G, Murray RM (1997) The Maudsley Family Study. 4. Normal planum temporale asymmetry in familial schizophrenia. A volumetric MRI study. *The British Journal of Psychiatry* **170**, 328–333.
- Fusar-Poli P, Deste G, Smieskova R, Barlati S, Yung AR, Howes O, Stieglitz R-D, Vita A, McGuire P, Borgwardt S (2012) Cognitive functioning in prodromal psychosis: a meta-analysis. American Medical Association. *Archives of General Psychiatry* **69**, 562–571.
- Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S (2013) Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neuroscience & Biobehavioral Reviews* **37**, 1680–1691.
- Geschwind DH, Flint J (2015) Genetics and genomics of psychiatric disease. *Science* **349**, 1489–1494.
- Gladisjo JA, McAdams LA, Palmer BW, Moore DJ, Jeste DV, Heaton RK (2004) A six-factor model of cognition in schizophrenia and related psychotic disorders: relationships with clinical symptoms and functional capacity. *Schizophrenia Bulletin* **30**, 739.
- Glahn DC, Bearden CE, Cakir S, Barrett JA, Najt P, Serap Monkul E, Maples N, Velligan DI, Soares JC (2006) Differential working memory impairment in bipolar disorder and schizophrenia: effects of lifetime history of psychosis. *Bipolar Disorders* **8**, 117–123.
- Gogtay N, Sporn A, Clasen LS, Greenstein D, Giedd JN, Lenane M, Gochman PA, Zijdenbos A, Rapoport JL (2003) Structural brain MRI abnormalities in healthy siblings of patients with childhood-onset schizophrenia. *American Journal of Psychiatry* **160**, 569–571.
- González-Blanch C, Crespo-Facorro B, Álvarez-Jiménez M, Rodríguez-Sánchez JM, Pelayo-Terán JM, Pérez-Iglesias R, Vázquez-Barquero JL (2007) Cognitive dimensions in first-episode schizophrenia spectrum disorders. *Journal of Psychiatric Research* **41**, 968–977.
- Goodin DS, Squires KC, Henderson BH, Starr A (1978) Age-related variations in evoked potentials to auditory stimuli in normal human subjects. *Electroencephalography and Clinical Neurophysiology* **44**, 447–458.
- Gottesman II, Gould TD (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry* **160**, 636–645.
- Gratten J, Wray NR, Keller MC, Visscher PM (2014) Large-scale genomics unveils the genetic architecture of psychiatric disorders. *Nature Research. Nature Neuroscience* **17**, 782–790.
- Green EK, Rees E, Walters JTR, Smith K-G, Forty L, Grozeva D, Moran JL, Sklar P, Ripke S, Chambert KD, Genovese G, McCarrroll SA, Jones I, Jones L, Owen MJ, O’Donovan MC, Craddock N, Kirov G (2015) Copy number variation in bipolar disorder. Macmillan Publishers Limited. *Molecular Psychiatry* **21**, 89.
- Grozeva D, Conrad DF, Barnes CP, Hurles M, Owen MJ, O’Donovan MC, Craddock N, Kirov G (2011) Independent estimation of the frequency of rare CNVs in the UK population confirms their role in schizophrenia. *Schizophrenia Research* **135**, 1–7.
- Gur RE, Calkins ME, Gur RC, Horan WP, Nuechterlein KH, Seidman LJ, Stone WS (2007) The consortium on the genetics of schizophrenia: neurocognitive endophenotypes. *Schizophrenia Bulletin* **33**, 49–68.
- Gur RERC, Braff DL, Calkins ME, Dobie DJ, Freedman R, Green MF, Greenwood TA, Lazzaroni LC, Light GA, Nuechterlein KH, Olincy A, Radant AD, Seidman LJ, Siever LJ, Silverman JM, Sprock J, Stone WS, Sugar CA, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Gur RERC (2015) Neurocognitive performance in family-based and case-control studies of schizophrenia. Elsevier B.V. *Schizophrenia Research* **163**, 17–23.

- Habets P, Marcelis M, Gronenschild E, Drukker M, Van Os J (2011) Reduced cortical thickness as an outcome of differential sensitivity to environmental risks in schizophrenia. *Biological Psychiatry* **69**, 487–494.
- Hajima SV, Van Haren N, Cahn W, Koolschijn PCMP, Hulshoff Pol HE, Kahn RS (2013) Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophrenia Bulletin* **39**, 1129–1138.
- Hall M-H, Levy DL, Salisbury DF, Haddad S, Gallagher P, Lohan M, Cohen B, Öngür D, Smoller JW, Ongür D, Smoller JW (2014) Neurophysiologic effect of GWAS derived schizophrenia and bipolar risk variants. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* **165B**, 9–18.
- Hall MH, Schulze K, Bramon E, Murray RM, Sham P, Rijdsdijk F (2006a). Genetic overlap between P300, P50, and duration mismatch negativity. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics* **141**, 336–343.
- Hall MH, Schulze K, Rijdsdijk F, Picchioni M, Ettinger U, Bramon E, Freedman R, Murray RM, Sham P (2006b). Heritability and reliability of P300, P50 and duration mismatch negativity. Kluwer Academic Publishers-Plenum Publishers. *Behavior Genetics* **36**, 845–857.
- Hall MH, Smoller JW (2010) A new role for endophenotypes in the GWAS era: functional characterization of risk variants. *Harvard Review Psychiatry* **18**, 67–74.
- Harrison PJ (2015) Recent genetic findings in schizophrenia and their therapeutic relevance. *Journal of Psychopharmacology (Oxford, England)* **29**, 85–96.
- Hartberg CB, Sundet K, Rimol LM, Haukvik UK, Lange EH, Nesvåg R, Melle I, Andreassen OA, Agartz I (2011) Subcortical brain volumes relate to neurocognition in schizophrenia and bipolar disorder and healthy controls. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **35**, 1122–1130.
- Heinrichs RW, Zakzanis KK (1998) Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* **12**, 426–445.
- Hermens DF, Ward PB, Hodge MAR, Kaur M, Naismith SL, Hickie IB (2010) Impaired MMN/P3a complex in first-episode psychosis: cognitive and psychosocial associations. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **34**, 822–829.
- Heslenfeld DJ (2003) Visual mismatch negativity. In *Detection of Change: Event-Related Potential and fMRI Findings* (ed. J. Polich), pp. 41–59. Springer US: Boston.
- Ho B-C, Andreasen NC, Ziebell S, Pierson R, Magnotta V (2011) Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. American Medical Association. *Archives of General Psychiatry* **68**, 128–137.
- Horan WP, Braff DL, Nuechterlein KH, Sugar CA, Cadenhead KS, Calkins ME, Dobie DJ, Freedman R, Greenwood TA, Gur RE, Gur RC, Light GA, Mintz J, Olincy A, Radant AD, Schork NJ, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Green MF (2008) Verbal working memory impairments in individuals with schizophrenia and their first-degree relatives: findings from the consortium on the genetics of schizophrenia. *Schizophrenia Research* **103**, 218–228.
- Huhtaniska S, Jääskeläinen E, Hirvonen N, Remes J, Murray GK, Veijola J, Isohanni M, Miettunen J (2017) Long-term antipsychotic use and brain changes in schizophrenia – a systematic review and meta-analysis. *Human Psychopharmacology: Clinical and Experimental* **32**, e2574.
- Hulshoff Pol HE, Schnack HG, Bertens MGBC, van Haren NEM, van der Tweel I, Staal WG, Baaré WFC, Kahn RS (2002) Volume changes in gray matter in patients with schizophrenia. *The American Journal of Psychiatry* **159**, 244–250.
- Ian K, Jenner JA, Cannon M (2010) Psychotic symptoms in the general population – an evolutionary perspective. *The British Journal of Psychiatry: The Journal of Mental Science* **197**, 167–169.
- Ivleva EI, Morris DW, Osuji J, Moates AF, Carmody TJ, Thaker GK, Cullum M, Tamminga CA (2012) Cognitive endophenotypes of psychosis within dimension and diagnosis. Elsevier B.V. *Psychiatry Research* **196**, 38–44.
- Jasper H (1958) Report to the committee on methods of clinical examination in electroencephalography. *Electroencephalography and Clinical Neurophysiology* **10**, 371–375.
- Johns LC, van Os J (2001) The continuity of psychotic experiences in the general population. *Clinical Psychology Review* **21**, 1125–1141.
- Johnstone EC, Ebmeier KP, Miller P, Owens DGC, Lawrie SM (2005) Predicting schizophrenia: findings from the Edinburgh High-Risk Study. *The British Journal of Psychiatry* **186**, 18–25.
- Kaur M, Battisti RA, Ward PB, Ahmed A, Hickie IB, Hermens DF (2011) MMN/p3a deficits in first episode psychosis: comparing schizophrenia-spectrum and affective-spectrum subgroups. Elsevier B.V. *Schizophrenia Research* **130**, 203–209.
- Keilp JG, Sweeney JA, Jacobsen P, Solomon C, St. Louis L, Deck M, Frances A, Mann JJ (1988) Cognitive impairment in schizophrenia: specific relations to ventricular size and negative symptomatology. *Biological Psychiatry* **24**, 47–55.
- Kempton MJ, Stahl D, Williams SCR, DeLisi LE (2010) Progressive lateral ventricular enlargement in schizophrenia: a meta-analysis of longitudinal MRI studies. *Schizophrenia Research* **120**, 54–62.
- Kim D, Kim J, Koo T, Yun H, Won S (2015a). Shared and distinct neurocognitive endophenotypes of schizophrenia and psychotic bipolar disorder. *Clinical Psychopharmacology and Neuroscience* **13**, 94–102.
- Kim M, Seo H-J, Yun H, Jung Y-E, Park JH, Lee C-I, Moon JH, Hong S-C, Yoon B-H, Bahk W-M (2015b). The relationship between cognitive decline and psychopathology in patients with schizophrenia and bipolar disorder. *Clinical Psychopharmacology and Neuroscience* **13**, 103–108.
- Kim M-S, Kang S-S, Youn T, Kang D-H, Kim J-J, Kwon JS (2003) Neuropsychological correlates of P300 abnormalities in patients with schizophrenia and obsessive-compulsive disorder. *Psychiatry Research: Neuroimaging* **123**, 109–123.
- Konopaske GT, Dorph-Petersen KA, Pierri JN, Wu Q, Sampson AR, Lewis DA (2007) Effect of chronic exposure to antipsychotic medication on cell numbers in the parietal cortex of macaque monkeys. *Neuropsychopharmacology* **32**, 1216–1223.
- Korver N, Quee PJ, Boos HBM, Simons CJP, de Haan L (2012) Genetic Risk and Outcome of Psychosis (GROUP), a multi site longitudinal cohort study focused on gene-environment interaction: objectives, sample characteristics, recruitment and assessment methods. *International Journal of Methods in Psychiatric Research* **21**, 205–221.
- Kujala A, Naatanen R (2003) Auditory environment and change detection as indexed by the mismatch negativity (MMN). In *Detection of Change: Event-Related Potential and fMRI Findings* (ed. J. Polich), pp. 1–22. Springer US: Boston.
- Kumra S, Giedd JN, Vaituzis AC, Jacobsen LK, McKenna K, Bedwell J, Hamburger S, Nelson JE, Lenane M, Rapoport JL (2014) Childhood-onset psychotic disorders: magnetic resonance imaging of volumetric differences in brain structure. *American Journal of Psychiatry* **171**, 1467–1474.
- Lee J, Green MF, Calkins ME, Greenwood TA, Gur RERC, Gur RERC, Lazzaroni LC, Light GA, Nuechterlein KH, Radant AD, Seidman LJ, Siever LJ, Silverman JM, Sprock J, Stone WS, Sugar CA, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Braff DL (2015) Verbal working memory in schizophrenia from the Consortium on the Genetics of Schizophrenia (COGS) Study: the moderating role of smoking status and antipsychotic medications. Elsevier. *Schizophrenia Research* **163**, 24–31.
- Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, Mowry BJ, Thapar A, Goddard ME, Witte JS, Absher D, Agartz I, Akil H, Amin F, Andreassen OA, Anjorin A, Anney R, Anttila V, Arking DE, Asherson P, Azevedo MH, Backlund L, Badner JA, Bailey AJ, Banaschewski T, Barchas JD, Barnes MR, Barrett TB, Bass N, Battaglia A, Bauer M, Bayés M, Bellivier F, Bergen SE, Berrettini W, Betancur C, Bettecken T, Biederman J, Binder EB, Black DW, Blackwood DHR, Bloss CS, Boehnke M, Boomsma DI, Breen G, Breuer R, Bruggeman R, Cormican P, Buccola NG, Buitelaar JK, Bunney WE, Buxbaum JD, Byerley WF, Byrne EM, Caesar S, Cahn W, Cantor RM, Casas M, Chakravarti A, Chambert K, Choudhury K, Cichon S, Cloninger CR, Collier DA, Cook EH, Coon H, Cormand B, Corvin A, Coryell WH, Craig DW, Craig IW, Crosbie J, Cuccaro ML, Curtis D, Czamara D, Datta S, Dawson G, Day R, De Geus EJ, Deghardt F, Djurovic S, Donohoe GJ, Doyle AE, Duan J, Dudbridge F, Duketis E, Ebstein RP, Edenberg HJ, Elia J, Ennis S, Etain B, Fanous A,

- Farmer AE, Ferrier IN, Flickinger M, Fombonne E, Foroud T, Frank J, Franke B, Fraser C, Freedman R, Freimer NB, Freitag CM, Friedl M, Frisén L, Gallagher L, Gejman PV, Georgieva L, Gershon ES, Geschwind DH, Giegling I, Gill M, Gordon SD, Gordon Smith K, Green EK, Greenwood TA, Grice DE, Gross M, Grozeva D, Guan W, Gurling H, De Haan L, Haines JL, Hakonarson H, Joachim Hallmayer J, Hamilton SP, Hamshere ML, Hansen TF, Hartmann AM, Hautzinger M, Heath AC, Henders AK, Herms S, Hickie IB, Hipolito M, Hoefels S, Holmans PA, Holsboer F, Hoogendijk WJ, Hottenga JJ, Hultman CM, Hus V, Ingason A, Ising M, Jamain S, Jones EG, Jones I, Jones L, Jung-Ying T, Kähler AK, Kahn RS, Kandaswamy R, Keller MC, Kennedy JL, Kenny E, Kent L, Kim Y, Kirvo GK, Klauck SM, Klei L, Knowles JA, Kohli MA, Koller DL, Konte B, Korszun A, Krabbendam L, Krasucki R, Kuntsi J, Kwan P, Landén M, Långström N, Lathrop M, Lawrence J, Lawson WB, Leboyer M, Ledbetter DH, Hyoun Lee P, Lencz T, Lesch KP, Levinson DF, Lewis CM, Li J, Lichtenstein P, Lieberman JA, Lin DY, Linszen DH, Liu C, Lohoff FW, Loo SK, Lord C, Lowe JK, Lucae S, MacIntyre DJ, Madden PAF, Maestrini E, Magnusson PKE, Mahon PB, Maier W, Malhotra AK, Mane SM, Martin CL, Martin NG, Mattheisen M, Matthews K, Mattingdal M, McCarroll SA, McGhee KA, McGough JJ, McGrath PJ, McGuffin P, McInnis MG, McIntosh A, McKinney R, McLean AW, McMahon FJ, McMahon WM, McQuillin A, Medeiros H, Medland SE, Meier S, Melle I, Meng F, Meyer J, Middeldorp CM, Middleton L, Milanova V, Miranda A, Monaco AP, Montgomery GW, Moran JL, Moreno-De-Luca D, Morken G, Morris DW, Morrow EM, Moskvina V, Muglia P, Mühleisen TW, Muir WJ, Müller-Myhsok B, Murtha M, Myers RM, Myin-Germeys I, Neale MC, Nelson SF, Nivergelt CM, Nikolov I, Nimgaonkar V, Nolen WA, Nöthen MM, Nurnberger JI, Nwulia EA, Nyholt DR, O'Dushlaine C, Oades RD, Ann Olincy A, Guiomar Oliveira G, Olsen L, Ophoff RA, Osby U, Owen MJ, Palotie A, Parr JR, Paterson AD, Pato CN, Pato MT, Penninx BW, Pergadia ML, Pericak-Vance MA, Pickard BS, Pimm J, Piven J, Posthuma D, Potash JB, Poustka F, Propping P, Puri V, Queded DJ, Quinn EM, Ramos-Quiroga JA, Rasmussen HB, Raychaudhuri S, Rehnström K, Reif A, Ribasés M, Rice JP, Rietschel M, Roeder K, Roeyers H, Rossin L, Rothenberger A, Rouleau G, Ruderfer D, Rujescu D, Sanders AR, Sanders SJ, Santangelo S, Sargeant JA, Schachar R, Schalling M, Schatzberg AF, Scheftner WA, Schellenberg GD, Scherer SW, Schork NJ, Schulze TG, Schumacher J, Schwarz M, Scolnick E, Scott LJ, Shi J, Shilling PD, Shyn SI, Silverman JM, Slager SL, Smalley SL, Smit JH, Smith EN, Sonuga-Barke EJS, St Clair D, State M, Steffens M, Steinhausen HC, Strauss JS, Strohmaier J, Stroup TS, Sutcliffe J, Szatmari P, Szeflinger S, Thirumalai S, Thompson RC, Todorov AA, Tozzi F, Treutlein J, Uhr M, van den Oord EJCG, Van Grootheest G, Van Os J, Vicente AM, Vieland VJ, Vincent JB, Visscher PM, Walsh CA, Wassink TH, Watson SJ, Weissman MM, Werge T, Wienker TF, Wiersma D, Wijsman EM, Willemsen G, Williams N, Willsey AJ, Witt SH, Xu W, Young AH, Yu TW, Zammit S, Zandi PP, Zhang P, Zitman FG, Zöllner S, International Inflammatory Bowel Disease Genetics Consortium (IIBDGC), Devlin B, Kelsoe JR, Sklar P, Daly MJ, O'Donovan MC, Craddock N, Sullivan PF, Smoller JW, Kendler KS, Wray NR (2013) Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature Genetics* 45, 984–994.
- Light GA, Swerdlow NR, Thomas ML, Calkins ME, Green MF, Greenwood TA, Gur RE, Gur RC, Lazzaroni LC, Nuechterlein KH, Pela M, Radant AD, Seidman LJ, Sharp RF, Siever LJ, Silverman JM, Sprock J, Stone WS, Sugar CA, Tsuang DW, Tsuang MT, Braff DL, Turetsky BI (2015) Validation of mismatch negativity and P3a for use in multi-site studies of schizophrenia: characterization of demographic, clinical, cognitive, and functional correlates in COGS-2. *Elsevier B.V. Schizophrenia Research* 163, 63–72.
- Massuda R, Bücker J, Czepielewski LS, Narvaez JC, Pedrini M, Santos BT, Teixeira AS, Souza AL, Vasconcelos-Moreno MP, Vianna-Sulzbach M, Goi PD, Belmonte-de-Abreu P, Gama CS (2013) Verbal memory impairment in healthy siblings of patients with schizophrenia. *Schizophrenia Research* 150, 580–582.
- Mata I, Perez-Iglesias R, Roiz-Santiañez R, Tordesillas-Gutierrez D, Gonzalez-Mandly A, Vazquez-Barquero JL, Crespo-Facorro B (2009) A neuregulin 1 variant is associated with increased lateral ventricle volume in patients with first-episode schizophrenia. *Society of Biological Psychiatry. Biological Psychiatry* 65, 535–540.
- McDonald C, Grech A, Touloupoulou T, Schulze K, Chapple B, Sham P, Walshe M, Sharma T, Sigmundsson T, Chitnis X, Murray RM (2002) Brain volumes in familial and non-familial schizophrenic probands and their unaffected relatives. *American Journal of Medical Genetics* 114, 616–625.
- McDonald C, Marshall N, Sham PC, Bullmore ET, Schulze K, Chapple B, Bramon E, Filbey F, Quraishi S, Walshe M, Murray RM (2006) Regional brain morphometry in patients with schizophrenia or bipolar disorder and their unaffected relatives. *The American Journal of Psychiatry* 163, 478–487.
- McIntosh AM, Harrison LK, Forrester K, Lawrie SM, Johnstone EC (2005a). Neuropsychological impairments in people with schizophrenia or bipolar disorder and their unaffected relatives. *The British Journal of Psychiatry: The Journal of Mental Science* 186, 378–385.
- McIntosh AM, Job DE, Moorhead TWJ, Harrison LK, Forrester K, Lawrie SM, Johnstone EC (2004) Voxel-based morphometry of patients with schizophrenia or bipolar disorder and their unaffected relatives. *Biological Psychiatry* 56, 544–552.
- McIntosh AM, Job DE, Moorhead TWJ, Harrison LK, Lawrie SM, Johnstone EC (2005b). White matter density in patients with schizophrenia, bipolar disorder and their unaffected relatives. *Biological Psychiatry* 58, 254–257.
- Moberget T, Doan NT, Alnæs D, Kaufmann T, Córdova-Palomera A, Lagerberg TV, Diedrichsen J, Schwarz E, Zink M, Eisenacher S, Kirsch P, Jönsson EG, Fatouros-Bergman H, Flyckt L, Pergola G, Quarto T, Bertolino A, Barch D, Meyer-Lindenberg A, Agartz I, Andreassen OA, Westlye LT (2017) Cerebellar volume and cerebellocerebral structural covariance in schizophrenia: a multisite mega-analysis of 983 patients and 1349 healthy controls. *Nature Publishing Group. Molecular Psychiatry*.
- Nätäänen R (1990) The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. *Behavioral and Brain Sciences* 13, 201–233.
- Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM (2011) Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. *Biological Psychiatry* 70, 88–96.
- Park S, Gooding DC (2014) Working memory impairment as an endophenotypic marker of a schizophrenia diathesis. The Authors. *Schizophrenia Research: Cognition* 1, 127–136.
- Perneger TV (1998) What's wrong with Bonferroni adjustments. *British Medical Journal* 316, 1236–1238.
- Pierson A, Jouvent R, Quintin P, Perez-Diaz F, Leboyer M (2000) Information processing deficits in relatives of manic depressive patients. *Psychological Medicine* 30, 545–555.
- Pilowsky LS, Kerwin RW, Murray RM (1993) Schizophrenia: a neurodevelopmental perspective. *Neuropsychopharmacology* 9, 83–91.
- Polich J (1992) On the correlation between P300 amplitude and latency. *Bulletin of the Psychonomic Society* 30, 5–8.
- Polich J (1996) Meta-analysis of P300 normative aging studies. *Psychophysiology* 33, 334–353.
- Polich J (2007) Updating P300: an integrative theory of P3a and P3b. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology* 118, 2128–2148.
- Polich J (2011) Neurophysiology of P300. In *The Oxford Handbook of Event-Related Potential Components* (ed. E. S. Kappenman and S. J. Luck), pp. 89–294. Oxford University Press: New York.
- Polich J, Alexander JE, Bauer LO, Kuperman S, Morzorati S, O'Connor SJ, Porjesz B, Rohrbaugh J, Begleiter H (1997) P300 topography of amplitude/latency correlations. *Brain Topography* 9, 275–282.

- Polich J, Howard L, Starr A (1983) P300 latency correlates with digit span. *Psychophysiology* 20, 665–669.
- Polich J, Howard L, Starr A (1985) Effects of age on the P300 component of the event-related potential from auditory stimuli: peak definition, variation, and measurement. *Journal of Gerontology* 40, 721–726.
- Prie GW, Michie PT, Johnston J, Innes-Brown H, Kent A, Clissa P, Jablensky AV (2006) A multivariate electrophysiological endophenotype, from a unitary cohort, shows greater research utility than any single feature in the Western Australian Family Study of schizophrenia. *Biological Psychiatry* 60, 1–10.
- Psychosis Endophenotypes International Consortium PEI, Wellcome Trust Case-Control Consortium 2 WTC-CC, Bramon E, Pirinen M, Strange A, Lin K, Freeman C, Bellenguez C, Su Z, Band G, Pearson R, Vukcevic D, Langford C, Deloukas P, Hunt S, Gray E, Dronov S, Potter SC, Tashakkori-Ghanbaria A, Edkins S, Bumpstead SJ, Arranz MJ, Bakker S, Bender S, Bruggeman R, Cahn W, Chandler D, Collier DA, Crespo-Facorro B, Dazzan P, de Haan L, Di Forti M, Dragović M, Giegling I, Hall J, Iyegbe C, Jablensky A, Kahn RS, Kalaydjieva L, Kravartiti E, Lawrie S, Linszen DH, Mata I, McDonald C, McIntosh A, Myin-Germeys I, Ophoff RA, Pariante CM, Paunio T, Picchioni M, Psychiatric Genomics Consortium, Ripke S, Rujescu D, Sauer H, Shaikh M, Sussmann J, Suvisaari J, Tosato S, Touloupoulou T, Van Os J, Walshe M, Weisbrod M, Whalley H, Wiersma D, Blackwell JM, Brown MA, Casas JP, Corvin A, Duncanson A, Jankowski JAZ, Markus HS, Mathew CG, Palmer CNA, Plomin R, Rautanen A, Sawcer SJ, Trembath RC, Wood NW, Barroso I, Peltonen L, Lewis CM, Murray RM, Donnelly P, Powell J, Spencer CCA (2014) A genome-wide association analysis of a broad psychosis phenotype identifies three loci for further investigation. Elsevier. *Biological Psychiatry* 75, 386–397.
- Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P (2009) Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 460, 748–752.
- Ramchurn A, de Fockert JW, Mason L, Darling S, Bunce D (2014) Intraindividual reaction time variability affects P300 amplitude rather than latency. *Frontiers in Human Neuroscience* 8, 557.
- Ranlund S, Nottage J, Shaikh M, Dutt A, Constance M, Walshe M, Hall MH, Friston K, Murray R, Bramon E (2014) Resting EEG in psychosis and at-risk populations – A possible endophenotype? The Authors. *Schizophrenia Research* 153, 96–102.
- Reichenberg A, Caspi A, Harrington H, Houts R, Keefe RSE, Murray RM, Poulton R, Moffitt TE (2010) Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. *The American Journal of Psychiatry* 167, 160–169.
- Rey A (1964) *L'Examen Clinique en Psychologie*. Presses Universitaires de France: Paris.
- Ripke S, Neale BM, Corvin A, Walter JTR, Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511, 421–427.
- Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kähler AK, Akterin S, Bergen SE, Collins AL, Crowley JJ, Fromer M, Kim Y, Lee SH, Magnusson PKE, Sanchez N, Stahl EA, Williams S, Wray NR, Xia K, Bettella F, Borglum AD, Bulik-Sullivan BK, Cormican P, Craddock N, de Leeuw C, Durmishi N, Gill M, Golimbet V, Hamshere ML, Holmans P, Hougaard DM, Kendler KS, Lin K, Morris DW, Mors O, Mortensen PB, Neale BM, O'Neill FA, Owen MJ, Milovancevic MP, Posthuma D, Powell J, Richards AL, Riley BP, Ruderfer D, Rujescu D, Sigurdsson E, Silagadze T, Smit AB, Stefansson H, Steinberg S, Suvisaari J, Tosato S, Verhage M, Walters JT, Consortium MGS of S, Consortium PEI, 2 WTCCC, Bramon E, Corvin AP, O'Donovan MC, Stefansson K, Scolnick E, Purcell S, McCarroll SA, Sklar P, Hultman CM, Sullivan PF (2013) Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nature Genetics* 45, 1150–1159.
- Rothman KJ (1990) No adjustments are needed for multiple comparisons. *Epidemiology (Cambridge, Mass.)* 1, 43–46.
- Saperstein AM, Fuller RL, Avila MT, Adami H, McMahon RP, Thaker GK, Gold JM (2006) Spatial working memory as a cognitive endophenotype of schizophrenia: assessing risk for pathophysiological dysfunction. *Schizophrenia Bulletin* 32, 498–506.
- Savitz DA, Olshan AF (1995) Multiple comparisons and related issues in the interpretation of epidemiologic data. *American Journal of Epidemiology* 142, 904–908.
- Schulze K, MacCabe JH, Rabe-Hesketh S, Crawford T, Marshall N, Zanelli J, Walshe M, Bramon E, Murray RM, McDonald C (2006) The relationship between eye movement and brain structural abnormalities in patients with schizophrenia and their unaffected relatives. *Journal of Psychiatric Research* 40, 589–598.
- Schulze KK, Hall MHM-H, McDonald C, Marshall N, Walshe M, Murray RM, Bramon E (2008) Auditory P300 in patients with bipolar disorder and their unaffected relatives. *Bipolar Disorders* 10, 377–386.
- Seidman LJ, Helleman G, Nuechterlein KH, Greenwood TA, Braff DL, Cadenhead KS, Calkins ME, Freedman R, Gur RE, Gur RC, Lazzaroni LC, Light GA, Olincy A, Radant AD, Siever LJ, Silverman JM, Sprock J, Stone WS, Sugar C, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Green MF (2015) Factor structure and heritability of endophenotypes in schizophrenia: findings from the Consortium on the Genetics of Schizophrenia (COGS-1). Elsevier B.V. *Schizophrenia Research* 163, 73–79.
- Semlitsch HV, Anderer P, Schuster P, Presslich O (1986) A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. *Psychophysiology* 23, 695–703.
- Shaikh M, Hall M-H, Schulze K, Dutt A, Li K, Williams I, Walshe M, Constance M, Broome M, Picchioni M, Touloupoulou T, Collier D, Stahl D, Rijdsdijk F, Powell J, Murray RM, Arranz M, Bramon E (2013) Effect of DISC1 on the P300 waveform in psychosis. Oxford University Press. *Schizophrenia Bulletin* 39, 161–167.
- Sharma T, Lancaster E, Lee D, Lewis S, Sigmundsson T, Takei N, Gurling H, Barta P, Pearson G, Murray R (1998) Brain changes in schizophrenia. Volumetric MRI study of families multiply affected with schizophrenia – the Maudsley Family Study 5. *The British Journal of Psychiatry: The Journal of Mental Science* 173, 132–138.
- Sheffield JM, Gold JM, Strauss ME, Carter CS, MacDonald AW, Ragland JD, Silverstein SM, Barch DM (2014) Common and specific cognitive deficits in schizophrenia: relationships to function. *Cognitive, Affective & Behavioral Neuroscience* 14, 161–174.
- Shenton ME, Dickey CC, Frumin M, McCarley RW (2001) A review of MRI findings in schizophrenia. *Schizophrenia Research* 49, 1–52.
- Sitskoorn MM, Aleman A, Ebisch SJH, Appels MCM, Kahn RS (2004) Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophrenia Research* 71, 285–295.
- Sklar P, Ripke S, Scott LJ, Andreassen OA, Psychiatric GWAS Consortium Bipolar Disorder Working Group (2011) Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved. *Nature Genetics* 43, 977–983.
- Smoller JW, Finn CT (2003) Family, twin, and adoption studies of bipolar disorder. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 123C, 48–58.
- Smoller JW, Kendler KS, Craddock N, Lee PH, Neale BM, Nurnberger JJ, Ripke S, Santangelo S, Sullivan PF, Purcell S, Anney R, Buitelaar J, Fanous A, Faraone SV, Hoogendijk W, Lesch KP, Levinson DF, Perlis RH, Shaun P, Rietschel M, Riley B, Sonuga-Barke E, Schachar R, Schulze TG, Thapar A, Fanous A, Neale B, Neale M, Nurnberger JJ, Perlis R, Bender P, Cichon S, Daly MJ, Kelsoe J, Lehner T, Levinson D, O'Donovan M, Gejman P, Sebat J, Sklar P (2013) Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *The Lancet* 381, 1371–1379.
- Snitz BE, Macdonald AW, Carter CS (2006) Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophrenia Bulletin* 32, 179–194.
- Souza VBN, Muir WJ, Walker MT, Glabus MF, Roxborough HM, Sharp CW, Dunan JR, Blackwood DHR (1995) Auditory P300 event-related potentials and neuropsychological performance in schizophrenia and bipolar affective disorder. *Biological Psychiatry* 37, 300–310.
- Spitzer RL, Williams JW, Gibbon M, First MB (1992) The structured clinical interview for DSM-III-r (SCID): I: History, rationale, and description. *Archives of General Psychiatry* 49, 624–629.

- Steel RM, Whalley HC, Miller P, Best JJK, Johnstone EC, Lawrie SM (2002) Structural MRI of the brain in presumed carriers of genes for schizophrenia, their affected and unaffected siblings. *Journal of Neurology Neurosurgery & Psychiatry* 72, 455–458.
- Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA (2006) Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *The British Journal of Psychiatry: The Journal of Mental Science* 188, 510–518.
- Stefansson H, Rujescu D, Cichon S, Pietiläinen OPH, Ingason A, Steinberg S, Fossdal R, Sigurdsson E, Sigmundsson T, Buizer-Voskamp JE, Hansen T, Jakobsen KD, Muglia P, Francks C, Matthews PM, Gylfason A, Halldorsson BV, Gudbjartsson D, Thorgerisson TE, Sigurdsson A, Jonasdottir A, Jonasdottir A, Bjornsson A, Mattiasdottir S, Blondal T, Haraldsson M, Magnusdottir BB, Giegling I, Möller H-J, Hartmann A, Shianna KV, Ge D, Need AC, Crombie C, Fraser G, Walker N, Lonnqvist J, Suvisaari J, Tuulio-Henriksson A, Paunio T, Touloupoulou T, Bramon E, Di Forti M, Murray R, Ruggeri M, Vassos E, Tosato S, Walshe M, Li T, Vasilescu C, Mühleisen TW, Wang AG, Ullum H, Djurovic S, Melle I, Olesen J, Kiemenev LA, Franke B, Sabatti C, Freimer NB, Gulcher JR, Thorsteinsdottir U, Kong A, Andreassen OA, Ophoff RA, Georgi A, Rietschel M, Werge T, Petursson H, Goldstein DB, Nöthen MM, Peltonen L, Collier DA, St Clair D, Stefansson K, Kahn RS, Linszen DH, van Os J, Wiersma D, Bruggeman R, Cahn W, de Haan L, Krabbendam L, Myin-Germeys I (2008) Large recurrent microdeletions associated with schizophrenia. Nature Publishing Group. *Nature* 455, 232–236.
- Stone JL, O'Donovan MC, Gurling H, Kirov GK, Blackwood DHR, Corvin A, Craddock NJ, Gill M, Hultman CM, Lichtenstein P, McQuillin A, Pato CN, Ruderfer DM, Owen MJ, St Clair D, Sullivan PF, Sklar P, Purcell SM, Korn J, Macgregor S, Morris DW, O'Dushlaine CT, Daly MJ, Visscher PM, Holmans PA, Scolnick EM, Williams NM, Georgieva L, Nikolov I, Norton N, Williams H, Toncheva D, Milanova V, Thelander EF, Sullivan PF, Kenny E, Waddington JL, Choudhury K, Datta S, Pimm J, Thirumalai S, Puri V, Krasucki R, Lawrence J, Quedest D, Bass N, Curtis D, Crombie C, Fraser G, Leh Kwan S, Walker N, Muir WJ, McGhee KA, Pickard B, Malloy P, Maclean AW, Van Beck M, Pato MT, Medeiros H, Middleton F, Carvalho C, Morley C, Fanous A, Conti D, Knowles JA, Paz Ferreira C, Macedo A, Helena Azevedo M, McCarroll SA, Daly MJ, Chambert K, Gates C, Gabriel SB, Mahon S, Ardlie K (2008) Rare chromosomal deletions and duplications increase risk of schizophrenia. Macmillan Publishers Limited. All rights reserved. *Nature* 455, 237–241.
- Stone WS, Giuliano AJ, Tsuang MT, Braff DL, Cadenhead KS, Calkins ME, Dobie DJ, Faraone SV, Freedman R, Green MF, Greenwood TA, Gur RE, Gur RC, Light GA, Mintz J, Nuechterlein KH, Olincy A, Radant AD, Roe AH, Schork NJ, Siever LJ, Silverman JM, Swerdlow NR, Thomas AR, Tsuang DW, Turetsky BI, Seidman LJ (2011) Group and site differences on the California verbal learning test in persons with schizophrenia and their first-degree relatives: findings from the Consortium on the Genetics of Schizophrenia (COGS). Elsevier B.V. *Schizophrenia Research* 128, 102–110.
- Stone WS, Mesholam-Gately RI, Braff DL, Calkins ME, Freedman R, Green MF, Greenwood TA, Gur RERC, Gur RERC, Lazzaroni LC, Light GA, Nuechterlein KH, Olincy A, Radant AD, Siever LJ, Silverman JM, Sprock J, Sugar CA, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Seidman LJ (2015) California Verbal Learning Test-II performance in schizophrenia as a function of ascertainment strategy: comparing the first and second phases of the Consortium on the Genetics of Schizophrenia (COGS). Elsevier. *Schizophrenia Research* 163, 32–37.
- Strasser HC, Lilyestrom J, Ashby ER, Honeycutt NA, Schretlen DJ, Pulver AE, Hopkins RO, Depaulo JR, Potash JB, Schweizer B, Yates KO, Kurian E, Barta PE, Pearlson GD (2005) Hippocampal and ventricular volumes in psychotic and nonpsychotic bipolar patients compared with schizophrenia patients and community control subjects: a pilot study. *Biological Psychiatry* 57, 633–639.
- Sullivan PF, Daly MJ, O'Donovan M (2012) Genetic architectures of psychiatric disorders: the emerging picture and its implications. Nature Publishing Group. *Nature Reviews Genetics* 13, 537–551.
- Sullivan PF, Kendler KS, Neale MC (2003) Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Archives of General Psychiatry* 60, 1187.
- Thaker GK (2008) Neurophysiological endophenotypes across bipolar and schizophrenia psychosis. *Schizophrenia Bulletin* 34, 760–773.
- Toomey R, Faraone SV, Seidman LJ, Kremen WS, Pepple JR, Tsuang MT (1998) Association of neuropsychological vulnerability markers in relatives of schizophrenic patients. *Schizophrenia Research* 31, 89–98.
- Touloupoulou T, Goldberg TE, Mesa IR, Picchioni M, Rijdsdijk F, Stahl D, Cherny SS, Sham P, Faraone SV, Tsuang M, Weinberger DR, Seidman LJ, Murray RM (2010) Impaired intellect and memory: a missing link between genetic risk and schizophrenia? American Medical Association. *Archives of General Psychiatry* 67, 905–913.
- Turetsky BI, Cannon TD, Gur RE (2000) P300 subcomponent abnormalities in schizophrenia: III. Deficits in unaffected siblings of schizophrenic probands. *Biological Psychiatry* 47, 380–390.
- Turetsky BI, Dress EM, Braff DL, Calkins ME, Green MF, Greenwood TA, Gur RE, Gur RC, Lazzaroni LC, Nuechterlein KH, Radant AD, Seidman LJ, Siever LJ, Silverman JM, Sprock J, Stone WS, Sugar CA, Swerdlow NR, Tsuang DW, Tsuang MT, Light G (2015) The utility of P300 as a schizophrenia endophenotype and predictive biomarker: clinical and socio-demographic modulators in COGS-2. Elsevier B.V. *Schizophrenia Research* 163, 53–62.
- Üçok A, Direk N, Koyuncu A, Keskin-Ergen Y, Yüksel Ç, Güler J, Karadayi G, Akturan E, Devrim-Üçok M (2013) Cognitive deficits in clinical and familial high risk groups for psychosis are common as in first episode schizophrenia. *Schizophrenia Research* 151, 265–269.
- van Dinteren R, Arns M, Jongsma MLA, Kessels RPC (2014) P300 development across the lifespan: a systematic review and meta-analysis. Ed. F Di Russo. *PLoS ONE* 9, e87347.
- van Erp TGM, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, Agartz I, Westlye LT, Haukvik UK, Dale AM, Melle I, Hartberg CB, Gruber O, Kraemer B, Zilles D, Donohoe G, Kelly S, McDonald C, Morris DW, Cannon DM, Corvin A, Machielsen MWJ, Koenders L, de Haan L, Veltman DJ, Satterthwaite TD, Wolf DH, Gur RC, Gur RE, Potkin SG, Mathalon DH, Mueller BA, Preda A, Macciardi F, Ehrlich S, Walton E, Hass J, Calhoun VD, Bockholt HJ, Sponheim SR, Shoemaker JM, van Haren NEM, Pol HEH, Ophoff RA, Kahn RS, Roiz-Santiañez R, Crespo-Facorro B, Wang L, Alpert KI, Jönsson EG, Dimitrova R, Bois C, Whalley HC, McIntosh AM, Lawrie SM, Hashimoto R, Thompson PM, Turner JA (2016) Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Nature Publishing Group. *Molecular Psychiatry* 21, 547–553.
- Van Haren NE, Cahn W, Hulshoff Pol HE, Kahn RS (2013) Confounders of excessive brain volume loss in schizophrenia. *Neuroscience and Biobehavioral Reviews* 37, 2418–2423.
- Walhovd KB, Fjell AM (2003) The relationship between P3 and neuropsychological function in an adult life span sample. *Biological Psychology* 62, 65–87.
- Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, Nord AS, Kusenda M, Malhotra D, Bhandari A, Stray SM, Rippey CF, Rocanova P, Makarov V, Lakshmi B, Findling RL, Sikich L, Stromberg T, Merriman B, Gogtay N, Butler P, Eckstrand K, Noory L, Gochman P, Long R, Chen Z, Davis S, Baker C, Eichler EE, Meltzer PS, Nelson SF, Singleton AB, Lee MK, Rapoport JL, King M-C, Sebat J (2008) Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* 320, 539–543.
- Walters JTR, Corvin A, Owen MJ, Williams H, Dragovic M, Quinn EM, Judge R, Smith DJ, Norton N, Giegling I, Hartmann AM, Möller H-J, Muglia P, Moskvina V, Dwyer S, O'Donoghue T, Morar B, Cooper M, Chandler D, Jablensky A, Gill M, Kaladjeva L, Morris DW, O'Donovan MC, Rujescu D, Donohoe G, Article O (2010) Psychosis

- susceptibility gene ZNF804A and cognitive performance in schizophrenia. *Archives of General Psychiatry* **67**, 692–700.
- Waters F, Price G, Dragović M, Jablensky A** (2009) Electrophysiological brain activity and antisaccade performance in schizophrenia patients with first-rank (passivity) symptoms. *Psychiatry Research* **170**, 140–149.
- Wechsler D** (1981) *Wechsler Adult Intelligence Scale – Revised Manual*. Psychological Corporation: New York.
- Wechsler D** (1997) *Wechsler Adult Intelligence Scale, Third Edition: Administration and Scoring Manual*. Psychological Corporation: London.
- Weisbrod M, Hill H, Niethammer R, Sauer H** (1999) Genetic influence on auditory information processing in schizophrenia: p300 in monozygotic twins. *Biological Psychiatry* **46**, 721–725.
- Wiles NJ, Zammit S, Bebbington P, Singleton N, Meltzer H, Lewis G** (2006) Self-reported psychotic symptoms in the general population: results from the longitudinal study of the British national psychiatric morbidity survey. *The British Journal of Psychiatry: The Journal of Mental Science* **188**, 519–526.
- Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, Jablenski A, Regier D, Sartorius N** (1990) SCAN. Schedules for clinical assessment in neuropsychiatry. *Archives of General Psychiatry* **47**, 589–593.
- Winterer G, Coppola R, Sc D, Goldberg TE, Ph D, Egan MF, Jones DW, Sanchez CE, Weinberger DR, Raedler T, Sanchez CE, Jones DW, Coppola R, Weinberger DR** (2003) P300 and genetic risk for schizophrenia. American Medical Association. *Archives of General Psychiatry* **60**, 1158–1167.
- Wittorf A, Klingberg S, Wiedemann G** (2004) Secondary verbal memory: a potential endophenotype of schizophrenia. *Journal of Psychiatric Research* **38**, 601–612.
- Wobrock T, Gruber O, Schneider-Axmann T, Wölwer W, Gaebel W, Riesbeck M, Maier W, Klosterkötter J, Schneider F, Buchkremer G, Möller H-J, Schmitt A, Bender S, Schlösser R, Falkai P** (2009) Internal capsule size associated with outcome in first-episode schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience* **259**, 278–283.
- Wright IC, Rabe-Hesketh S, Woodruff PWR, David AS, Murray RM, Bullmore ET** (2000) Meta-analysis of regional brain volumes in schizophrenia. *The American Journal of Psychiatry* **157**, 16–25.
- Xu B, Roos JL, Levy S, van Rensburg EJ, Gogos JA, Karayiorgou M** (2008) Strong association of de novo copy number mutations with sporadic schizophrenia. Nature Publishing Group. *Nature Genetics* **40**, 880–885.