Full title:

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 -0.12–0.01, 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.

Keywords:

Schizophrenia; Unaffected relatives; P300; Working memory; Verbal memory; Lateral ventricular volume

Introduction

Psychotic disorders, including schizophrenia and bipolar disorder, have considerable heritability with estimates ranging between 60-85% (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 (Xu *et al.* 2008; Stefansson *et al.* 2008; Stone *et al.* 2008; Walsh *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 to 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 to controls (Sharma *et al.* 1998; Wright *et al.* 2000; Fannon *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 United Kingdom) (see 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; Steel *et al.* 2002; Hulshoff Pol *et al.* 2002; McDonald *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; Waters *et al.* 2009; Wobrock *et al.* 2009; Crespo-Facorro *et al.* 2009; Toulopoulou *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; Toulopoulou *et al.* 2010; Walters *et al.* 2010; Korver *et al.* 2012).

EEG data collection and processing

Electrophysiological data were obtained from three sites (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 1000Hz and rare (‘target’) tones of 1500Hz.

The number of tones presented varied from 150 to 800, the tones were 80dB or 97dB, lasted for 20-50ms, and the inter-stimulus interval was between 1 and 2 seconds. 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: 500Hz sampling rate and 0.03-120Hz band pass filter; 200Hz sampling rate and 0.05-30Hz band pass filter; or 400Hz sampling rate and 70Hz 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 250-550ms 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, 2005b; Schulze *et al.* 2006; Wobrock *et al.* 2009; Crespo-Facorro *et al.* 2009; Dutt *et al.* 2009; Mata *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 by 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 (Bramon et al, 2014; Ranlund et al., 2014; Shaikh et al., 2013).

We examined the distribution of residuals and plots of residuals versus 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 7 endophenotypes, we expect measurements within domains to be correlated and thus a correction of p-values by 7 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 3 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 to 13.4; p<0.001) and 11.9 years younger than controls (95% CI: 11.1 to 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 Figure 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 RVLT immediate recall. When compared to 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 to 0.26, p=0.009) and block design (coef. 0.19, 95% CI 0.10 to 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 Figure 2 (and 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 supplementary Table S3 for full results.

Discussion

This study examined the relationships between different multi-modal 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 to 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 and colleagues (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 to 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 (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 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.* 2015b). 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.* 2015b). 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 to 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.* 2015a). A limitation of our study is the heterogeneity of the MRI methodology between study sites, which might have obscured any true associations. We 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 regards to group comparisons, although patients showed enlarged lateral ventricles compared to 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 (Üçok *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 to 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 in 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 versus patients, controls versus 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 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' socioeconomic 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-analyzed 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 somme 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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Figure legends

Figure 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.

Figure 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.

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 (SD)†	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)†	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	N=397	N=379	N=313	N=1089
(μV)	10.5 (6.1)	11.0 (6.7)	13.7 (7.0)	11.6 (6.7)
P300 latency	N=401	N=386	N=315	N=1102
(ms)	382.6 (55.3)	390.8 (56.1)	356.9 (39.1)	378.2 (53.3)
Lateral Ventricular Volume	N=700	N=337	N=684	N=1721
(cm^3)	17.9 (9.9)	18.7 (11.2)	15.8 (8.8)	17.1 (9.8)
Block Design	N=850	N=895	N=3746	N=5491
(% of max. score)	49.9 (27.9)	47.4 (25.6)	60.4 (21.2)	56.6 (23.8)
Digit Span	N=460	N=136	N=2531	N=3127
(% of max. score)	47.4 (15.9)	40.0 (4.5)	51.5 (14.5)	50.4 (14.9)
RAVLT immediate recall	N=1232	N=934	N=1377	N=3543
(No. of words recalled)	7.6 (2.2)	8.4 (2.1)	8.7 (2.0)	8.2 (2.2)
RAVLT delayed recall	N=1224	N=927	N=1358	N=3509
(No. of words recalled)	2.1 (1.0)	2.9 (1.0)	2.9 (0.9)	2.6 (1.0)

SD = Standard deviation; NOS = Not otherwise specified; RAVLT = Rey Auditory Verbal Learning Task; † Missing data for age (717 subjects) and gender (6 subjects). The group differences in endophenotype performance adjusted by covariates are reported in table 2.

Table 2. Endophenptype performance comparison across clinical groups.

Endophenotype:	**Total Sample** Global p-value*	**Patients – Controls** Mean difference (95% CI)	**Patients – Relatives** Mean difference (95% CI)	**Relatives – Controls** Mean difference (95% CI)
P300 amplitude	< 0.001	-0.50 (-0.71 to -0.29) p < 0.001	-0.16 (-0.32 to -0.01) p = 0.061	-0.34 (-0.54 to -0.14) p = 0.001
P300 latency	< 0.001	0.47 (0.33 to 0.61) p < 0.001	0.03 (-0.14 to 0.19) p = 0.749	0.44 (0.29 to 0.60) p < 0.001
Lateral Ventricular Volume		0.20 (0.08 to 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) p < 0.001	-0.14 (-0.32 to 0.05) p = 0.141	-0.58 (-0.77 to -0.39) p < 0.001
Block Design	< 0.001	-0.91 (-1.07 to -0.75) p < 0.001	-0.08 (-0.21 to 0.04) p = 0.190	-0.83 (-0.97 to -0.69) p < 0.001
RAVLT immediate recall	< 0.001	-1.32 (-2.29 to -0.37) p = 0.007	-1.24 (-2.22 to -0.27) p = 0.012	-0.08 (-0.24 to 0.07) p = 0.286
RAVLT delayed recall	=0.123	-0.98 (-2.21 to 0.25) p =0.118	-0.94 (-2.18 to 0.30) p =0.136	-0.03 (-0.20 to 0.13) p = 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 by 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.

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