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The P300 as a possible endophenotype for schizophrenia and bipolar disorder: Evidence from twin and patient studies

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ABSTRACT

It has been proposed that psychophysiological abnormalities in schizophrenia, such as decreased amplitude of the evoked potential component P300, may be genetically influenced. Studies of heritability of the P300 have used different and typically more complex tasks than those used in clinical studies of schizophrenia. Here we present data on P300 parameters on the same set of auditory and visual tasks in samples of twins, and patients with schizophrenia or bipolar disorder to examine the P300 as a possible endophenotype. Evidence from the twin study indicated that the auditory, but not visual, P300 amplitude is genetically influenced at centro-parietal sites. Similarly, auditory and to a lesser extent visual P300 amplitude were decreased in schizophrenia and bipolar disorder. Results indicate that the auditory P300 may serve as an endophenotype for schizophrenia. However, given that schizophrenia and bipolar disorder patients could not be distinguished on these measures at midline sites, it appears that the P300 may be a marker for functional psychosis in general rather than being specific to schizophrenia.

1. Introduction

It has long been argued that there is a genetic component to schizophrenia (Harrison and Law, 2006). However, the complex phenotype of schizophrenia makes it difficult to find the genes associated with the illness. Endophenotypes are quantifiable characteristics that reflect the actions of fewer genes than the complex phenotype and should therefore be able to simplify genetic analyses with the aim of identifying susceptibility genes (Bramon et al., 2005; Turetsky et al., 2007). There are several criteria an endophenotype needs to fulfil (Gould and Gottesman, 2006; Gottesman and Shields, 1972). First, an endophenotype must be under genetic control. Second, it must be associated with an increased likelihood of the illness so that the abnormal behaviour is more often present in the affected individuals than the healthy population. Further, the endophenotype must be state independent and it must be related to the transmission of the illness (i.e. the characteristic must be found in probands as well as their unaffected relatives at a higher rate than in the general population).

A positive event-related potential (ERP) component, the P300, evoked during tasks that require the detection of rare target stimuli may serve as an endophenotype for certain forms of psychopathology, e.g. alcoholism (Almasy et al., 1999) or schizophrenia (Hall et al., 2007b; Sponheim et al., 2006). Independent of modality, the P300 amplitude elicited with these traditional "oddball" tasks is thought to reflect working memory function and/or attention (Donchin and Coles, 1988), whereas its latency is assumed to index stimulus processing speed (Leuthold and Sommer, 1998).

Heritability is one of the main requirements for endophenotypes. Several studies investigating the P300 in identical and non-identical pairs of healthy twins have shown that the P300 at the centro-parietal electrode site (Pz) is genetically influenced (Hall et al., 2006; Katsanis et al., 1997; Yoon et al., 2006). Researchers have also explored the heritability of the P300 variables in unaffected relatives of patients with schizophrenia with equivocal results. Some studies have found the P300 amplitude to be reduced in relatives (Frangou et al., 1997; Roxborough et al., 1993) suggesting that the P300 may be heritable and transmitted along with a given disorder (Katsanis et al., 1997). Other studies have found no evidence of a P300 reduction in relatives (Bramon et al., 2005; Winterer et al., 2003). These contradictory results could be due to the P300 abnormality only being present in a subset of relatives.

The purpose of the following studies was to investigate two requirements for the auditory and visual P300 to represent an endophenotype for schizophrenia. More specifically, using oddball tasks suitable for clinical populations, we investigated in the first experiment whether the P300 parameters are genetically influenced in a set of healthy identical and non-identical twins. Second, we tested whether the P300 in either modality is abnormal in schizophrenia

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and whether this abnormality is specific to schizophrenia compared with a related illness (bipolar disorder).

2. Experiment 1: Genetic influence on the visual and auditory P300

The P300 amplitude has repeatedly been shown to be under genetic control despite large individual variability. Evidence for a significant genetic contribution to the P300 amplitude comes from both family studies (Almasy et al., 1999; Hansell et al., 2005) and as well as in twin studies (e.g., for visual P300 see Katsanis et al., 1997; van Beijsterveldt et al., 1998, 2001; van Beijsterveldt and van Baal, 2002; Wright et al., 2001; Yoon et al., 2006; for auditory P300, see Hall et al., 2006; O'Connor et al., 1994) with heritability estimates ranging between 39% and 79%. Based on five twin studies, van Beijsterveldt and van Baal (2002) showed that the estimated meta-heritability of the P300 amplitude is 60%. There is still some debate to which extent genetic versus environmental factors contribute to the P300 latency (Katsanis et al., 1997; O'Connor et al., 1994). van Beijsterveldt and van Baal (2002) showed that the estimated meta-heritability of the P300 latency is 51%.

Research has also addressed the effects of age and gender on heritability estimates of the P300. Recently, a study by Smit et al. (2007) has shown that although the P300 amplitude is smaller in middle-aged adults than in young adults, there were no differences in heritability between the two cohorts. Carlson and Iacono (2006) found similar results when testing and retesting twins at roughly 3-year intervals. There may, however, be effects of gender on the heritability of the P300. O'Connor et al. (1994) found no gender-specific differences in the heritability of the P300 amplitude (see also Wright et al., 2001 for a similar finding using a complex working memory task to elicit the P300). However, studies by van Beijsterveldt et al. (1998, 2001) observed that the P300 amplitude is more heritable in teenage boys than girls. Similarly, Yoon et al.'s (2006) study suggests that the heritability of the P300 amplitude, at least in teenage twins, is larger in males than females.

When trying to relate findings from twin studies to those demonstrating P300 abnormalities in schizophrenia, one problem which emerges is that different paradigms have been used in the studies. The paradigms used in twin studies were typically more complex than the ones used in patient studies (Katsanis et al., 1997; van Beijsterveldt et al., 1998; Yoon et al., 2006). To elicit the P300, clinical studies tend to use traditional oddball tasks, i.e. simple two-stimulus discrimination tasks consisting of common standard stimuli (e.g. circles) and rare target stimuli (e.g. squares). In contrast, most recent twin studies have employed substantially more demanding cognitive tasks (e.g. delayed response tasks) or more complex stimuli (e.g. line drawings of cats (target) and dogs (standard); van Beijsterveldt et al., 1998). Experimental paradigms for cognitively impaired patients such as individuals with schizophrenia or bipolar disorder need to be simple enough to be manageable by the patient. Given that measurements resulting from more difficult cognitive tasks could reveal differences in heritability (van Beijsterveldt and van Baal, 2002), it is especially important to investigate correlations in twins on simple paradigms suitable for clinical populations.

To our knowledge, no other study has tested twins and patients on identical paradigms in the two modalities. The strength of the current P300 twin and patient studies reported here is therefore that both use the same paradigms appropriate for patients with attentional deficits (Polich, 2004). In addition, most recent twin studies have examined the visual P300 even though there is some dispute over whether the visual P300 is actually impaired in schizophrenia (Roth et al., 1999; Vohs et al., 2005).

Experiment 1 was designed to examine whether the P300 is genetically influenced in the visual and auditory modality. Samples of monozygotic (MZ) and dizygotic (DZ) twins were compared to assess the similarity of the P300 variables by means of intraclass correlations (McGraw and Wong, 1996). If the waveforms' amplitude and latency are genetically rather than environmentally influenced, correlations should be higher in individuals who share more genetic material.

2.1. Methods

2.1.1. Participants

Fourteen pairs of monozygotic (MZ) and 14 pairs of dizygotic (DZ) twins were recruited from a database of twins compiled by a previous study at the University of Aberdeen (McNeill et al., 2003). Zygosity analysis was conducted using DNA fingerprinting in the Department of Medical Genetics. The sample of MZ twins included two male pairs and was of a mean age of 34.1 years (S.D. = 12.01). The DZ sample also included two male pairs and was of a mean age of 33.8 years (S.D. = 11.28). All participants reported no neurological and psychiatric disorders. Participants had normal or corrected-to-normal hearing and vision. One member of a female MZ twin pair did not complete the visual oddball task due to time constraints and therefore only 13 MZ pairs were analysed for the visual task.

2.1.2. P300 paradigms

The auditory paradigm consisted of high (2000 Hz, 70 dB SPL) oddball and low (1000 Hz, 70 dB SPL) standard tones of 70 ms duration (10 ms rise/fall time). The tones were presented via two speakers positioned on either side of the stimulus monitor. The visual paradigm consisted of Xs (oddball) and Os (standard) each presented for 100 ms at the centre of the screen (Polich and Herbst, 2000). Stimulus size of the Xs and Os was approximately 18 cm × 12 cm. The stimuli in both paradigms were presented pseudo-randomly (each oddball stimulus had to be followed by at least three standard stimuli before the onset of the next oddball) with randomised inter-stimulus intervals of 2000, 2250, 2500, 2750 or 3000 ms.

2.1.3. Procedure

To minimise the effects of season, blood sugar level, ultradian rhythm and other confounds on the P300, the two individuals of each twin set were asked to arrange testing sessions within 1 week and at the same time of day. In a dimly lit and quiet room, participants were seated in front of a computer screen at an approximate viewing distance of 57 cm. Participants were provided with specific task instructions and asked to rest in between stimulus blocks. The EEG was recorded in response to two different P300 paradigms, one visual and one auditory. The order of paradigms was counterbalanced, and participants were asked to complete 20 practice trials before the start of the first visual and auditory block. During both tasks, participants were asked to fixate at a cross presented in the centre of the computer screen.

Each of the two paradigms consisted of 150 stimuli that were presented in two blocks. Oddball stimuli appeared with a probability of 20%. Participants were instructed to press one of two buttons with their index finger as soon as possible after the presentation of the oddball and the second button with the other index finger in response to the standard stimulus. Button responses were reversed after the presentation of the first block of 75 stimuli.

2.1.4. Recording conditions

Data acquisition was done at 500 Hz using amplifiers by Contact Precision Instruments coupled to a PC computer. The analog low-pass filter was set at 100 Hz and the analog 50-Hz notch filter was used. The high-pass filter was set at 0.01 Hz. Impedance for all electrodes was maintained at 5 kΩ or less. The EEG was recorded from eight tin electrodes mounted on an elasticated cap (Electro-cap International, Inc.) and placed at Fz, Cz, Pz, Oz, T7, P7, T8, and P8 and referenced to the right mastoid. The electro-oculogram was recorded with one electrode placed at the inner and another at the outer canthus of the left and right eye.

Analysis of the recordings was done offline. Ocular artefacts were corrected with a regression-based weighting procedure (Gratton