Effect of \textit{DISC1} on the P300 Waveform in Psychosis

Madiha Shaikh \textsuperscript{1}, Mei-Hua Hall\textsuperscript{2}, Katja Schulze\textsuperscript{3}, Anirban Dutt\textsuperscript{1}, Kuang Li\textsuperscript{1}, Ian Williams\textsuperscript{1}, Muriel Walshe\textsuperscript{1}, Miguel Constante\textsuperscript{1}, Matthew Broome\textsuperscript{1}, Marco Picchioni\textsuperscript{3}, Timothea Toulopoulou\textsuperscript{1}, David Collier\textsuperscript{1,4}, Daniel Stahl\textsuperscript{1}, Fruhling Rijsdijk\textsuperscript{4}, John Powell\textsuperscript{1}, Robin M. Murray\textsuperscript{1}, Maria Arranz\textsuperscript{1}, and Elvira Bramon\textsuperscript{1}

\textsuperscript{1}Department of Psychosis Studies, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King's College London and The South London and Maudsley NHS Foundation Trust, London SE5 8AF, UK; \textsuperscript{2}Psychology Research Laboratory, Harvard Medical School, McLean Hospital, Belmont, MA; \textsuperscript{3}St Andrew's Academic Centre, Institute of Psychiatry, King's College London, Northampton, UK; \textsuperscript{4}Medical Research Council, Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, King's College, London, UK

*To whom correspondence should be addressed; tel: +0044-207-848-0541, fax: +0044-207-848-0287, e-mail: madiha.1.shaikh@kcl.ac.uk

Coauthors are listed in Appendix A

\textbf{Introduction:} Abnormalities in the neurophysiological measures P300 amplitude and latency constitute endophenotypes for psychosis. Disrupted-in-Schizophrenia-1 (\textit{DISC1}) has been proposed as a promising susceptibility gene for schizophrenia, and a previous study has suggested that it is associated with P300 deficits in schizophrenia. \textbf{Methods:} We examined the role of variation in \textit{DISC1} polymorphisms on the P300 endophenotype in a large sample of patients with schizophrenia or psychotic bipolar disorder (\textit{n} = 149), their unaffected relatives (\textit{n} = 130), and unrelated healthy controls (\textit{n} = 208) using linear regression and haplotype analysis. \textbf{Results:} Significant associations between P300 amplitude and latency and \textit{DISC1} polymorphisms/haplotypes were found. Those homozygous for the A allele of single-nucleotide polymorphism (SNP) rs821597 displayed significantly reduced P300 amplitudes in comparison with homozygous for the G allele (\textit{P} = .009) and the heterozygous group (\textit{P} = .018). Haplotype analysis showed a significant association for \textit{DISC1} haplotypes (rs3738401|rs6675281|rs821597|rs821616|rs967244|rs980989) and P300 latency. Haplotype GCGTCG and ACGTTT were associated with shorter latencies. \textbf{Discussion:} The P300 waveform appears to be modulated by variation in individual SNPs and haplotypes of \textit{DISC1}. Because \textit{DISC1} is involved in neurodevelopment, one hypothesis is that disruption in neural connectivity impairs cognitive processes illustrated by P300 deficits observed in this sample.

\textbf{Key words:} psychosis/schizophrenia/bipolar disorder/EEG/ERP/P300/DISC1/endophenotype/neurophysiology/family study/haplotype analysis/biomarker

\textbf{Introduction}

Endophenotypes (intermediate quantitative traits) are one strategy to aid gene identification for complex disorders.\textsuperscript{1} The auditory P300 event-related potential (ERP) is well studied in the schizophrenia literature. P300 amplitude is believed to index working memory, while its latency is believed to index stimulus evaluation time\textsuperscript{2} and correlates negatively with mental function in nonclinical samples. Shorter latencies reflecting superior cognitive performance.\textsuperscript{4} There are convincing reports of significant P300 amplitude reductions and latency delays in patients with schizophrenia and bipolar disorder,\textsuperscript{5,6} their unaffected first-degree relatives,\textsuperscript{5,9} and individuals at high-risk for developing psychosis.\textsuperscript{10} These findings support P300 deficits as putative endophenotypes for genetic investigations.\textsuperscript{11}

There is evidence of a specific genetic association between reduced P300 amplitude from a large Scottish pedigree with a balanced translocation of the long arm of chromosome 1 and the short arm of chromosome 11 (t 1:11).\textsuperscript{12} This translocation disrupts the \textit{DISC1} gene at the chromosome 1 breakpoint and is strongly linked to schizophrenia (logarithm of the odds [LOD] score = 3.6). However, an even greater LOD score of 7.1 is achieved when schizophrenia, bipolar disorder, and recurrent major depression are collapsed as a broad diagnostic class, suggesting that the translocation as a risk factor is not specific to schizophrenia.\textsuperscript{13} Among the members of this family, those with the translocation exhibited reduced P300 amplitudes compared with both noncarrier relatives and unrelated control subjects. This association was observed even among carriers of the translocation with no psychiatric symptoms, strongly implicating a cosegregation between P300 amplitude and the \textit{DISC1} translocation.\textsuperscript{14} Many studies have found associations between candidate genes and endophenotypes for psychosis\textsuperscript{15-19}; however, some studies have failed to show such
Table 1. Demographic Information for the Combined Sample of 487 Individuals

<table>
<thead>
<tr>
<th></th>
<th>Patient (N = 154)</th>
<th>Relatives (N = 128)</th>
<th>Controls (N = 205)</th>
<th>Statistic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:Female (% male)</td>
<td>94:60 (61)</td>
<td>53:75 (41)</td>
<td>79:126 (39)</td>
<td>$\chi^2$ = 19.65</td>
<td>&lt;.000</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>40.8 (11.4)</td>
<td>45.5 (13.0)</td>
<td>38.1 (12.4)</td>
<td>$t = -5.18$, 95% CI $-10.17$ to $-4.57^a$</td>
<td>&lt;.001$^a$</td>
</tr>
<tr>
<td>DSM-IV</td>
<td></td>
<td></td>
<td></td>
<td>$t = -2.10$, 95% CI $-5.20$ to $-1.70^b$</td>
<td>.036$^b$</td>
</tr>
<tr>
<td>Schizophrenia (90)</td>
<td>No psychiatric illness (89)</td>
<td>No psychiatric illness (181)</td>
<td>na</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Schizoaffective disorder (11)</td>
<td>Depression without psychosis (34)</td>
<td>Depression without psychosis (19)</td>
<td>na</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Psychotic Bipolar disorder (51)</td>
<td>Anxiety disorder (3)</td>
<td>Anxiety disorder (2)</td>
<td>na</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Psychosis not otherwise specified (2)</td>
<td>Panic disorder (2)</td>
<td>Anorexia (3)</td>
<td>na</td>
<td>na</td>
<td></td>
</tr>
</tbody>
</table>

Note: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

$^a$Relatives vs controls.

$^b$Patients vs controls.

$^c$Nineteen controls had a lifetime history of depression but were euthymic at the time of testing.

observations. Since the original linkage report of translocation of DISC1 gene and its cosegregation with P300 ERP deficits, to our knowledge, no follow-up studies have been reported that examine the association between P300 ERP abnormalities and DISC1 in schizophrenia and bipolar disorder. As false positives are common in psychiatric genetic research, this study seeks to replicate findings for DISC1 in a larger sample in an attempt to examine the effects of DISC1 variants on the working memory related P300 ERP endophenotype. This study investigates the influence of 6 well-researched SNPs (rs3738401|rs6675281|rs821597|rs821616|rs967244|rs980989) and haplotypes of the DISC1 gene on the P300 waveform in patients with schizophrenia or psychotic bipolar disorder, their unaffected family members, and control subjects.

Methods

Sample
The total sample included 487 Caucasian subjects from the Maudsley Family Psychosis Study and Maudsley Twin Psychosis Study who agreed to donate DNA and undergo an electroencephalogram (EEG) recording. Patients satisfied Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (DSM-IV) criteria for schizophrenia, schizoaffective disorder, or psychotic bipolar disorder. Their unaffected first-degree relatives and the healthy control subjects were free of any personal history of psychotic illness, while in addition, the controls had no family history of psychotic disorders (up to second-degree relatives). Subjects were excluded from the study if they had a diagnosis of alcohol or substance dependence in the last 12 months, neurological disorders, or head injury with loss of consciousness longer than 10 minutes. After a complete description of the study, all participants gave written informed consent. The study was approved by the Joint South London and Maudsley and the Institute of Psychiatry NHS Research Ethical Committee. Demographic information for the sample is provided in table 1.

Clinical Assessments
Structured interviews using the Schedule for Affective Disorders and Schizophrenia-Lifetime version or the Structured Clinical Interview for DSM-IV Axis I Disorders were completed and additional clinical information regarding the timing and nature of symptoms obtained to enable DSM-IV diagnoses to be made or ruled out in all participants. Interviews were supplemented with information from relatives and medical notes where available. Information regarding psychiatric diagnoses of family members not directly assessed was collected from the most reliable informant(s) with the Family Interview for Genetic Studies and from medical notes when available.

P300 Data Acquisition and Analysis
This is described in more detail elsewhere. The EEG was collected during a standard auditory P300 oddball task. Stimuli were four hundred 80 dB tones, with variable $2 \pm 0.2$ second interstimulus interval presented through bilateral intraaural earphones. 80% of the tones were ‘nontargets’ of 1000 Hz and 20% were ‘targets’ of 1500 Hz in a random sequence. Subjects were instructed to press a button in response to targets only. EEG data were collected from 3 midline scalp sites (FZ, CZ, and PZ) according to the 10/20 International System. Data were continuously digitized at 500 Hz with a 0.03
to 120 Hz band-pass filter (24 dB/octave roll-off). Impedances were kept below 5 kΩ. Ocular artefacts were corrected using regression based weighting coefficients. P300 latency and peak amplitude were measured at the largest possible value between 280 and 500 ms with a computer algorithm and thus blind to affectedness group.

Molecular Genetics
The 6 DISC1 SNPs (rs3738401|rs6675281|rs821597|rs821616|rs967244|rs980989) were genotyped (blind to clinical information) by Prevention Genetics (www.preventiongenetics.com) using the Amplifluor SNPs genotyping system (Chemicon International). SNPs were chosen because they had previously been associated with psychotic disorders and cognitive deficits.27–29

The genotype frequencies of control, relative, patient, and combined samples were all consistent with Hardy–Weinberg equilibrium for rs3738401, rs967244, and rs980989. Single-nucleotide polymorphism (SNP) rs6675281 deviated from Hardy–Weinberg equilibrium in the controls (χ² = 7.37, df = 1, P = .01) and in the combined sample (χ² = 12.35, df = 1, P = .0004). SNP rs821616 deviated from Hardy–Weinberg equilibrium in the relatives (χ² = 6.47, df = 1, P = .01) and SNP rs821597 in the patients (χ² = 4.14, df = 1, P = .04). This was because there were only between 2 and 5% homozygous for the rare alleles, certainly a chance deviation, while acknowledging that within this family study design, the observations were nonindependent.30

Statistical Analysis
The statistical software packages used were SPSS (Version 15.0, SPSS Inc, Chicago, IL) and STATA (Version 10.1, StataCorp, TX). The effects of genotype on P300 amplitude and latency at PZ were examined using regression analysis. The P300 index (amplitude/latency) was the dependent variable, genotype was the independent variable while controlling for the effects of clinical group (patient and relative control), age, gender, and EEG laboratory used (accounting for the main upgrades in the equipment used for EEG data collection). The neurophysiological equipment was upgraded few times, although the paradigm remained the same. For this reason, equipment (laboratory) was also adjusted for in the analyses. These analyses used random intercepts for family clusters to account for the cluster-correlated nature of the observations inherent to the family-based nature of the data.

Haplotype association studies were performed for the combination of 6 DISC1 polymorphisms and P300 indices using version 1.07, PLINK software31 (http://pngu.mgh.harvard.edu/purcell/plink/).

Results
Effect of Genotype on P300 Indices
DISC1 Effects on P300 Amplitude
SNP rs821597 had a significant effect on P300 amplitude. Those homozygous for the A allele had a reduced P300 amplitude in comparison with those homozygous for the G allele (Estimated difference [Est diff]: −2.64 μV; 95% CI: −4.62 to −0.67 μV; P = .009) and the heterozygous group (Est diff: −2.33 μV; 95% CI: −4.27 to −0.40 μV; P = .018). There no significant group × gene interactions and the final model explained 21% (R² = .21) of the variance in P300 amplitude. No other DISC1 SNPs or haplotypes were associated with P300 amplitude (table 2).

DISC1 Effects on P300 Latency
There were no main effects of the individual SNPs on P300 latency. Haplotype analysis showed a significant association for DISC1 haplotypes (rs3738401|rs6675281|rs821597|rs821616|rs967244|rs980989). Haplotype GCGTCG (beta = −38.19, P = .03) and ACGTTT (beta = −23.49, P = .05) were associated with shorter latencies.

Group Differences in P300 Indices
The P300 amplitude in a sample of 660 individuals (277 controls, 183 relatives, and 200 patients) is significantly impaired in patients when compared with controls (Est diff = −2.2 μV, 95% CI = −3.44 to 0.97, P = .001). The P300 latency is impaired in both the patient group (Est diff = 29.25 ms, 95% CI = 21.35–37.14, P = .001) and unaffected relatives (Est diff = 17.76 ms, 95% CI = 9.61–25.91, P = .001) when compared with controls.

Discussion
This study demonstrates P300 deficits in psychotic patients and also in their first-degree relatives and provides evidence in support of an association between DISC1 and the P300 endophenotype, which is particularly relevant to the neurobiology of schizophrenia and psychosis. We investigated the effects of the DISC1 gene on brain neurophysiology by examining associations between each of the 6 individual SNPs in the DISC1 gene and P300 amplitude and latency as well as associations between haplotypes and P300 components. We found a significant association between P300 amplitude and rs821597 as well as a haplotype association between GCGTCG and ACGTTT (rs3738401|rs6675281|rs821597|rs821616|rs967244|rs980989) and shorter P300 latencies. The haplotype associations appear to be protective, resulting in improved P300 performance marked by shorter latencies. Haplotypes GC(G)TCG and AC(G)TTT contain the G allele of rs821597 that was associated with larger P300
Table 2. P300 Amplitude and Latency by Genotype Group (Unadjusted Means ± 1 SD)

<table>
<thead>
<tr>
<th>SNP</th>
<th>N</th>
<th>P300 Amplitude μV</th>
<th>P300 Latency (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISC1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs3738401</td>
<td>GG</td>
<td>12.00 (6.6)</td>
<td>360.93 (49.21)</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>12.80 (6.37)</td>
<td>370.08 (47.49)</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>12.8 (6.37)</td>
<td>371.21 (56.39)</td>
</tr>
<tr>
<td>rs6675281</td>
<td>CC</td>
<td>12.27 (6.46)</td>
<td>365.02 (48.43)</td>
</tr>
<tr>
<td></td>
<td>TC</td>
<td>12.62 (6.55)</td>
<td>372.28 (52.66)</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>14.42 (6.00)</td>
<td>366.33 (37.77)</td>
</tr>
<tr>
<td>rs821616</td>
<td>TT</td>
<td>12.61 (6.48)</td>
<td>368.35 (51.68)</td>
</tr>
<tr>
<td></td>
<td>AT</td>
<td>12.2 (6.59)</td>
<td>364.5 (46.65)</td>
</tr>
<tr>
<td>rs967244</td>
<td>TT</td>
<td>12.22 (6.63)</td>
<td>371.44 (46.05)</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>12.34 (6.10)</td>
<td>373.21 (49.23)</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>12.10 (6.18)</td>
<td>350.50 (74.45)</td>
</tr>
<tr>
<td>rs821597</td>
<td>GG</td>
<td>13.04 (6.57)</td>
<td>365.14 (47.61)</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>11.82 (6.53)</td>
<td>377.70 (48.63)</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>10.75 (4.63)</td>
<td>364.60 (50.21)</td>
</tr>
<tr>
<td>rs980989</td>
<td>GG</td>
<td>12.38 (6.58)</td>
<td>371.50 (50.7)</td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td>12.49 (6.13)</td>
<td>369.07 (41.29)</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>12.98 (6.28)</td>
<td>370.09 (56.23)</td>
</tr>
</tbody>
</table>

Thus the results suggest that the G allele of SNP rs821597 confers shorter P300 latency and increased amplitude. The association between P300 amplitude/latency and the SNPs investigated here suggests that variation in DISC1, or another locus in linkage disequilibrium with them, could influence the cognitive processing of auditory stimuli. We found that no significant associations between DISC1 polymorphisms and psychosis in our sample (data are available from authors). This is expected since our sample was underpowered to detect small genetic effects and justified the rationale to use P300 as an endophenotype to increase statistical power.

DISC1 is expressed in neurons and supporting cells (glia) and is translated to a protein that impacts on neurodevelopmental and neurochemical processes thought to be involved in the pathophysiology of schizophrenia, including neurite outgrowth, neuronal migration, synaptogenesis, and glutamatergic transmission. Thus, it is plausible to say DISC1 will have an influence on biological endophenotypes for psychosis. Our results are consistent with other studies documenting an association between DISC1 and developmental and functional abnormalities in psychosis, including modified hippocampal, gray matter, and frontal white matter volume, reduced prefrontal cortical gray matter and lateral ventricular enlargement, impairments in short and long-term memory and P300 characteristics. It is plausible to speculate that DISC1 influences memory function. This is consistent with the results of the present study in that P300 ERP components index working memory and information processing speed. The present study replicates and extends the association between DISC1 and P300 originally reported by Blackwood et al., by refining the association to specific polymorphisms in the DISC1 region and estimating their effect sizes (0.2–0.4).

Historically, bipolar disorder and schizophrenia have been considered distinct nosological entities, differing fundamentally in their etiology and prognosis. The validity of maintaining such a distinction is increasingly unclear. Psychosis, for example, is a core feature of schizophrenia and is common in bipolar disorder. One working hypothesis is that some risk genes are common to schizophrenia, schizoaffective disorder, and bipolar disorder and that these shared susceptibility genes predispose individuals to psychosis in general. Our results support this view.

This study was not designed to address possible medication effects; only self-report data on prescribed dosages rather than blood levels or other objective measures of medication status were collected. Therefore, medication as a contributing factor to P300 responses in patients cannot be ruled out. However, the fact that P300 deviations were also observed in unaffected relatives suggests that medication effects alone cannot account for the findings.

Casual or intermittent use of any number of illicit substances and tobacco may have long-term effects on electrophysiological measures and thus drug/tobacco usage could be a potential confounding factor. While substance (except nicotine) and alcohol use meeting criteria for dependence in the last 12 months was an exclusion criterion for all participants, substance and alcohol use...
misuse was not. Information on use of a number of illicit substances and tobacco use was collected by self-report and is available for a subset of the sample. Only a small proportion (2 patients and 3 relatives) reported regularly using one or more illicit substances over the last year. The low prevalence of reported substance use in this sample suggests that even if underreported, substance use was unlikely to be a major factor in this sample. As can be expected, the proportion of current regular smokers was significantly higher in patients (38%) compared with controls (17%) and patients smoked significantly more cigarettes per day than control subjects. Relatives showed no significant differences from controls in smoking habits. Therefore, significant findings of P300 deficits in the relatives who do not differ in smoking habits compared with controls shows that there is an association between P300 and genetic liability for schizophrenia not confounded by the use of tobacco.

While P300 abnormalities are reliably found in schizophrenia and bipolar disorder, the deficits are not specific to these illnesses. P300 abnormalities have been demonstrated in patients with Alzheimer’s disease and their unaffected children, in children diagnosed with attention deficit hyperactivity disorder, in patients with unipolar depression, and in alcohol dependence. This suggests that P300 abnormalities detected in psychosis might reflect a more general biological and cognitive vulnerability or risk factor that cuts across current psychiatric diagnostic categories. Though the sensitivity, specificity, and predictive value for the P300 are low and therefore not useful for diagnostic purposes, it is however useful for genetic association studies to understand the function of genes associated with psychosis.

Since Bonferroni adjustments for multiple testing are prone to additional faults, specifically over correction, the uncorrected values are given in the results to allow a full interpretation of the data. Using a Bonferroni corrected alpha level of 0.05/12 = 0.004; these results no longer remain statistically significant. To summarize, an SNP of DISC1 and haplotypes of DISC1 contribute to variation in the P300 endophenotype, suggestive of possible genetic mechanisms underlying the disease liability indexed in this way. However, these variants need to be tested in independent samples and in large cohorts with comprehensive data on endophenotypes related to disease liability. Lastly, it will be important to consider potential gene-environment interactions in subsequent analyses and future studies could focus on potential epistatic interactions of the DISC1 gene with other genes that may increase risk for psychosis.

Funding
Wellcome Trust; Schizophrenia Research Fund; National Alliance for Research on Schizophrenia and Depression; British Medical Association; Psychiatry Research Trust.

Acknowledgments
We are grateful to all those who participated in our research study. E. Bramon holds an MRC new investigator award. We also thank the NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Kings College London’ for financial support. The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Appendix A

Coauthors
Mei Hua Hall, Post Doctoral Researcher, Psychology Research Laboratory, Harvard Medical School, McLean Hospital, Belmont, Massachusetts, USA
Katja Schulze, Clinical Psychologist, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King’s College London and The South London and Maudsley NHS Foundation Trust, London, UK
Ian Williams, Researcher, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King’s College London and The South London and Maudsley NHS Foundation Trust, London, UK
Anirban Dutt, Clinical Lecturer, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King’s College London and The South London and Maudsley NHS Foundation Trust, London, UK
Muriel Walshe, Lecturer, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King’s College London and The South London and Maudsley NHS Foundation Trust, London, UK
Miguel Constante, PhD Student, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King’s College London and The South London and Maudsley NHS Foundation Trust, London, UK
Matthew Broome, Senior Lecturer, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King’s College London and The South London and Maudsley NHS Foundation Trust, London, UK
Marco Picchioni, Senior Lecturer, St Andrew’s Academic Centre, Institute of Psychiatry, King’s College London, Northampton, NN1
Timothea Toulopoulou, Lecturer, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King’s College London and The South London and Maudsley NHS Foundation Trust, London, UK
Fruhling Rijsdijk, Senior Lecturer, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King’s College London and The South London and Maudsley NHS Foundation Trust, London, UK

P300 Amplitude and Latency by Genotype Group (Unadjusted Means)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>29</td>
<td>11.63 (6.02)</td>
</tr>
<tr>
<td>AG</td>
<td>196</td>
<td>12.80 (6.37)</td>
</tr>
<tr>
<td>CT</td>
<td>57</td>
<td>12.34 (6.10)</td>
</tr>
<tr>
<td>TT</td>
<td>21</td>
<td>14.42 (6.00)</td>
</tr>
<tr>
<td>GG</td>
<td>125</td>
<td>11.82 (6.53)</td>
</tr>
<tr>
<td>AT</td>
<td>197</td>
<td>12.20 (6.59)</td>
</tr>
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<td>AG</td>
<td>90</td>
<td>11.82 (6.53)</td>
</tr>
<tr>
<td>GG</td>
<td>125</td>
<td>11.82 (6.53)</td>
</tr>
</tbody>
</table>

Table 2.
Psychiatry, King’s College London and The South London and Maudsley NHS Foundation Trust, London, UK

John Powell, Reader, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King’s College London and The South London and Maudsley NHS Foundation Trust, London, UK

Maria Arranz, Senior Lecturer, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King’s College London and The South London and Maudsley NHS Foundation Trust, London, UK

Robin Murray, Professor, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King’s College London and The South London and Maudsley NHS Foundation Trust, London, UK

Elvira Bramon, Senior Lecturer, NIHR Biomedical Research Centre for Mental Health at the Institute of Psychiatry, King’s College London and The South London and Maudsley NHS Foundation Trust, London, UK

M. Shaikh et al.

References


