# Supplement

**Table S1.** Study sites and sample sizes.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Affiliation** | **City** | **Country** | **Number of participants** | | | | **Endophenotypes contributed** |
| **Total** | **C** | **R** | **P** |
| The University of Western Australia | Perth | Australia | 893 | 224 | 260 | 409 | P300, RAVLT |
| Heidelberg University | Heidelberg | Germany | 78 | 23 | 19 | 36 | P300, LVV |
| Ludwig-Maximilians, University of Munich | Munich | Germany | 2185 | 2185 | - | - | Block Design, Digit Span |
| *GROUP consortium*: University of Amsterdam, University of Groningen, Maastricht University, University of Utrecht | Amsterdam, Groningen, Maastricht, Utrecht | Holland | 2993 | 1484 | 722 | 787 | Block Design, RAVLT, LVV |
| Fundacion Argibide, Pamplona | Pamplona | Spain | 69 | - | - | 69 | Digit Span, RAVLT |
| Universidad de Cantabria, Santander | Santander | Spain | 630 | 359 | - | 271 | LVV, Digit Span, RAVLT |
| University of Edinburgh | Edinburgh | United Kingdom | 160 | 87 | - | 73 | LVV, Block Design, Digit Span |
| Institute of Psychiatry, King's College London | London | United Kingdom | 1746 | 693 | 486 | 567 | P300, LVV, Block Design, Digit Span, RAVLT |
| C = controls; R = relatives, P = patients; LVV = lateral ventricular volume; RAVLT = Ray Auditory Verbal Learning Task | | | | | | | |

**Additional MRI methods**

MRI data acquisition and image processing varied between sites and are references and outlined briefly here.

### Germany (Heidelberg)

Scanner used: 1.5 T (Tesla) Phillips. Acquisition sequence: Magnetisation prepared rapid acquisition gradient echo (MPRAGE). Acquisition protocol: Flip angle = 15°, TR = 11.4 ms, TE = 4.4 ms. Images were analysed using a region of interest tool in the software Analyze, and lateral ventricular volume was defined according to borders described in the literature (Shenton *et al.*, 2001). For full details see (Wobrock *et al.*, 2009).

### Holland (Maastricht)

Scanner used: 3 T Siemens (Erlangen, Germany). Acquisition sequence: Either a modified driven equilibrium Fourier transform (MDEFT), or a magnetization prepared rapid acquisition gradient echo (MPRAGE). Acquisition protocol either; i) Flip angle = 15°, TR = 7.92 ms, TE = 2.4 ms, or ii) Flip angle = 9°, TR = 2250 ms, TE = 2.6 ms. Images were analysed using Freesurfer. Automatic labelling of each MRI voxel was carried out based on probabilistic information derived from training on a manually labelled dataset (Fischl *et al.*, 2002). For full details see (Collip *et al.*, 2013; Habets *et al.*, 2011).

### Holland (Utrecht)

Scanner used: 1.5 T Philips NT. Acquisition sequence: Fast field echo (FFE). Acquisition protocol: Flip angle = 30°, TR = 30 ms, TE = 4.6 ms. Images were analysed using a Histogram method validated previously by the research group (Schnack *et al.*, 2001b). For full details see (Hulshoff Pol *et al.*, 2002; Schnack *et al.*, 2001a).

### United Kingdom (Edinburgh)

Scanner used: 1 T Siemens Magnetom (Erlangen, Germany). Acquisition sequence: Magnetisation prepared rapid acquisition gradient echo (MPRAGE). Acquisition protocol: Flip angle = 12°, repetition time (TR) = 10 ms, echo time (TE) = 4 ms. Images were analysed using a regions of interest analysis using the semi-automated programme Analyze, and lateral ventricular volume was defined by the autotrace and included frontal, occipital and temporal horns. For full details see (McIntosh *et al.*, 2004, 2005a, 2005b).

### United Kingdom (London)

Scanner used: 1.5 T General Electric (USA) Signa System. Acquisition sequence: Spoiled gradient recall (SPGR) echo. One of the following acquisition protocols was used: Flip angle = 35°, TR = 35 ms, TE = 5 ms; Flip angle = 20°, TR = 14.7 ms, TE = 3.7 ms; Flip angle = 20°, TR = 9.8 ms, TE = 2.3 ms; or Flip angle = 20°, TR = 13.1 ms, TE = 5.8 ms. Images were analysed using MEASURE, an image analysis program that uses stereologically unbiased estimation of volume. Lateral ventricular volume included the body, frontal, occipital and temporal horns, and choroid plexus where visible. For full details see (Dutt *et al.*, 2009; Frangou *et al.*, 1997; McDonald *et al.*, 2002, 2006; Schulze *et al.*, 2006).

### Spain (Santander)

Scanner used: 1.5 T General Electric Signa System (GE Medical Systems, Milwaukee, WI). Acquisition sequence: Spoiled gradient-recalled acquisition in the steady state (GRASS) (SPGR). Acquisition protocol: Flip angle = 45°, TR = 24 ms, TE = 5 ms. Images were analysed using the software BRAINS2, including automatic measurements of brain areas. For full details see (Crespo-Facorro *et al.*, 2009; Mata *et al.*, 2009)

**Table S2.** Family sizes.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Number of family members participating** | **Number of families** | **% of families** | **Number of individuals** | **% of total sample** |
| 1 | 5545 | 84.00% | 5545 | 63.34% |
| 2 | 456 | 6.91% | 912 | 10.42% |
| 3 | 306 | 4.64% | 918 | 10.49% |
| 4 | 214 | 3.24% | 856 | 9.78% |
| 5 | 49 | 0.74% | 245 | 2.80% |
| 6 | 17 | 0.26% | 102 | 1.17% |
| 7 | 10 | 0.15% | 70 | 0.80% |
| 8 | 2 | 0.03% | 16 | 0.18% |
| 9 | 1 | 0.02% | 9 | 0.11% |
| 11 | 1 | 0.02% | 11 | 0.13% |

**Table S3.** Group interactions on associations between endophenotypes.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Endophenotype relationship** | **Controls**  Standardised increase in association (95% CI) | **Relatives**  Est. difference from controls (95% CI) | **Patients**  Est. difference from controls (95% CI) | **Overall test of interaction effect** |
| **Digit Span x**  **Block Design**  N=2754 | 0.31  (0.27 to 0.34)  p < 0.001 | 0.18  (0.02 to 0.35)  p = 0.028 | 0.28  (0.19 to 0.38)  p < 0.001 | p < 0.001 |
| **RAVLT del x**  **Block Design**  N=2137 | 0.21  (0.15 to 0.26)  p < 0.001 | -0.04  (-0.14 to 0.05)  p = 0.390 | 0.19  (0.09 to 0.29)  p < 0.001 | p < 0.001 |
| **RAVLT imm x Block Design** | 0.24  (0.18 to 0.29)  p < 0.001 | -0.02  (-0.14 to 0.06)  p = 0.427 | 0.12  (0.02 to 0.23)  p = 0.018 | p = 0.010 |
| Regressions on standardised scores including interactions terms between group (patient, relative, controls) and predictor, adjusted for covariates (age, gender and study site), using robust standard errors to account for correlations within families. Shown for controls are the regression coefficients for the associations between the two cognitive tasks, and shown for relatives and patients are the changes in slope from that of controls. RAVLT del = Rey Auditory Verbal Learning Task delayed recall;  CI = Confidence Interval. | | | | |

**Table S4.** Comparison between full models1 (in the paper, including age, sex and group) and models excluding age and sex2.

This table shows that despite imbalances in demographic variables across the clinical groups, the full and reduced models are stable and there is no collinearity between clinical group and demographic variables.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total Sample** | **Patients – Controls** | **Patients – Relatives** | **Relatives – Controls** |
| **Endophenotype:** | Global p-value\* | Mean difference (95% CI) | Mean difference (95% CI) | Mean difference (95% CI) |
| **P300 amplitude1** | < 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 amplitude2** | < 0.001 | -0.57  (-0.79 to -0.36)  p < 0.001 | -0.14  (-0.30 to -0.02)  p = 0.091 | -0.44  (-0.63 to -0.25)  p < 0.001 |
| **P300 latency1** | < 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 |
| **P300 latency2** | < 0.001 | 0.43  (0.29 to 0.58)  p < 0.001 | -0.17  (-0.34 to 0.02)  p = 0.030 | 0.61  (0.46 to 0.75)  p < 0.001 |
| **Lateral Ventricular Volume1** | = 0.145 | 0.20  (0.08 to 0.32) | 0.09  (-0.06 to 0.23) | 0.11  (-0.04 to 0.25) |
| **Lateral Ventricular Volume2** | = 0.056 | 0.27  (0.16 to 0.37) | 0.06  (-0.08 to 0.20) | 0.11  (-0.04 to 0.25) |
| **Digit Span1** | < 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 |
| **Digit Span2** | < 0.001 | -0.72  (-0.88 to -0.55)  p < 0.001 | -0.04  (-0.22 to 0.13)  p = 0.627 | -0.67  (-0.86 to -0.49)  p < 0.001 |
| **Block Design1** | < 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 |
| **Block Design2** | < 0.001 | -0.88  (-1.03 to -0.73)  p < 0.001 | 0.22  (0.11 to 0.34)  p < 0.001 | -1.11  (-1.24 to -0.98)  p < 0.001 |
| **RAVLT**  **immediate recall1** | < 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**  **immediate recall2** | < 0.001 | -1.40  ( -2.14 to -0.66)  p < 0.001 | -1.21  (-1.98 to -0.46)  p = 0.002 | -0.18  (-0.36 to -0.01)  p = 0.041 |
| **RAVLT**  **delayed recall1** | < 0.001 | -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 |
| **RAVLT**  **delayed recall2** | < 0.001 | -1.07  ( -2.05 to -0.09)  p =0.033 | -0.96  ( -1.95 to 0.04)  p =0.059 | -0.11  (-0.29 to 0.65)  p = 0.221 |
| All the regression models are conducted on standardised scores for each endophenotype. All models are adjusted for study site and use robust standard errors to account for correlations within families.  1 Full models (reported in the manuscript) include clinical group, age, sex, study site and where significant a group by study site interaction term.  2 Reduced models include the same variables as above except for age and sex.  \* 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. | | | | |