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Brief Report

Preliminary findings on the heritability of the neural correlates of response inhibition

Christine Macare[a], Thomas Meindl[b], Igor Nenadic[c], Dan Rujescu[d], Ulrich Ettinger[e,*]

[a] MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, United Kingdom
[b] Institute for Clinical Radiology, University of Munich, Munich, Germany
[c] Department of Psychiatry and Psychotherapy, Jena University Hospital, Friedrich-Schiller-University, Jena, Germany
[d] Department of Psychiatry, University of Halle, Halle, Germany
[e] Department of Psychology, University of Bonn, Bonn, Germany

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ABSTRACT

Imaging genetics examines genetic influences on brain structure and function. This preliminary study tested a fundamental assumption of that approach by estimating the heritability of the blood oxygen level dependent (BOLD) signal during antisaccades, a measure of response inhibition impaired in different psychiatric conditions. One hundred thirty-two healthy same-sex reared-together twins (90 monozygotic (MZ; 32 male) and 42 dizygotic (DZ; 24 male)) performed antisaccades in the laboratory. Of these, 96 twins (60 MZ, 28 male; 36 DZ, 22 male) subsequently underwent functional magnetic resonance imaging (fMRI) during antisaccades. Variation in antisaccade direction errors in the laboratory showed significant heritability (47%; 95% confidence interval (CI) 22–65). In fMRI, the contrast of antisaccades with prosaccades yielded BOLD signal in fronto-parietal-subcortical networks. Twin modelling provided tentative evidence of significant heritability (50%, 95% CI: 18–72) of BOLD in the left thalamus only. However, due to the limited power to detect heritability in this study, replications in larger samples are needed.

1. Introduction

The molecular genetic imaging approach applies "brain imaging in genetically informative designs" (De Geus, Goldberg, Boomsma, & Posthuma, 2008, p.1) in order to illuminate the pathways from gene action to risk for psychopathology via alterations in brain structure or function (see e.g., Meyer-Lindenberg, 2010). A fundamental assumption of the approach is the heritability of inter-individual variation in brain structure and function. However, the evidence for this assumption to date is scant (De Geus et al., 2008).

In this preliminary study, we aimed to address this issue by estimating the proportion of variation in inhibitory control and its associated BOLD signal that is attributable to genetic influences. We applied the antisaccade task as a prominent measure of prepotent response inhibition (Friedman & Miyake, 2004). Heritability (h^2) of the key performance measure, the rate of direction errors, has in previous studies of monozygotic (MZ) and dizygotic (DZ) twins been found to be significant (h^2 = 56% in healthy adults, h^2 = 42%, 95% confidence interval (CI): 27–57% and h^2 = 57%, 95% CI: 51–63%, in Friedman et al., 2008; Greenwood et al., 2007; Malone & Iacono, 2002, respectively). Response inhibition is an important function of cognitive control (Friedman & Miyake, 2004) and is known to be impaired in a number of psychiatric conditions (Greenwood et al., 2007; Sweeney, Luna, Keedy, McDowell, & Clementz, 2007).

In the current study of healthy MZ and DZ twins, we expected to find roughly equal amounts of additive genetic and unique environmental influences on direction errors at the behavioural level. For the contrast comparing BOLD signal during antisaccades with prosaccades, a saccadic control condition, we expected to find significant h^2 for brain areas within the fronto-parietal and subcortical network, which has previously been implicated in inhibition and antisaccade generation (Aichert, Williams, Moller, Kumari, & Ettinger, 2012; Brown, Goltz, Vilis, Ford, & Everling, 2006; Ford, Goltz, Brown, & Everling, 2005; Matsuda et al., 2004; Raemaekers, Vink, van den Heuvel, Kahn, & Ramsey, 2006; Sweeney et al., 2007).

* Corresponding author at: Department of Psychology, University of Bonn, Kaiser-Karl-Ring 9, 53111 Bonn, Germany. Tel.: +49 228 73 4208; fax: +49 228 73 62323.
E-mail addresses: ulrich.ettinger@uni-bonn.de, u.ettinger@iop.kcl.ac.uk (U. Ettinger).

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Table 1
Task performance by zygosity.

	MZ[a]		DZ[b]	
	Mean	Standard deviation	Mean	Standard deviation
Laboratory sample				
Antisaccade error rate (in %)	35.34	23.00	34.02	22.95
Antisaccade latency (in ms)	285.79	41.49	287.22	43.00
Antisaccade correction rate (in %)	98.91	3.36	98.95	2.89
fMRI sample				
Antisaccade error rate (in %)	17.22	12.36	21.67	15.93
Antisaccade latency (in ms)	251.84	41.62	254.27	34.21
Antisaccade correction rate (in %)	85.78	24.70	92.63	15.18
Prosaccade latency (in ms)	189.37	30.15	183.05	30.52

[a] MZ = monozygotic.
[b] DZ = dizygotic.

2. Method

2.1. Participants

One-hundred thirty-two same-sex, reared-together, healthy (90 MZ, 42 DZ) twins participated in the laboratory, 96 of these (60 MZ, 36 DZ) in the fMRI session. Recruitment and zygosity determination are outlined in the Supplementary Materials. Ethical approval was obtained and participants provided written, informed consent.

2.2. Procedure

The study involved a telephone screening, a laboratory session and a subsequent fMRI session. Exclusion criteria for the laboratory session were identical to those of Aichert and colleagues (2012). Participants in the fMRI session were additionally required to be right-handed and to fulfil standard inclusion criteria for MRI.

2.3. Measures and materials

2.3.1. Laboratory

Verbal intelligence (Lehrl, 2005) and antisaccades (EyeLink 1000, SR Research Ltd.; see Aichert et al., 2012) were first assessed in the laboratory. The dependent variables of antisaccade performance were the rate of direction errors (number of direction errors/number of valid antisaccade trials, in %), the latency of directionally correct antisaccades (in ms) and the correction rate (number of corrected direction errors/number of direction errors made, in %; see Supplementary Materials).

2.3.2. fMRI

A block design task of antisaccades, prosaccades and fixation was used (Ettinger et al., 2009). T2*-weighted MR echo planar images showing brain BOLD were collected at 3T (see Supplementary Materials). Eye movement data acquisition and analysis was as previously described (Aichert, Williams, Moller, Kumari, & Ettinger, 2012; Ettinger et al., 2009; see Supplementary Materials). The mean antisaccade direction error rates, correction rates and latencies as well as prosaccade latencies were extracted for analysis.

2.4. Statistical analysis

Demographic, verbal intelligence and antisaccade data were analysed using the Predictive Analysis SoftWare (PASW; SPSS-Inc, 2009).

Imaging data were preprocessed and analysed using a general linear model in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/) running in MATLAB® R2008a (The MathWorks Inc, 2008). Regions of interest (ROIs) were extracted for twin modelling. To avoid biasing the data towards a group effect, ROIs were selected from an independent sample of 94 non-twin participants scanned under the same protocol on the same scanner. Coordinates of significant clusters from the second level one-sample *t*-test of the contrast antisaccades > prosaccades of the non-twin data were used as ROIs and analysed using quantitative genetic modelling.

3. Results

3.1. Sample

The $N = 66$ twin pairs in the laboratory session were 23.64 years on average ($SD = 6.10$) (45 MZ: 16 male, 29 female, 21 DZ: 12 male, 9 female). Age differed significantly between MZ ($M = 24.76$, $SD = 6.96$) and DZ ($M = 21.26$, $SD = 2.35$) twins ($F(1.64) = 4.94$, $p = .03$, $\eta_p^2 = 0.7$) and was included further as covariate. More MZ than DZ females participated ($\chi_1^2 = 5.46$, $p = .02$) (Kendler & Prescott, 2006). Verbal intelligence test scores (out of a maximum of 37) did not differ between zygosity ($F(1,64) = .89$, $p = .35$, $\eta_p^2 = 0.1$, MZ: $M = 29.92$, SD = 3.07, DZ: $M = 29.19$, SD = 3.75) or birth-order groups ($F(1,64) = .45$, $p = .51$, $\eta_p^2 = 0.1$).

The $N = 48$ fMRI twin pairs (30 MZ: 14 male, 16 female; 18 DZ: 11 male, 7 female) differed non-significantly in age ($F(1,46) = 3.83$; $p = .056$, $\eta_p^2 = .08$, MZ: $M = 24.83$, $SD = 6.83$; DZ: $M = 21.53$, $SD = 2.38$). Gender was distributed evenly across zygosity groups ($\chi_1^2 = 1.88$, $p = .17$). Verbal intelligence did not differ between zygosity ($F(1,46) = .30$, $p = .59$, $\eta_p^2 = .02$, MZ: $M = 30.02$, SD = 3.45, DZ: $M = 29.50$, SD = 3.80) or birth-order groups ($F(1,46) = .01$, $p = .93$, $\eta_p^2 < .01$).

Twins participating in both sessions were comparable to those participating only in the laboratory session in age or years in education (all $p > .05$). Gender was distributed differently between both sessions due to the frequent use of orthodontic retainers in females, making them unsuitable for fMRI.

3.2. Antisaccade performance

Zygosity groups did not differ significantly in direction errors ($F(1,63) = .17$, $p = .68$, $\eta_p^2 < .01$; $F(1,45) = .20$, $p = .66$, $\eta_p^2 = .01$), latencies ($F(1,63) = .09$, $p = .77$, $\eta_p^2 < .01$; $F(1,45) = .2.00$, $p = .16$, $\eta_p^2 < .01$) or correction rates ($F(1,63) < .01$, $p = .99$, $\eta_p^2 < .01$; $F(1,45) = .14$, $p = .71$, $\eta_p^2 < .01$) during the laboratory and the fMRI sessions, respectively (Table 1).

Correlations between laboratory and fMRI performance were significant for direction errors ($rMZ = .36$, $p < .01$; $rDZ = .77$, $p < .01$) and latencies ($rMZ = .60$, $p < .01$; $rDZ = .62$, $p < .01$) but not correction rates ($rMZ = -.21$, $p = .11$; $rDZ = -.07$, $p = .68$).

Larger MZ than DZ twin cross-twin correlations indicate familial influences. These were observed for laboratory direction errors ($rMZ = .51$, $p < .01$; $rDZ = .20$, $p = .41$) but not for latencies ($rMZ = .34$,