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ORIGINAL ARTICLE

Effects of two dopamine-modulating genes (*DAT1* 9/10 and *COMT* Val/Met) on n-back working memory performance in healthy volunteers

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Background. Impairments in working memory are present in many psychiatric illnesses such as attention-deficit hyperactivity disorder (ADHD) and schizophrenia. The dopamine transporter and catechol-*O*-methyltransferase (COMT) are proteins involved in dopamine clearance and the dopamine system is implicated in the modulation of working memory (WM) processes and neurochemical models of psychiatric diseases. The effects of functional polymorphisms of the dopamine transporter gene (*DAT1*) and the *COMT* gene were investigated using a visuospatial and numerical n-back working memory paradigm. Our n-back task was designed to reflect WM alone, and made no demands on higher executive functioning.

Method. A total of 291 healthy volunteers (aged 18–45 years) were genotyped and matched for age, sex, and Barratt Impulsivity Scale (BIS) and National Adult Reading Test (NART) scores. To assess individual gene effects on WM, factorial mixed model analysis of variances (ANOVAs) were conducted with the between-subjects factor as genotype and difficulty level (0-, 1-, 2- and 3-back) entered as the within-subjects factor.

Results. The analysis revealed that the *DAT1* or *COMT* genotype alone or in combination did not predict performance on the n-back task in our sample of healthy volunteers.

Conclusions. Behavioral effects of *DAT1* and *COMT* polymorphisms on WM in healthy volunteers may be non-existent, or too subtle to identify without exceedingly large sample sizes. It is proposed that neuroimaging may provide more powerful means of elucidating the modulatory influences of these polymorphisms.

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Introduction

The search to isolate genes associated with psychiatric illnesses has been difficult. Psychiatric linkage and association studies have often reported contradictory results despite relatively large sample sizes and similar methodologies (Riley & McGuffin, 2000; Faraone *et al*. 2005; Levinson, 2006). This may have arisen because of multiple genes with small effect sizes and interactions with environmental factors (Risch, 1990). There also exists significant heterogeneity in the population and thus even larger sample sizes are needed for reliable findings (Crow, 2007). One approach attempts to circumvent some of these issues by dissecting complex disorders into endophenotypes such as working memory (WM) (Gottesman & Gould, 2003). This allows the identification of susceptibility genes by linking alleles to discrete behavioral traits that make up these disorders (Flint & Munafo, 2007). Impairments in WM occur across several psychiatric illnesses including attention-deficit hyperactivity disorder (ADHD), schizophrenia and depression (Goldman-Rakic, 1994; Barkley, 1997; Chamberlain *et al*. 2007; Taylor Tavares *et al*. 2007). The dopamine transporter gene (*DAT1* or *SLC6A3*) and the catechol-*O*-methyltransferase gene (*COMT*) code for proteins that affect neurochemical clearance and have been implicated in the manifestation of these illnesses and WM (Castellanos & Tannock, 2002; Bertolino *et al*. 2006; Ettinger *et al*. 2006; Meyer-Lindenberg & Weinberger, 2006; Lopez-Leon *et al*. 2007). The aim of the present study was to investigate the effects of functional polymorphisms of *DAT1* and *COMT* on WM in healthy volunteers.

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An untranslated variable number of tandem repeat (VNTR) polymorphism exists at the 15th exon of the *DAT1* gene, where the most common forms present are the alleles with 9 or 10 40-bp repeats (Vandenbergh *et al*. 1992*a*). Although DAT is marginally present in the prefrontal cortex (PFC), it is abundant in the striatum and midbrain (Sesack *et al*. 1998; Lewis *et al*. 2001). WM is thought to result from the reciprocal interaction of regions within these areas, namely the striato-thalamo-cortical system (Chudasama & Robbins, 2006). Tonic dopamine in the striatum, along with D1 transmission in the PFC, is thought to be responsible for both the stability of this neural network and the maintenance of task-relevant information in WM, whereas phasic dopamine in the striatum regulates the resetting and updating of WM when novel information is presented (Bilder *et al*. 2004; Hazy *et al*. 2006). Individuals who are homozygous for the 10-repeat alleles have been shown to have the most focused engagement of WM networks during an episodic memory task (Schott *et al*. 2006) and a WM n-back task, but similar overall behavioral performances (Bertolino *et al*. 2006; Caldu *et al*. 2007). Furthermore, 10-repeat allele homozygotes show enhanced evoked gamma band activity (Demiralp *et al*. 2007) and these 30–70 Hz waves affect cognitive processes including WM (Gray *et al*. 1989; Lutzenberger *et al*. 2002; Howard *et al*. 2003). Thus, these data implicate the *DAT1* gene in aspects of cognition including WM, although the effect of this polymorphism at a cellular level remains disputed (Lynch *et al*. 2003; van Dyck *et al*. 2005; VanNess *et al*. 2005).

A missense mutation for the *COMT* gene leads to the substitution of methionine for valine (Lachman *et al*. 1996), with the Val allele coding for a more thermolabile protein with increased enzymatic activity (Chen *et al*. 2004). The *COMT* alleles are co-dominant with three genotypes possible: the most active Val/Val, followed by Val/Met, and the least active Met/Met. The effects of *COMT* on cognition have been studied extensively. Healthy individuals with the low-activity Met/Met allele were found to perform significantly better on the Wisconsin Card Sorting Test (WCST; Egan *et al*. 2001; Barnett *et al*. 2007). However, association studies between *COMT* and WM using n-back tasks remain inconsistent (Egan *et al*. 2001; Goldberg *et al*. 2003; Stefanis *et al*. 2004; Bruder *et al*. 2005), with a recent meta-analysis showing no significant association (Barnett *et al*. 2008). Functional magnetic resonance imaging (fMRI) studies have demonstrated that Met/Met individuals manifest more focused cortical response in the dorsolateral PFC, with a similar performance on the n-back task compared to the other genotypes (Bertolino *et al*. 2006; Caldu *et al*. 2007). This suggests a higher signal-to-noise ratio in the WM networks and thus more efficient processing, or less 'work' for the same outcome. A gene–gene interaction has also been reported whereby individuals with the Met/Met *COMT* genotype in combination with the 10/10 *DAT1* genotype manifested the most focused responses (Bertolino *et al*. 2006; Caldu *et al*. 2007).

The aim of this study was to further investigate the effect of the most common *DAT1* and *COMT* polymorphisms on WM performance in healthy volunteers. The WM paradigm deployed is a variant of the n-back task designed to elicit a pure WM manipulation not confounded by response conflicts or other higher executive processes. Most studies investigating these polymorphisms with n-back tasks have had sample sizes of less than 100 participants (Bertolino *et al*. 2006; Caldu *et al*. 2007), and only two published studies have had sample sizes of more than 200 (Goldberg *et al*. 2003; Stefanis *et al*. 2004). In our sample of 291 participants, we predicted a *DAT1* × NBACK difficulty interaction and a *COMT* × NBACK difficulty interaction; it was expected that all genetic subgroups would perform similarly on the control trials but differently on the more difficult trials. *DAT1* and *COMT* are analyzed independently of each other, with 10/10 individuals and Met/Met individuals expected to perform the best on the more difficult n-back conditions compared to the other genotypes in their respective groups. Finally, on account of two recent fMRI studies reporting an additive effect of both genotypes on WM (Bertolino *et al*. 2006; Caldu *et al*. 2007), we also predicted a *COMT* × *DAT1* × NBACK difficulty interaction with the 10/10-Met/Met group outperforming the other groups on the more difficult trials of the n-back task.

Method

Participants

Individuals aged 18–45 years were recruited from the general population using media advertisements (Cambridge, UK, and surrounding areas). All participants gave written informed consent. Genotyping and baseline testing was part of a protocol approved by the Cambridge Research Ethics Committee (no. 03/266). Exclusion criteria with regard to lifestyle were: smoking >10 cigarettes per day, use of recreational drugs in the previous 5 years, and average weekly alcohol consumption >25 units per week. With respect to medical history, exclusion criteria were: history of heart failure, hypertension, diabetes, mental illness, stroke, or head trauma. Participants were asked to refrain from drinking caffeinated stimulant beverages on the test day. The National Adult Reading Test

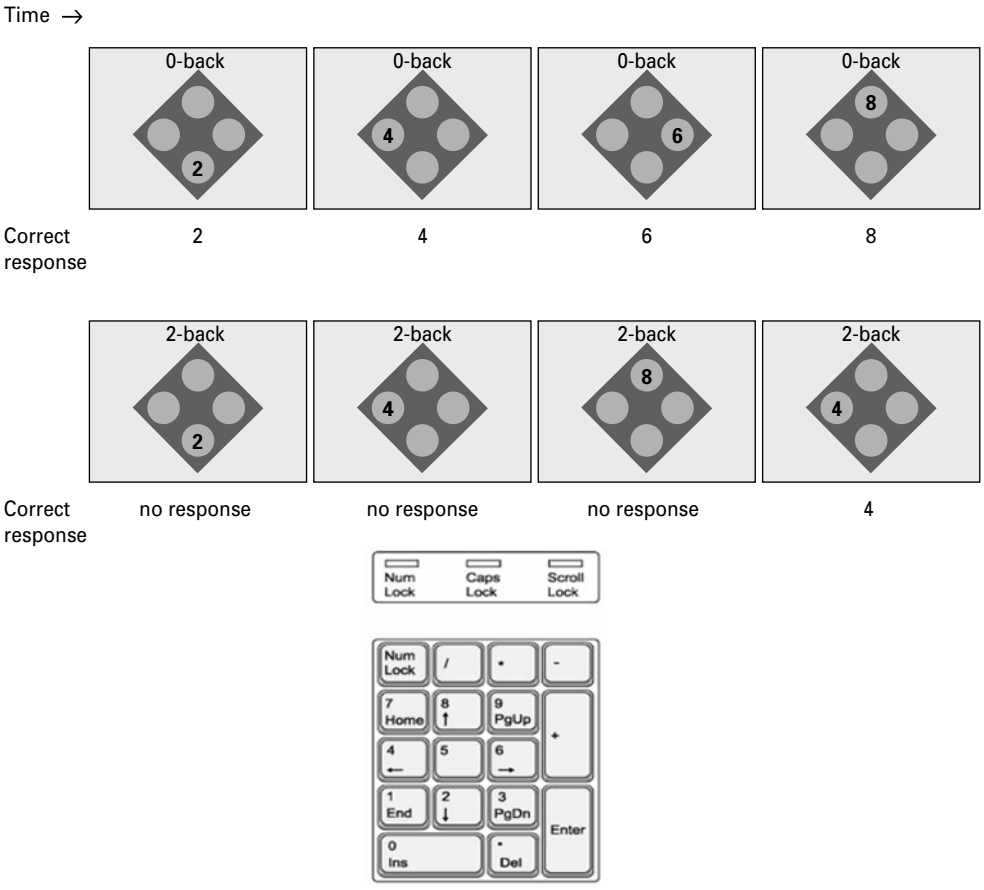

Fig. 1. Computerized n-back task. In the 0-back control condition participants were asked to respond to every stimulus presented. During the 2-back condition participants were instructed to respond to a stimulus that was shown two stimuli back. The 2-back condition was an expansion of the 1-back, where participants were asked to respond if the number appearing on the screen was the same as the number that appeared two presentations before the current number.

(NART; Nelson & Willison, 1991) and the Barratt Impulsivity Scale (BIS; Patton *et al*. 1995) were administered to assess intelligence and impulsivity respectively.

WM paradigm

The spatial WM task used in this study was a behavioral variant of the computerized n-back task, which has been widely used in neuroimaging and behavioral research. Stimuli consisted of four numbers on a screen, each appearing within a circle (see Fig. 1). The numbers on the screen corresponded geometrically with the numbers on the right-hand side of a standard keyboard that was used for responding, and stimuli appeared on-screen for 400 ms with an interstimulus interval of 1400 ms. We used non-memory trials (0-back) and three working memory conditions (1-back, 2-back, 3-back) (see Fig. 1 for explanation). Each condition included six blocks of 14 stimuli. Hit rate and reaction times were calculated to assess behavioral performance. Participants who performed very poorly on the task [i.e. below 2 standard deviations (S.D.) away from the mean on at least two measures from the raw data, or 3 S.D. away from the mean in any one measure] were excluded.

Genotyping

Blood samples were collected after cognitive testing on-site, and were analyzed at the Molecular Genetics Laboratory, Addenbrooke's Hospital, Cambridge, UK. Genotypes for *COMT* and *DAT1* were analyzed following polymerase chain reaction (PCR) amplification, which was performed using methods and primers described previously (Vandenbergh *et al*. 1992*a*; Lachman *et al*. 1996). Full details of the methodology are available from the corresponding author on request.

Statistical analysis

Demographic characteristics were analyzed using one-way analysis of variance (ANOVA) or χ^2 tests as appropriate. To assess gene effects on WM, factorial

Table 1. *Demographic and control data*

	COMT genotypes				
	Val/Val	Val/Met	Met/Met	Test	*p*
n	82	148	61	χ^2	0.492
Sex (% female)	35.1	30.3	39.0	χ^2	0.463
Age (years), mean ± S.D.	26.7 ± 6.8	25.4 ± 5.9	22.8 ± 4.2	*F*	0.001*
Ethnicity (w : a : na)	55 : 4 : 1	105 : 10 : 1	47 : 1 : 1	χ^2	0.596
NART, mean ± S.D.	117.3 ± 8.9	116.7 ± 9.1	116.1 ± 8.9	*F*	0.740
BIS, mean ± S.D.	63.84 ± 8.9	65.7 ± 9.6	63.1 ± 8.2	*F*	0.185
	DAT1 genotypes				
	9/9	9/10	10/10	Test	*p*
n	17	91	146	χ^2	< 0.001*
Sex (% female)	23.5	39.8	28.5	χ^2	0.152
Age (years), mean ± S.D.	25.0 ± 6.1	25.5 ± 6.1	25.0 ± 6.0	*F*	0.828
Ethnicity (w : a : na)	12 : 1 : 0	64 : 3 : 3	97 : 10 : 0	χ^2	0.157
NART, mean ± S.D.	117.7 ± 5.4	115.6 ± 8.5	115.8 ± 9.9	*F*	0.681
BIS, mean ± S.D.	65.2 ± 9.6	65.1 ± 8.5	65.4 ± 9.6	*F*	0.975

COMT, Catechol-*O*-methyltransferase; *DAT1*, dopamine transporter gene; NART, National Adult Reading Test; BIS, Barratt Impulsivity Scale; Val, valine; Met, methionine; S.D., standard deviation; w, White (mostly European Caucasian); a, Asian; na, North African.

* Indicates significant.

mixed model ANOVAs were conducted (between-subject factor: genotype; within-subject factor: difficulty level, 0-back, 1-back, 2-back, and 3-back).

To assess a possible gene–gene interaction, a factorial 3 (9/9, 9/10, 10/10) × 3 (Val/Val, Val/Met, Met/Met) mixed model ANOVA was performed. The dependent variables were hit rate (%) and reaction times (ms), and a two-tailed level of significance of $p < 0.05$ was applied to all analyses. Contrasts between homozygote groups (Val/Val *v.* Met/Met and 9/9 *vs.* 10/10) for the 3-back condition were also conducted. Hit-rate percentages were converted using an arcsine transform to make the data normally distributed. SPSS version 12 (SPSS Inc., USA) for Windows was used for all analyses.

Results

Demographic and control data

The sample demographics and control data are summarized in Table 1. *COMT* genotype distribution was in Hardy–Weinberg equilibrium but the *DAT1* distribution was skewed positively, as expected (Vandenbergh *et al*. 1992*b*; Heinz *et al*. 2000). The *COMT* group was larger than the *DAT1* group because *DAT1* genotyping was initiated at a later time point and not all participants of the original *COMT* screening project gave prospective consent for further genotyping. Other than a disparity of age in the *COMT* group, no significant difference was apparent between genotyping groups for any of the demographic or control variables. NART IQ scores were positively correlated to the 2-back [$r(308) = 0.133$, $p < 0.05$] and 3-back [$r(308) = 0.129$, $p < 0.05$] but not the 0- or 1-back hit rates, indicating a significant effect of intelligence on WM performance. Age was inversely proportional for the 3-back condition [$r(303) = -0.133$, $p < 0.05$]. Impulsivity scores did not correlate significantly with any measure.

Genotype effect on n-back performance

The statistical analyses are summarized in Table 2. There was no significant association of hit rate or reaction time with either *DAT1* (Fig. 2) or *COMT* (Fig. 3), and no interaction between the two. The results were similar when age was entered as a covariate for *COMT*. The contrast analysis between the *COMT* homozygotes in the 3-back condition was initially significant, but after entering age as a covariate the effect disappeared. n-back data are presented in

Table 2. *Statistical analyses of genotype effect on n-back performance*

	Variable	*n*	*F* or *t*	*p*
COMT × NBACK	Hit rate	291	0.818	0.556
(mixed ANOVA)	Reaction time (ms)		0.168	0.985
Val/Val *v.* Met/Met	Hit rate	291	1.16	0.247
3-BACK (*t* test)				
DAT1 × NBACK	Hit rate	254	0.378	0.893
(mixed ANOVA)	Reaction time (ms)		1.34	0.235
9/9 *v.* 10/10	Hit rate	254	0.000	0.985
3-BACK (*t* test)				
COMT × *DAT1* × NBACK	Hit rate	253	0.590	0.851
(mixed ANOVA)	Reaction time (ms)		0.813	0.638

COMT, Catechol-*O*-methyltransferase; *DAT1*, dopamine transporter gene.

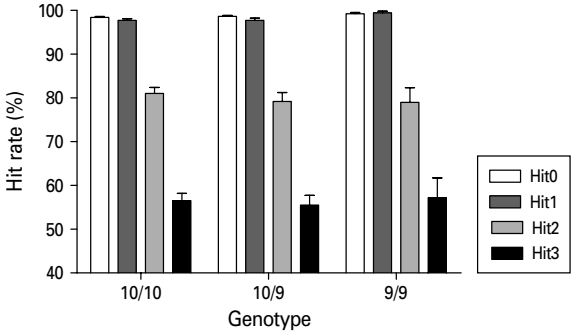

Fig. 2. Effect of dopamine transporter gene (*DAT1*) polymorphism on n-back hit-rate performance.

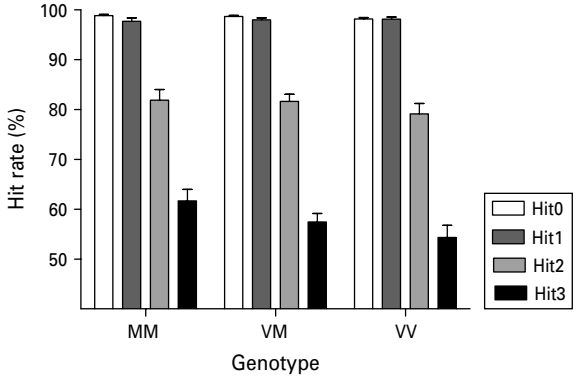

Fig. 3. Effect of catechol-*O*-methyltransferase (*COMT*) genotype on n-back hit-rate performance.

Table 3. The results remained non-significant in a supplementary analysis that included subjects who had difficulty understanding the task.

Power analysis

For *COMT*, with 82 participants in the Val/Val group and 61 in the Met/Met group, we had 80% power to detect an effect size of $d = 0.48$ between the genetic subgroups at $p = 0.05$. Previously, Goldberg *et al*. (2003) reported an effect size of 0.44 for this contrast in the 2-back condition, which we had 73% power to detect at $p = 0.05$. Our actual detected effect sizes for differences between the two homozygous *COMT* subgroups (Met/Met > Val/Val) were $d = 0.13$ for the 2-back condition and $d = 0.35$ for the 3-back condition (calculated using transformed data). Note that these calculations do not take into account the small but significant age difference between the genetic subgroups. For *DAT1*, because of the relative rarity of the 9 allele, the two homozygous groups were very unbalanced, resulting in reduced power to detect effects. With 146 participants in the 10/10 group and 17 participants in the 9/9 group, we had 80% power to detect an effect size of $d = 0.72$ between the genetic subgroups at $p = 0.05$. However, previous studies have not found significant effects of this polymorphism on n-back performance (Bertolino *et al*. 2006; Caldu *et al*. 2007). Consistent with these reports, our actual detected effect sizes for differences between the two homozygous *DAT* subgroups (10/10 > 9/9) were $d = 0.1$ for the 2-back condition and $d = -0.005$ for the 3-back condition (calculated using transformed data).

Discussion

We report no significant effects of *DAT1*, *COMT* or *DAT1* × *COMT* on n-back task performance. This is the largest sample so far investigating *DAT1* and n-back performance and one of the largest for *COMT*. An impairment in WM, and visuospatial WM in particular, is an attractive potential endophenotype for psychiatric diseases as it meets several criteria outlined previously, such as being continuously quantifiable, having good psychometric properties, and being more closely related to the genetic underpinnings of

Table 3. *Mean and standard deviation of n-back hit rates stratified by genotype*

	COMT genotype			*DAT1* genotype		
n-back	Val/Val	Val/Met	Met/Met	9/9	9/10	10/10
0-back	98.14 (2.74)	98.66 (2.19)	98.81 (1.92)	99.23 (1.23)	98.63 (2.17)	98.39 (2.54)
1-back	98.10 (3.91)	97.99 (4.12)	97.66 (5.47)	99.45 (1.56)	97.74 (4.61)	97.71 (4.64)
2-back	79.08 (19.13)	81.63 (17.33)	81.66 (16.74)	96 (13.96)	79.19 (19.64)	81.00 (16.84)
3-back	54.32 (22.26)	57.43 (20.61)	61.66 (17.86)	57.18 (18.69)	55.51 (21.02)	56.52 (20.39)

COMT, Catechol-*O*-methyltransferase; *DAT1*, dopamine transporter gene.

the illnesses than the disease itself or the core symptoms (Waldman, 2005). Although we did not find an association in our sample, we offer two potential explanations for our negative results.

Even though this study had a relatively large sample size, it may still have been underpowered to detect subtle overt behavioral effects of genotype. Imaging studies have reported effects for both of these polymorphisms in WM, without differences in behavioral n-back task performance (Bertolino *et al*. 2006; Caldu *et al*. 2007), indicating that neuroimaging parameters are closer to the neural correlates of gene effects and thus may be more powerful for detecting gene effects (Meyer-Lindenberg & Weinberger, 2006). Flint & Munafo (2007) estimated that a sample of 1700 individuals would be required to obtain 80% power to detect an effect of *COMT* on n-back performance. Initial reports and publication bias may have overestimated the influence that single genes have on cognitive processes (Barnett *et al*. 2008). Many studies investigating these polymorphisms suffer as a result of low power, leading to increases in the ratio of false positive to true positive findings among studies that achieve nominal statistical significance.

Our non-significant results are in line with the notion that *COMT*, and possibly other dopamine-modulating genes such as *DAT1*, may regulate higher-order cognitive functions that involve not only maintenance and updating of information but also mental manipulation (Bruder *et al*. 2005). From previous studies that investigated the effect of *COMT* effect on n-back performance (Egan *et al*. 2001; Stefanis *et al*. 2004; Bruder *et al*. 2005; Bertolino *et al*. 2006; Caldu *et al*. 2007; de Frias *et al*. 2010), only one found a significant effect, with Met/Met homozygotes performing better than the rest (Goldberg *et al*. 2003). However, the n-back task used in their study required individuals to respond to each stimulus whereas our study did not (Goldberg *et al*. 2003). Our version of the n-back task, with a pure WM instruction, makes no heavy demand on higher executive functions (e.g. inhibition of response conflicts) and may therefore be less susceptible to the effects of dopamine-modulating genes. Taken together, these studies and our results suggest that cognition may only be sensitive to *COMT* after a certain threshold of cognitive load has been passed.

A potential limitation of this study was the small number of participants in the 9/9 genotype group. The 9-repeat allele is rare compared to the 10-repeat allele and the allelic distribution in this present study was similar to previous studies (Vandenbergh *et al*. 1992*b*; Heinz *et al*. 2000). Conversely, a strong feature of this study was the use of the NART and the BIS as control variables. Impulsivity is known to affect WM performance and alter dopamine-dependent changes during WM (Cools *et al*. 2007); however, to our knowledge, no other study investigating *COMT* or *DAT1* in WM has controlled for trait impulsivity.

In summary, we attribute our non-significant results to a lack of statistical power or to the possibility that these two dopamine-modulating genes may affect higher-order cognitive processes that were not present in our n-back task. Thus, more original studies with very large sample sizes are needed. Although meta-analyses are important in this field, the heterogeneity of the n-back tasks used between studies is problematic. We suggest that more multi-centre studies be conducted to attain such large sample sizes and investigate the potential influence that genes may have on cognitive endophenotypes.

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Declaration of Interest

None.

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