

**Title page**

**Title:** Endophenotypes of executive functions in Obsessive Compulsive Disorder? A meta-analysis in unaffected relatives

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## **Abstract**

*Background:* Endophenotypes are mediator traits between genetic influences and a clinical phenotype. Meta-analyses have consistently shown modest impairments of executive functioning in OCD patients when compared to healthy controls. Similar deficits have also been reported in unaffected relatives of OCD patients, but have not been quantified.

*Aim:* We conducted the first meta-analysis combining all studies investigating executive functioning in unaffected relatives of individuals with OCD in order to quantify any deficits.

*Methods:* A search of Pubmed, Medline and PsychInfo databases until February 2019 identified 21 suitable research papers comprising 707 unaffected relatives of patients with OCD and 842 healthy controls.

*Results:* Effect sizes were calculated using random effects models. Unaffected relatives displayed a significant impairment in global executive functioning ( $g = 0.24$ ; 95%CI 0.14 to 0.34). Analyses of specific executive functioning subdomains also revealed impairments in: planning, visuospatial working memory and verbal fluency. No significant differences were observed in inhibition/selective attention, decision making or set-shifting.

*Conclusions:* Deficits in executive functioning are promising endophenotypes for OCD. To identify further biomarkers of disease risk/resilience in OCD we suggest examining specific executive functioning domains.

**Keywords:** obsessive compulsive disorder (OCD), endophenotype, cognitive functioning, executive functioning, meta-analysis

## 1. Introduction

OCD is a complex neuropsychiatric disorder with a lifetime prevalence of 2-3% in the general population (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005). Despite several genetic loci being associated with OCD (Arnold et al., 2018; Fernandez, Leckman, & Pittenger, 2018; Mattheisen et al., 2015), its genetic architecture has not been fully deciphered yet and little is known about the mechanisms through which those genes lead to the disorder. The heterogeneity of symptomatology in OCD obscures the search for genetic mechanisms, leading to alternative approaches. One such approach is the investigation of endophenotypes, which are heritable mediator traits between genetic influences and clinical phenotypes and are risk factor for a disorder even if the person is not currently symptomatic (Gottesman & Shields, 1973; Gottesman & Gould, 2003; Gottesman, Shields, & Hanson, 1982). The rationale behind endophenotypes is that even if those traits are determined by multiple genes, their genetic architecture could be simpler than the clinically useful, but still based on diagnostic principles, psychiatric disorder (Flint & Munafò, 2007; Lenzenweger, 2013).

Endophenotypic traits are intermediate measures of ‘disease’ between phenotype and genotype, which should be less genetically complex, be defined more straightforwardly than the actual disorder, resemble a physiological trait, and involve the same biochemical pathways but be closer to the level of gene action compared to the psychiatric disorder (Almasy & Blangero, 2001; Flint & Munafò, 2007; Glahn et al., 2014). Therefore, the relationship between genes and those traits should be stronger than with the disorder itself, since psychiatric disorders result from a combination of genetic and non-genetic abnormalities impacted by environmental and socio-cultural factors.

Several family studies have demonstrated that recurrence rates of neurocognitive endophenotypes in relatives of individuals with a psychiatric disorder are higher than prevalence in the general population, albeit the relatives do not exhibit the symptomatology of

the psychiatric illness (Blakey et al., 2018; Drysdale, Knight, McIntosh, & Blackwood, 2013; Glahn et al., 2010; Kumar, Solanki, Satija, Gupta, & Singh, 2015). Research on neurocognitive endophenotypes had been partly led by evidence implicating structural and functional abnormalities in the frontal lobes (i.e. orbitofrontal cortex, anterior cingulate gyrus, and the basal ganglia) and their links with the pathogenesis of OCD (e.g. for overviews, see Chamberlain et al 2005; Piras et al 2015). In particular, a key focus has been on executive function deficits as an endophenotype of OCD and impairments have been found in OCD patients and, albeit to a lesser extent, in their unaffected relatives compared to healthy individuals (Bannon, Gonsalvez, Croft, & Boyce, 2006; Cavedini, Gorini, & Bellodi, 2006; Cavedini, Zorzi, Piccinni, Cavallini, & Bellodi, 2010; Chamberlain & Menzies, 2009; Kashyap et al 2013; Kloft, Reuter, Riesel, & Kathmann, 2013; Lawrence et al., 2006; Maltby, Tolin, Worhunsky, O'Keefe, & Kiehl, 2005; Mathews, Perez, Delucchi, & Mathalon, 2012; Olvet & Hajcak, 2008; Taylor, Abramowitz, McKay, & Cuttler, 2011).

Whether such executive deficits are a trait or state associated phenomenon has also received some attention in pre-post treatment studies. It is controversial whether executive functioning deficits in OCD patients are stable *trait*-like characteristics, or whether they might be *state* dependent, reflecting probable influences of the symptomatology on cognitive performance (Bannon et al, 2006). The findings on this issue are mixed in terms of whether neuropsychological deficits improve or not following symptomatic improvement (see Abramovitch & Cooperman 2015). Nevertheless, several studies have shown that executive deficits remain even in those whose OCD symptoms have remitted (Bannon et al 2006; Rao et al 2008; Sharma et al 2014).

A meta-analysis of 115 studies with a total of 3452 OCD patients, reported that, compared to controls, OCD patients performed significantly worse in cognitive functioning in general and executive functioning in particular with a moderate effect size of  $d=0.49$  for executive functioning (Abramovitch, Abramowitz, & Mittelman, 2013). Another meta-analysis of 88 published studies with a total of 3070 OCD patients and 3024 healthy controls, reported that the patients perform significantly worse in all cognitive domains, including executive functioning (Shin, Lee, Kim, & Kwon, 2013). This cognitive impairment in patients was mild and the effect size for executive functioning in particular was  $g=-0.49$ . Authors highlighted

how surprising that is, since executive functioning is supposed to be the main affected domain in OCD patients. A more recent meta-analysis of 110 studies with a total of 3162 OCD patients and 3153 healthy controls, focusing solely on executive functioning, reported that OCD patients were significantly more impaired in several domains including planning, inhibition, shifting and verbal fluency with effect sizes ranging from  $d=0.3$  to  $0.5$  (Snyder, Kaiser, & Warren, 2015).

The aim of this meta-analysis was to provide a quantitative evaluation of previously conducted research on executive functioning of unaffected relatives of patients with OCD and healthy subjects and also to check for moderator factors which may have affected the reported findings. Based on the majority of previous studies, it was expected that relatives would exhibit deficiencies in executive functioning compared to healthy controls. To the authors' knowledge, no previous meta-analysis of cognitive endophenotypes of OCD that includes unaffected relatives and healthy subjects has been conducted so far.

## **2. Method**

### **2.1. Search strategy and eligibility criteria**

A literature search was performed in Pubmed, Medline and PsychInfo databases, to identify papers investigating performance of unaffected relatives of OCD patients and unrelated healthy controls in executive functioning tasks. The search terms employed were: “(Obsessive Compulsive Disorder OR OCD) AND (cognit\* OR execut\* OR endophenot\*)”. The time scale covered by our search was from January 2000 up to and including February 2019. A manual search was also performed in the reference list of the retrieved articles.

### **2.2. Eligibility criteria**

The following criteria were set to assess eligibility for inclusion:

*Inclusion criteria:*

- Compare unaffected relatives of OCD patients with unrelated healthy controls
- Include tasks measuring executive functioning

- Report sufficient data to perform the statistical analyses. When means and standard deviations for the tasks of interest were not reported, we contacted the corresponding authors requesting additional information
- Full text published article
- English language restriction

*Exclusion criteria:*

- Grey literature (articles not published in peer review journals)
- Studies reporting their samples are entirely included in other larger samples
- Studies with non-human subjects
- Meta-analytic studies
- Systematic/Literature reviews
- Studies reporting only non-standardised tasks

The study selection procedure is illustrated graphically in the subsequent flow chart.

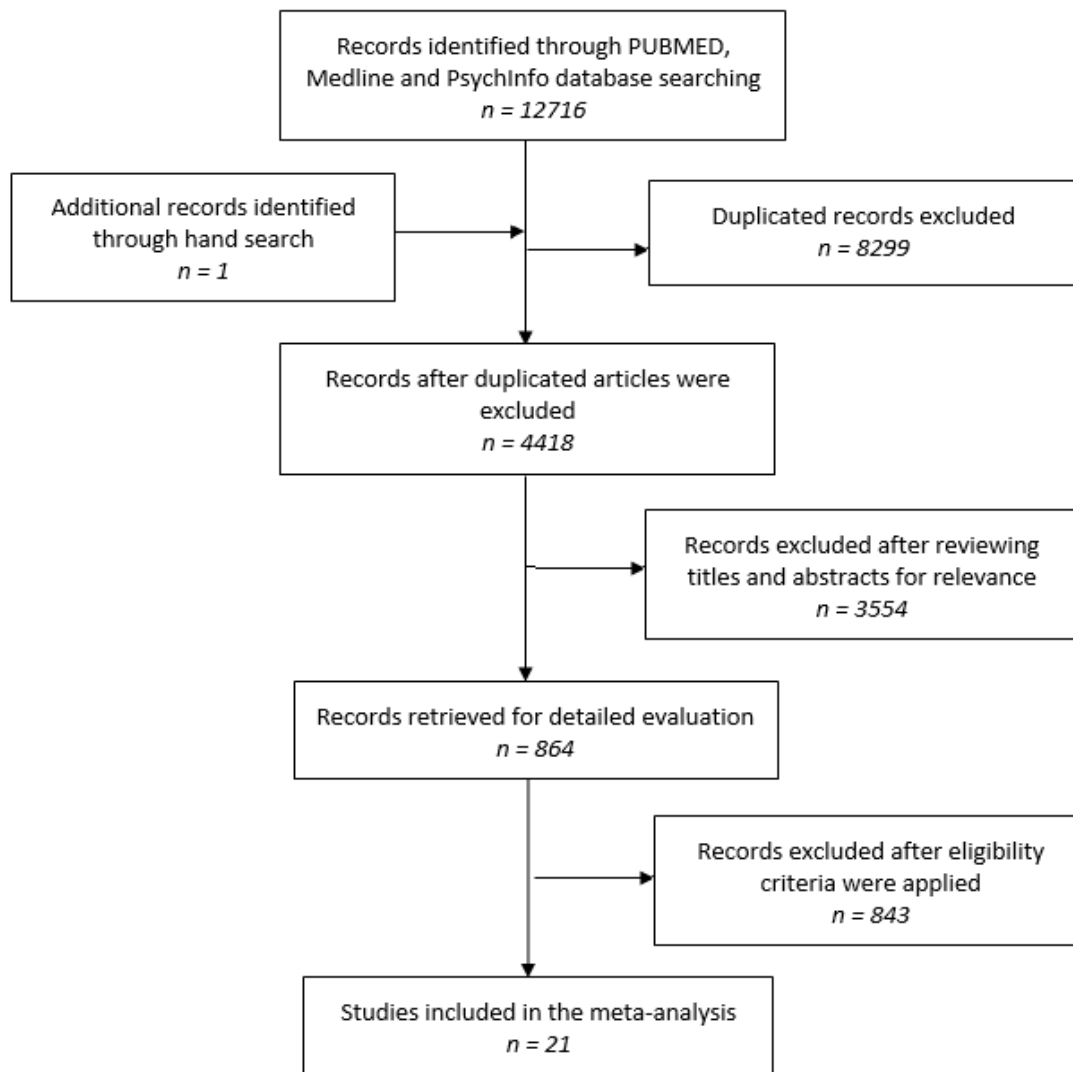


Figure 1. PRISMA (2009) flow diagram illustrating the study selection procedure

### 2.3. Data extraction and analysis

In the present meta-analysis, we compare unaffected relatives of OCD patients with healthy subjects. We did not compare OCD patients with healthy subjects since the meta-analyses by Shin and associates (2013), Abramovitch and colleagues (2013) and Snyder and associates (2015) have already quantified their differences and reported mild deficits in OCD patients.

The meta-analysis was conducted using the *Comprehensive Meta-Analysis* (CMA, version 3.3.070; Biostat, Englewood, NJ, USA). The executive function measures from each study included in the analysis are presented in supplementary Table 1. The mean and standard deviation from each task were extracted from each study. When these data were not available in a paper, authors were contacted. Some studies reported multiple scores for each test. To account for that we grouped the scores per test by study together to obtain one score per test. Then we grouped the tests by each study together as a weighted average in order to produce one effect size (ES) per study. Some studies were reporting the standard errors (SE) from which we calculated the standard deviations.

We calculated the Hedges'  $g$  effect sizes, which are similar to Cohen's  $d$ , but corrects any potential bias that might result from small sample sizes (Hedges & Olkin, 2014). Heterogeneity amongst studies was assessed by examining the distribution of effects sizes and calculating both Cochran's  $Q$  and Higgin's  $I^2$  statistics. Significant heterogeneity was found, indicating that differences across the effect sizes likely result from other sources than sampling error. Due to the moderate heterogeneity the random effects model was employed. Meta-regression analyses for the mean age (measured in years), proportion of females and severity of illness (measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)) were performed.

The tasks we included in the meta-analysis are: Cambridge Gambling task (CGT; Rogers et al., 1999), Iowa Gambling Task (IGT; Bechara et al., 1994), Game Of Dice task (GDT, Brand et al, 2005), Flanker task (Eriksen and Eriksen, 1974), Stroop task (Weschler, 1991), Stop signal task (Aron et al., 2004), Digit Vigilance Test (DVT; Lezak et al., 2004), Tower of London (TOL; Shallice, 1982), Tower of Hanoi (ToH; Welsh et al., 2000), One touch spatial planning task (Williams-Gray, 2007), Wisconsin Card Sorting Test (WCST; Milner, 1963), Intradimensional/Extradimensional Shift task (Cambridge Cognition, 1996), Trail Making Test Part B (TMT; Reittan, 1995), Digit Span Backward (Weschler, 1991), Figural memory test (FMT; Endicott, 1976), Visual organization test (VOT; Hooper, 1958), Delayed Alternation Test (DAT; Freedman, 1990), Design Fluency task (Benton, 1968), Situational Awareness test (SAtest; Endsley, 1995), Wechsler Memory Scale (WMS; Weschler, 1991), Visual Memory subtest (Weschler, 1991), Visual working memory test (Hooper, 1958), Verbal Fluency test (Jones-Gotman and Milner, 1977), Controlled Oral Word Association Test (COWA; Bechtoldt,



1962), Controlled Word Association Test (CWAT; Weschsler, 1991), Category Fluency test (CFT; Weschsler, 1991), Association fluency task (Delorme et al., 2017), Verbal Fluency task (Lezak et al., 2004).

Owing to the high heterogeneity between executive functions we analysed each specific executive functioning domain separately. Six domains were defined: Planning, Inhibition-Selective Attention, Set-Shifting, Decision Making, Visuospatial Working Memory and Verbal Fluency. Each task was categorised to one of the aforementioned domains and the tasks that were grouped together were then combined as a weighted average to obtain effect sizes for all studies in each domain. Eventually we performed an analysis evaluating global executive functioning by grouping all the domains together.

### **3. Results**

The number of papers yielded by the systematic review was 12716 and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were employed to identify the papers of interest. An additional paper was identified by hand search. Initially, 8299 duplicates were excluded. The titles and abstracts of the 4418 remaining papers were screened and 3554 papers were excluded for being extraneous, resulting in 864 papers. The retrieved set of articles was screened in relation to the eligibility criteria. Eventually, 21 studies were deemed relevant and were therefore included in the meta-analysis (For additional information regarding those papers see supplementary Table 1). Quality assessment tool for diagnostic accuracy studies (QUADAS) was employed to assess study quality (Whiting et al., 2004).

### 3.1. Demographics

Table 1. Demographic characteristics of the unaffected first-degree relatives (n=707) and healthy controls (n=842)

	<i>Unaffected relatives</i>				<i>Healthy Controls</i>		
	<i>Female %</i>	<i>Age (SD)</i>	<i>Age range</i>	<i>Y-BOCS</i>	<i>Female %</i>	<i>Age (SD)</i>	<i>Age range</i>
Carrasco et al. (2013)	31.6	13.9 (2.4)	10 - 17	-	50.0	13.8 (2.3)	10 - 17
Zhang J. et al. (2015)	50.0	25.3 (6.4)	18 - 40	-	47.5	25.0 (5.9)	18 - 40
Zhang L. et al. (2015)	52.7	28.4 (7.3)	-	1.9	56.4	27.9 (7.3)	-
Lochner et al. (2016)	84.6	46.9 (5.3)	18 – 59	-	59.3	31.4 (11.1)	18 – 59
Li et al. (2012)	-	-	-	-	45.0	22.6 (5.8)	-
Rajender et al. (2011)	60.0	26.4 (3.9)	-	-	60.0	26.9 (2.9)	-
Lennertz et al. (2012)	60.0	42.1 (14.3)	18 – 65*	0.1	70.0	42.7 (12.6)	18 – 65*
Bey et al. (2018)	78.4	48.8 (12.5)	-	-	57.8	34.1 (12.0)	-
Chamberlain et al. (2007)	65.0	34.2 (11.4)	-	3.7	65.0	33.1 (10.5)	-
Riesel et al. (2011)	56.7	45.9 (13.0)	18 – 65*	-	56.7	45.4 (12.8)	18 – 65*
Segalas et al. (2010)	52.0	44.9 (11.9)	-	-	52.0	43.6 (13.9)	-
Cavedini et al. (2010)	40.1	45.0 (17.7)	18 – 65*	-	71.0	34.7 (16.1)	18 – 65*
De Wit et al. (2012)	29.0	38.3 (13.4)	-	0.1	51.0	39.7 (11.6)	-
Menzies et al. (2007)	70.9	36.7 (13.4)	-	1.7	64.6	33.4 (11.1)	-

Ozscan et al. (2016)	38.9	31.8 (11.5)	18 – 65*	-	42.9	32.4 (8.0)	18 – 65*
Riesel et al. (2019)	64	45 (14.8)	-	-	58	32.1 (9.9)	-
Vaghi et al. (2017)	73.7	41.1 (10.6)	-	-	75.0	36.4 (8.5)	-
Van Velzen et al. (2015)	33.3	38.3 (13.4)	-	-	40.0	38.2 (11.6)	-
Delorme et al. (2007)	45.0	42.3 (15.0)	-	-	45.0	39.7 (18.2)	-
Tezscan et al. (2018)	62	37.9 (15.3)	18 – 65*	-	68.3	35.8 (12.5)	18 – 65*
Viswanath et al. (2009)	40.0	27.5 (6.9)	18 – 45*	-	40.0	27.4 (6.4)	18 - 45

*Note: YBOCS: Yale-Brown Obsessive Compulsive Scale*

*\*Studies only report the age ranges for eligibility in the study*

### **3.2. Analyses of executive functioning domains**

Executive functions can cover a range of different cognitive processes, and we grouped together tests measuring specific executive functioning domains. Table 3 lists the domains of executive functioning for which we conducted additional analyses, the number of studies providing data, and the tasks for each domain along with the number of participants.

Table 2. The executive function domains tested, the tasks measuring each function and the number of studies.

Executive functioning domain	Number of participants		Tasks	Number of participants	
	FDRs	Controls		FDRs	Controls
<b>Inhibition - Selective Attention</b> ( <i>k</i> =12)	347	479	Stop signal task ( <i>k</i> =4)	80	108
			Stroop task ( <i>k</i> =5)	168	171
			Digit Vigilance test ( <i>k</i> =1)	30	30
			Flanker task ( <i>k</i> =3)	99	200
<b>Verbal Fluency</b> ( <i>k</i> =8)	378	359	Controlled Word Association Test ( <i>k</i> =1)	18	21
			Category Fluency test ( <i>k</i> =1)	18	21
			Verbal Fluency Task ( <i>k</i> =4)	197	172
			Digit Span Backward ( <i>k</i> =4)	138	141
			Association Fluency Task ( <i>k</i> =1)	64	47
			Controlled Oral Word Association Test ( <i>k</i> =1)	25	25
<b>Set Shifting</b> ( <i>k</i> =10)	365	339	Wisconsin Card Sorting Test ( <i>k</i> =7)	251	242
			Trail Making Test Part B ( <i>k</i> =7)	280	258
			Intradimensional / Extradimensional Shift task ( <i>k</i> =1)	20	20

<b>Decision making (<math>k=5</math>)</b>	148	158	Cambridge Gambling task ( $k=2$ )	33	47
			Iowa Gambling Task ( $k=3$ )	115	111
			Game Of Dice task ( $k=1$ )	55	55
<b>Visuospatial Working Memory (<math>k=5</math>)</b>	171	157	Visual working memory test ( $k=1$ )	30	30
			Figural memory test ( $k=1$ )	18	21
			Visual organization test ( $k=1$ )	30	30
			Wechsler Memory Scale (WMS) Visual Memory subtest ( $k=1$ )	48	40
			Situational Awareness test ( $k=1$ )	50	41
			Delayed Alternation Test ( $k=1$ )	25	25
<b>Planning (<math>k=10</math>)</b>	486	467	Tower of Hanoi ( $k=3$ )	123	111
			Tower of London ( $k=6$ )	280	289
			Design Fluency task ( $k=1$ )	64	47
			One touch spatial planning task ( $k=1$ )	47	20

*Abbreviations: FDRs: Unaffected first degree relatives*

Initially, differences were observed in inhibition/selective attention, visuospatial working memory, verbal fluency and planning, with unaffected relatives underperforming in all domains compared to healthy controls. After adjusting for multiple comparisons, by dividing the threshold of significance by the number of comparisons ( $p = 0.008$ ) significant differences remained in the domains of visuospatial working memory, verbal fluency and planning with small to moderate effect sizes. The effect sizes for each comparison are summarised in Table 3.

Table 3. Statistics for each executive functioning domain

	Hedge's <i>g</i>	Lower 95% CI	Upper 95% CI	<i>p</i> value	<i>Q</i>
<b>Inhibition/ Selective Attention</b>	.27	.05	.49	.016	52.81 (df=11, $p < .001$ )
<b>Set Shifting</b>	.11	-.05	.28	.19	18.57 (df=9, $p = .029$ )
<b>Decision Making</b>	.45	.04	.86	.03	35.53 (df=4, $p < .001$ )
<b>Visuospatial Working Memory</b>	.36	.19	.53	< .001	7.20 (df=4, $p = .126$ )
<b>Verbal Fluency</b>	.20	.09	.32	< .001	5.09 (df=7, $p = .65$ )
<b>Planning</b>	.37	.19	.56	< .001	23.44 (df=9, $p = .003$ )

Note. Forest plots for each comparison are included in the supplementary material (Figures 1-6).

### 3.3. Comparison of unaffected first-degree relatives versus healthy controls in global executive functioning

When compared to controls, we found significant executive function impairments amongst the unaffected relatives of people with OCD. The pooled standardised difference in means between the unaffected relatives and control groups (with the 21 eligible studies included) was *Hedge's g* = 0.25 and was highly significant ( $p < 0.001$ ). We systematically assessed the heterogeneity

among studies which was found to be high ( $Q=66.41$ ,  $df = 20$ ,  $p < 0.001$ ,  $I^2=69.88$ ). Therefore, the random effects model is reported. The forest plot demonstrating the differences between the unaffected relatives and healthy controls is presented in Figure 2.



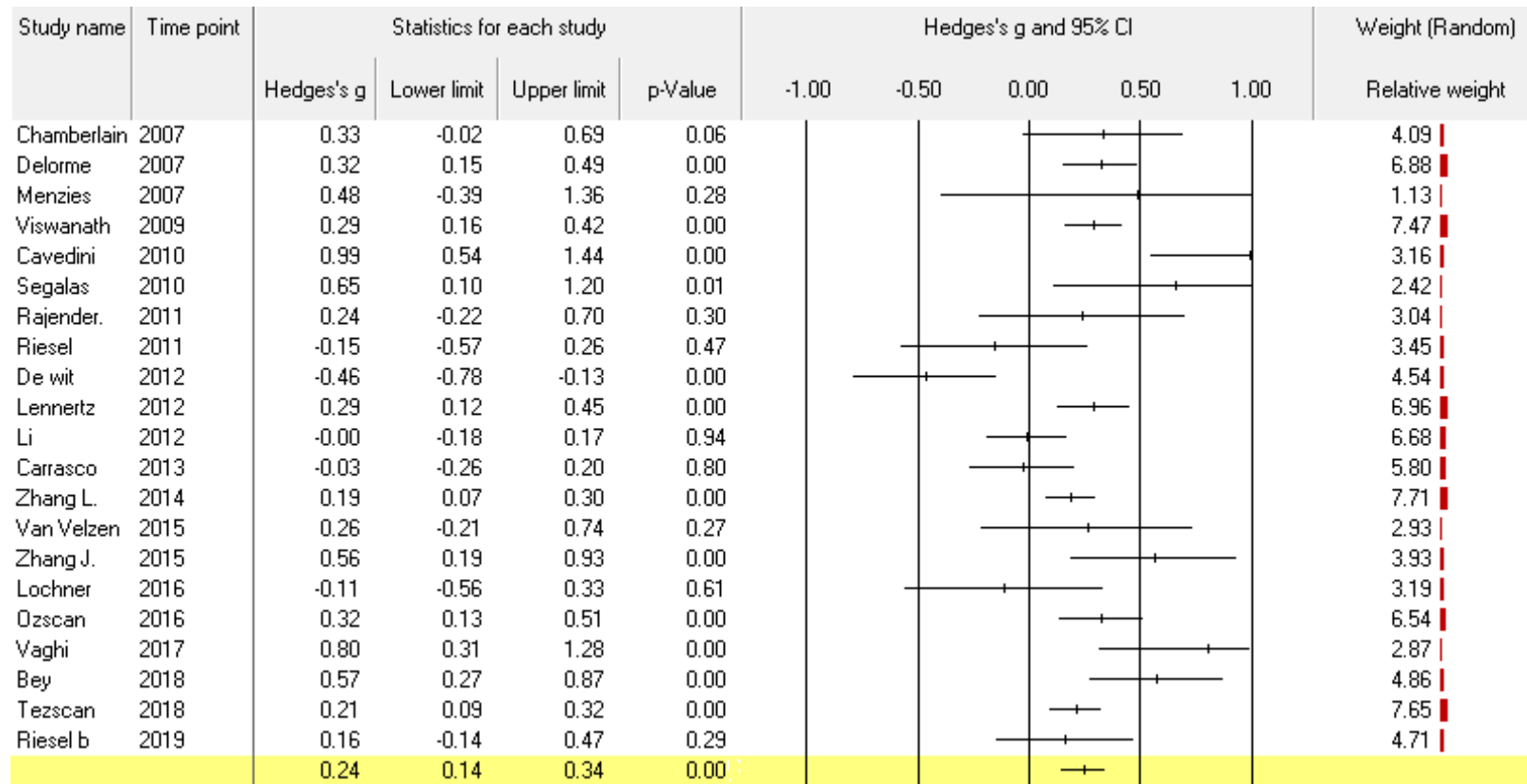


Figure 2: Forest plot of the meta-analysis of all 21 eligible primary studies comparing unaffected relatives of patients with OCD and unrelated healthy controls. Positive effect sizes favour healthy controls, whereas negative effect sizes favour unaffected relatives.

Funnel asymmetry was assessed with Egger's test (0.66) and showed no evidence of publication bias in the results ( $p = .51$ ). A funnel plot illustrating the distribution of studies around the combined effect size was produced (see supplementary Figure 7). The studies were distributed symmetrically around the combined effect size, without a higher concentration of studies on either side. Therefore, we can safely report no publication bias.

### 3.4. Moderator analyses

Given the heterogeneity across studies, meta-regression analyses were conducted to investigate whether additional characteristics contributed to the variation between study effect sizes. Mean age, proportion of females and severity of patient OCD as measured by the Y-BOCS scale in each study were examined as moderators. Only age was found to be a significant moderator with older samples exhibiting more deficits (see Table 4).

*Table 4. Statistics for the moderator analyses for age, proportion of females and severity of illness*

	<i>Q</i>	$\beta$	SE	Z	Lower CI	Upper CI	<i>p</i> value
Age ( $k=20$ )	9.11 ( $p = .002$ )	.013	.004	3.02	.005	.022	.002
Female proportion ( $k=20$ )	3.41 ( $p = .061$ )	.007	.004	1.85	-.001	.016	.064
Severity of illness ( $k=5$ )	1.46 ( $p = .002$ )	.005	.001	.68	-.011	.022	.49

### 3.5. Sensitivity analyses

Sensitivity analyses uncovered no outliers and confirmed the robustness of our results.

## 4. Discussion

The purpose of this meta-analysis was to provide a quantitative assessment of research comparing executive functioning in unaffected relatives of patients with OCD and healthy individuals. Our meta-analysis included 21 primary studies with 1549 subjects (707 unaffected relatives and 842 healthy controls). Our analysis revealed a small ( $g = 0.25$ ), but significant

overall executive function impairment in the unaffected first-degree relatives of those diagnosed with OCD.

Compared to healthy controls, the unaffected relatives of patients with OCD showed evidence of impairments in global executive functioning. Previous meta-analyses comparing people with OCD and healthy controls have consistently reported mild to moderate severity executive function deficits ( $d=0.49$ : Abramovitch et al., 2013;  $g=-0.49$ : Shin et al., 2013;  $d=0.3$  to  $0.5$ : Snyder et al., 2015), and the evidence presented here, suggests that such deficits extend to their unaffected relatives – albeit at a smaller level. Interestingly, the two meta-analyses that assessed overall executive function in OCD patients, both found effect sizes (Shin et al 2013:  $g=-0.49$ , 95% CI  $-0.55$  to  $-0.43$ ; Abramovitch et al 2013:  $-0.498$  95% CI  $-0.58$  to  $-0.42$ ) approximately twice that reported here for OCD relatives and notably the 95% confidence intervals did not overlap between OCD patients and OCD relatives reported here. A crucial criterion for an endophenotype is that it must be impaired in people with genetic predisposition for the disease and our data indicate this criterion is met.

In the analyses of specific domains of executive functioning, unaffected relatives significantly underperformed in visuospatial working memory, verbal fluency and planning with subtle to moderate deficits. We found no differences between unaffected relatives and controls in inhibition/selective attention, decision making and set-shifting. Indeed, of the 10 studies examining set-shifting, only one (Cavedini et al 2010) reported a significant impairment in OCD relatives. This appears to accord with Shin et al (2014) meta-analysis across a range of executive tasks in OCD patients. They found a wide range of performance across executive areas with set-shifting being amongst the smallest effect sizes and non-significant ( $-0.31$  for extra-dimensional shifting), while planning (ToL, ToH) the largest ( $-0.73$ ). Regarding decision making there were only five primary studies and power was probably limited for this domain.

Turning to moderators of executive impairment in the relatives of people with OCD, neither the proportion of females in each study nor severity of symptoms in the unaffected relatives (as measured by the Y-BOCS scale) were significant moderators of effect size. In line with the three meta-analyses comparing OCD patients with healthy controls, we also found that illness severity was not a significant moderator of cognitive performance. By contrast, age was

associated with executive impairment, with increasing age of relatives being associated with greater executive impairment. The three meta-analyses that have assessed executive function in OCD patients are inconsistent on the role of age - with findings that executive impairment and age were unrelated (Abramovitch et al., 2013) positively related (Snyder et al 2015) and negatively related (Shin et al., 2013). In line with the findings for OCD relatives reported here, Snyder et al (2015) found that deficits were greater for older OCD samples (for set-shifting, visuospatial WM, verbal fluency, and planning) and suggests that further research is required to examine the relationship— especially as age has not been a focus in the primary studies.

The tasks that are frequently used to assess executive functions are of course complex and multifactorial. The tests also often involve non-executive function abilities, making the interpretation of findings rather challenging (Aron, 2008; Miyake et al., 2000). Additionally, some tasks are viewed as executive (in nature) by some researchers, but not others. For example, inconsistencies exist in the literature concerning Rey's Complex Figure Test, with some arguing that aside from assessing visuoconstructional ability, it measures executive functioning, specifically the domains of planning and organisation (Watanabe et al., 2005; Somerville et al., 2000). Others however suggest the Rey Figure focuses almost exclusively on visuo-perceptual and visuoconstructional skills (Schwartz et al., 2009; Beebe et al, 2004). For the present meta-analysis we therefore chose not to include tasks such as Rey's Complex Figure Test (RCFT) and the Complex Figure Test (CFT), which might be contentious. Future research should employ tasks measuring specifically executive functioning to avoid this issue.

Although we did not find symptomatology to be a predictor of effect size, this is perhaps unsurprising given that few studies reported Y-BOCS scores and because the levels were close to floor in relatives. Nevertheless, symptomatology of OCD patients themselves is vastly heterogeneous with each symptom potentially impacting an individual's daily and cognitive functioning in a different manner. By way of example, patients with intrusive thoughts might perform worse in executive tasks owing to lack of concentration and depletion of cognitive resources, compared to patients with orderliness obsession. It has also been reported that OCD patients with hoarding symptoms exhibit relatively different neuropsychological deficits than OCD patients without hoarding (Tolin, Villavicencio, Umbach, & Kurtz, 2011). Studies typically do not report information regarding the specific symptomatology of their participants,

which could potentially be an important moderator to examine. We would therefore encourage empirical research aimed at recruiting patients with homogeneous symptomatology and report further information on the symptoms their participants exhibit.

Of course, poor performance on executive tasks by OCD patients may be confounded by a variety of factors, including symptomatology and medication. In the current meta-analysis, unaffected relatives were, of course, relatively symptom-free and not treated with psychotropic medication. Thus, the deficits reported here cannot be attributed to potential treatment confounds. Since less severe version of the same executive dysfunction occurs in healthy relatives is also consistent with the notion that the deficit in patients may be primary rather than secondary confounds.

The current meta-analysis contains several strengths. As far as we are aware, this is the first meta-analysis quantifying how unaffected relatives of OCD patients perform in executive functioning tasks compared to healthy unrelated individuals and the potential of executive functioning performance as disease endophenotype. It also investigates potential moderators and specific domains of executive functioning. All included studies employed the Y-BOCS scale to measure severity of OCD symptomatology, which ensured consistency. Furthermore, we found no evidence of publication bias. The limitations of this meta-analysis should be noted. In regards to the executive function domain analyses, there are not reliable criteria to classify each cognitive test under a specific domain; therefore, we did so based on existing psychometric evidence.

### **Concluding remarks**

In conclusion, this meta-analysis shows that the unaffected relatives of people with OCD have global executive function impairments and show mild to moderate deficits in several executive function domain analyses. These deficits have also been reported amongst patients with OCD and could therefore be endophenotypic markers of genetic predisposition. Therefore, our meta-analysis indicates that it is vital to examine specific cognitive sub-domains in the quest for endophenotypes and biomarkers of disease risk/resilience.

Our findings indicate that the deficits in executive functioning, which have been quantified by three previous large meta-analyses comparing OCD patients with healthy subjects (Abramovitch et al., 2013; Shin et al., 2013; Snyder et al., 2015), seem to be an endophenotype of OCD, since they do extend to the unaffected relatives of the patients. When we focused on specific domains, deficits in visuospatial working memory, verbal fluency and planning were also found in unaffected relatives, suggesting that some quite specific aspects of executive dysfunction have endophenotypic qualities. To substantiate our conclusion, we encourage future empirical research to focus on specific executive function domains instead of grouping the domains together, so as to identify any potential endophenotypes of OCD.

### **Contributors**

All authors have made significant contributions to this manuscript in one or more of the following areas: design of the study, data analysis and interpretation, drafting and revising the manuscript. All authors have given final approval of this manuscript.

### **Conflict of interest**

The authors declare that they have no competing interest.

### **Funding**

This study was supported by the NIHR Biomedical Research Centre at University College London (mental health theme).

Dr E. Bramon acknowledges the following support: BMA Margaret Temple grants 2016 and 2006, MRC- Korean Health Industry Development Institute Partnering Award (MC\_PC\_16014), MRC New Investigator Award and a MRC Centenary Award (G0901310), National Institute of Health Research UK post-doctoral fellowship, the Psychiatry Research Trust, the Schizophrenia Research Fund, the Brain and Behaviour Research foundation's NARSAD Young Investigator Awards 2005, 2008, Wellcome Trust Research Training Fellowship, the NIHR Biomedical Research Centre for Mental Health at the South London and

Maudsley NHS Foundation Trust and Institute of Psychiatry Kings College London and the NIHR Biomedical Research centre at UCL.

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