

Neuropsychological Endophenotypes in University Students with a Family History of Obsessive-Compulsive Disorder

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Received: March 20, 2021; Published: April 27, 2021

Abstract

Background: The ongoing search for a candidate endophenotype (immediate biomarkers) of obsessive-compulsive disorder (OCD) could contribute to identifying underlying genetic contributions. Disrupted cortico-striatal-thalamo-cortical (CSTC) circuits are believed to mediate dysfunctions of executive functioning (EF) seen in patients with OCD, such as, planning, inhibition and organisational strategies. For neuropsychological impairments to be a definable endophenotype, they should be independent of symptomology (trait-like) and exist in unaffected relatives. Therefore, the aim of this study was to investigate EF - deficits and obsessive compulsive (OC) traits in university students with a family history (FH) of OCD in order to establish whether impairments were independent of any OC traits.

Methods: 13 healthy university students with a first-degree and/or second-degree FH of OCD and 17 healthy control underwent a neuropsychological testing battery and an assessment examining OC symptomology.

Results: Students with a first and/or second-degree FH showed impairments in the Tower of London (ToL) test. Students with first-degree FH, but not second-degree FH, were unable to visually organise the Rey-Osterrieth Complex Figure (ROCF). Immediate and delayed recall of the ROCF was comparable to the control as well as intact Stroop performance. OC traits did not correlate with EF performance in any of the neuropsychological tests. Furthermore, a multiple-regression analysis demonstrated OCD FH was the only significant predictor of poor performance in the ToL and impaired organisation of the ROCF. OC traits did not account for a significant amount of variance.

Conclusion: Our findings suggest that impaired planning and organisational deficits indicate trait endophenotypes of OCD. The implication of these findings and scope for future research are discussed.

Keywords: Obsessive Compulsive Disorder; Executive Functioning; Endophenotypes; Neuropsychological; University Students; Family History; Obsessive Compulsive Traits

Introduction

Currently, the prevailing neuropsychological approach to the underlying aetiology of Obsessive Compulsive Disorder (OCD) [68], a highly heritable condition [42] characterised by recurrent and intrusive thoughts or impulses (obsessions) and repetitive and ritualistic behaviours (compulsions) is the frontostriatal model [68]. The model is derived from neuroimaging observations of structural, chemical and functional abnormalities within the cortico-striatal-thalamo-cortical (CSTC) circuits [38] and the abnormal activation of these circuits during the completion of tasks assessing executive functions (EF) [69]. Consequently, the disrupted CSTC circuits is hypothesised to underlie the EF deficits observed in OCD patients [45], such as weaknesses in decision making [2,24], planning ability [2,24,57],

set-shifting [57], visuospatial memory [2,73], inhibition [2], organisational strategy [72] and fluency [2]. While reported findings in the literature are mixed, likely due to confounding effects of psychotropic medication and comorbidity associated with clinical OCD, a meta-analysis of 88 studies with 3070 OCD patients reported largest effect sizes for deficits in immediate visuospatial memory ($g = -.74$), planning ability ($g = -.73$) and organisational strategy ($g = -.63$) [73].

Accumulating evidence report that EF impairment is independent from OCD symptomology [62] and persists, despite symptom remission after psychopharmaceutical treatment [55] or cognitive-behaviour therapy [82]. Furthermore, unaffected first-degree relatives of OCD patients also display pronounced deficits in EF, such as response inhibition [16], set-shifting [15], visuospatial memory [43,71], planning [43], organisational strategies [43] and decision making [85]. Therefore, the abnormal CSTC circuits and, consequently, the EF deficits may index a genetic biomarker (endophenotype) of OCD [59].

Neuropsychological endophenotype of obsessive compulsive disorder

Endophenotypes, which may be neuroanatomical, neuropsychological or biochemical, are intermediate biomarkers that lie between the observable phenotype and the genotype of a disease [30]. The endophenotype concept assists in bridging the gap between the gene-brain/cognitive-behavioural pathway [84], and, since genetic molecular studies have not identified a single gene with a strong association to OCD [80], the endophenotype approach could be more useful in the investigation of the disorder's etiology.

Each endophenotype is argued to underlie each behavioural phenotype of a neuropsychological condition, thus, linking the clinical expression of the disorder to its' neurobiological etiology. Therefore, the pronounced deficits in EF may be the major contributors to the lack of cognitive flexibility and repetitive behaviours in OCD [76]. More specifically, compulsive checking has been attributed to deficits in memory [88] and inhibition [33]. Disinhibition has also been argued to underlie repetitive rituals, obsessive thoughts [14] and symmetry compulsions [33]. Furthermore, deficits in planning goal-directed behaviours have also been attributed to chronic doubting [14] and ritualised behaviour [31]. And finally, planning impairments and poor organisational strategies has been strongly associated with symmetry and ordering compulsions [36].

Gould and Gottesman (2003) [30] argued that in order for a neuropsychological domain to be a definable trait endophenotype of a condition, it must be independent of symptomology and exist at a greater rate in individuals at familial risk compared to the general population. However, some studies contradict this with reports of obsessive compulsive (OC) symptomology correlating with EF deficits [46] and EF deficits existing in subclinical OC individuals (individuals with OC symptoms that are insufficient to meet diagnosis), such as, design fluency [46], response inhibition [1], memory [90], attention [35] and set-shifting [40]. Therefore, these studies indicate EF deficits are associated with OC symptomology and if they're dependent on OC trait, then they cannot be a definable endophenotype of OCD [30].

Obsessive compulsive traits

While the study of subclinical samples may be a valid approach in identifying OCD vulnerability markers [18], the cognitive profiles in subclinical OC individuals could be attributed to the particular thinking and OC cognitive style [37], instead of a vulnerability to developing clinical OCD. It has been argued that, like perfection, subclinical OC is a common thinking-style, mediated by restrictive processing of information, leading to behavioural actions resembling compulsions [37]. Hence, individuals who are more likely to self-doubt and engage in a ruminative thinking-style, may perform poorly in neuropsychological tasks, due to fixated doubting on their choice of action [56]. Therefore, any poor performance in EF tasks, performed by subclinical OC individuals, may not be due to a dysfunction in the CSTC circuits, but, rather, due to the thinking-style that disrupts optimal performance in the EF tasks.

Furthermore, since first-degree relatives of OCD patients are more likely to have OC traits [59]. Past studies may possibly have included participants with a family history of OCD in their subclinical OC sample. To our knowledge, prior studies have never distinguished wheth-

er their subclinical groups also consisted of individuals with a family history of OCD [90] [32,35,46] and therefore, these studies may have mistakenly provided evidence of familial endophenotypes. Likewise, studies with individuals at familial risk, may have had significant OC symptoms and, therefore, their OC thinking-style may have been the stronger predicting factor on their EF performance. Identifying whether poor performance in neuropsychological assessment are associated with impaired CTCS, or are dependent on symptomology, has great theoretical and clinical implications. If neuropsychological deficits are endophenotypes of OCD, mediated by impaired CTSC circuits, then researchers will be closer to the identification of genes that predispose individuals to OCD. However, if poor EF is due to the thinking-style, then researchers can devise appropriate behavioural and cognitive interventions to improve EF.

Aim of the Study

The aim of this study was to identify whether poor performance in EF are an endophenotype of the condition or if OC traits are associated with weak EF. This was done by investigating the neuropsychological profile and OC traits of healthy students with a family history (FH) of OCD and those without. Inhibition was assessed, due to its theoretical importance in the underlying OCD symptoms. Furthermore, since previous studies identified organisational strategies, planning and visuospatial memory are impaired in OCD patients [74], these domains were also measured.

The researcher approached this investigation with the theory that the impaired CTCS circuits indicate an intermediate endophenotype of OCD and, therefore, it was theorised that the presence of OCD FH is a significant predictor of neuropsychological deficits. OC traits, however, would not account for differences in EF.

Methods

Participants

30 Undergraduate students were recruited from Heriot-Watt University, University of Edinburgh, Edinburgh Napier and University of Stirling, all of whom were included in the study. Testing took place in the psychology laboratories onsite at Heriot-Watt University. Criteria for inclusion were the following: 1) individuals must be enrolled as an undergraduate university student, 2) absence of current or past diagnosis of any psychiatric/neurological disorder, 3) absence of a past traumatic brain injury, and 4) absence of colour-blindness. Ethics approval was obtained by the Heriot-Watt School of Social Science Ethics committee and, prior to the testing, informed consent was obtained from all individuals.

The sample consisted of 20 females and 10 males, aged 18 - 27 ($M = 22$, $SD = 2.9$). 13 students (8 females, age: $M = 22.3$, $S.D = 3.6$) had a first-degree family member (sharing 50% of genes, such as offspring, sibling or parents) and/or a second-degree family member (sharing 25% of genes, such as uncles, aunts, nephews, nieces, grandparents, grandchildren, half-siblings and double cousins) with OCD. Out of the 13 students, 4 students had a first-degree and a second-degree family member with OCD, 5 students had a first-degree family member with OCD and 4 students had a second-degree family member with OCD. The remaining 17 students (13 females, age: $M = 21.8$, $SD = 2.4$) had no known FH of OCD.

Materials

Screening for psychiatric and neurological history

In addition to obtaining demographic information, participants were screened for past and current diagnosis of psychiatric and neurological disorders, via a self-report questionnaire. Participants were only included if they reported no history of any psychiatric and neurological condition in addition to no traumatic brain injury and colour blindness.

Measure of obsessive-compulsiveness

OC symptomology was measured with the Washington State University Revision - Padua Inventory (WSUR - PI) [9]. The WSUR - PI is a 39-item, self-reported questionnaire, which measures five-dimensions of OCD: (1) obsessional thoughts about harm to self or others (OTAHTSO), (2) obsessional impulses to harm self or others (OITHSO), (3) contamination obsessions and washing compulsions (COAWC), (4) checking compulsions (CC) and (5) dressing/grooming compulsions (DGR). Items are presented in statements such as: "I think even slight contact with bodily secretions (perspiration, saliva, urine, etc.) may contaminate my clothes or somehow harm me" and requires a rating on a scale, from 0 - 4, on the disturbance the thoughts or behaviours causes the individual, with a higher score equating to a larger disturbance. The ratings were added up to reach a total PI score; the higher the score, the higher the OC traits. The highest score possible was 156.

Neuropsychological tests

The following neuropsychological tests were administered in a single setting lasting approximately 30 minutes: The Rey-Osterrieth Complex Figure (ROCF) task [64], the Tower of London (ToL) task [72] and the word-colour Stroop task [78].

Rey-Osterrieth complex figure

The ROCF task requires subjects to copy a complex geometric figure (copy condition) and, then, re-create the figure from memory in two separate conditions without prior warning: (1) immediate and (2) delayed recall. The copy condition is an assessment of visuospatial construction, which is the ability to see an object as separate components and to construct a replica from these parts [50]. Visuospatial construction depends on visuospatial perception and organisational strategy [7]. Thus, these aspects of EF are commonly assessed with the ROCF [11]. Performances in the immediate and delayed recall condition assesses visuospatial memory [77].

Organisational strategy was assessed with Shorr, Delis and Massman (1992) [75] scoring system by quantifying the extent an individual copies the figure, by clustering elements of the figure together into meaningful components. Memory performance was assessed with the Rey-Osterrieth scoring system [12] which quantifies the inclusion and accuracy of each element, giving a total score out of 36.

Tower of London

The ToL involves a disk-transfer paradigm and was, initially, developed to measure planning impairments in frontal lesion patients [72]. The ToL requires subjects to transfer three discs on three different sized pegs (constraining the number of discs on each peg), from an initial state to a goal state. Optimal performance involves implementing a plan to make as few moves as possible. The task included 30 trials with 3-levels of difficulties, differing in minimum moves to complete each trial (4, 5 and 6-move solutions). Each trial had a time-limit of 120 seconds and a move-limit (the minimum possible move); the trial would end and move onto the next trial if time-limit or move-limit was exceeded. Overall time to complete all 30-trials, as well as average initial thinking time (the time lapse before the first move was made), was measured. These measures were also investigated within each difficulty level. Number of successful trials were measured to give a total score out of 30 and a score out of 10 within each difficulty level.

Stroop

A computerised version of the colour-word Stroop task [78] was retrieved from PEBL [54]. The task measured the relative speeds of naming colours (colour condition), naming the colour of words (word condition) and naming the colour of discordant colour words (colour-word condition), which has an interference component, due to the requirement of inhibiting a reading response. Overcoming the interfering information creates longer reaction times [44]; thus, response time to complete each condition were measured as the interference variable.

Procedure

Each participant was individually tested in a psychology laboratory at Heriot-Watt University with only the experimenter present. Each participant was seated on a recliner chair approximately 50 centimetres across a computer screen. Signed consent and demographic information were collected. The WSUR - PI was then administered. After completion of the WSUR - PI, a printed copy of the ROCF was horizontally presented on an A4 piece of paper and participants were instructed to copy the figure. After completion of the copy condition, the ROCF and their copied drawing were taken away from sight. Participants were then given another piece of blank paper and were instructed to reproduce the figure from memory. If participants claimed they could not remember anything, the experimenter prompted them to draw anything they could remember, even if they couldn't recall the exact location. Once participants claimed they could not remember anything else, their drawing was taken away from sight. The ToL task was then administered through PEBL. Participants were given a full explanation of the nature of task and were given a practice trial to familiarise themselves on the layout of the task and how to execute it on the computer. Once participants were confident on how to use the mouse control in the ToL task, the test trial was brought up. Each participant were prompted to try planning each trial before executing it, in order to ensure no one failed the task due to failing to grasp the need to plan. Furthermore, participants were given the option to take a short break during the ToL if they felt tiredness to control for confounding factors of fatigue. The Stroop task was then administered through PEBL. Finally, participants were presented with a blank piece of A4 paper and were instructed to recall the geometric figure and reproduce the figure from memory again. The experimenter encouraged participants to draw anything they could remember if they claimed they couldn't. When the participants decided they had drawn everything they could recall, their drawing was taken away from them. Finally, participants were asked whether they had a first-degree or a second-degree family member with OCD, via a self-report questionnaire. They were then debriefed.

Statistical analysis

Data were analysed using the Statistical package for the Social Sciences (SPSS) version 24. Two separate statistical analysis were completed to investigate group differences on neuropsychological performance with an unrelated t-test. The first analysis investigated differences between individuals with a first and/or second-degree FH of OCD (FH +) compared to those without a first and/or second-degree FH (control/FH -). The second analysis was interested in investigating the neuropsychological profile in individuals with a first-degree FH only (first FH +) compared to individuals without a first FH (first FH -); hence, individuals with a second-degree FH was included in the first FH - group in the second part of the analysis. Demographical information was explored using a chi-squared analysis for sex differences and an unrelated t-test for age differences. Due to the skewness of PI scores, a man Whitney U test was conducted to explore for differences between groups. All data on the neuropsychological tests were analysed with an unrelated t-test and, where the data was skewed, equal variances were not assumed. Finally, a multiple regression analysis was conducted to explore the effect PI scores had on neuropsychological performance.

Results

The primary aim of this study to identify trait-like neuropsychological endophenotypes of OCD in students with a FH of OCD. To ensure any neuropsychological deficits were biomarkers of the condition, OC traits were investigated.

Performance in the ToL, ROCF and Stroop were assessed in healthy students with a FH of OCD (FH +), compared to students with no family history of OCD (FH -) (a between subject design). Neuropsychological performance was then assessed in healthy students with a first-degree FH of OCD (first FH +), compared to students with no first-degree FH of OCD (first FH -); hence, students with a second-degree FH were also included in the first FH - group. OC traits were measured with the WSUR-PI to investigate whether symptomology had an effect on EF.

Descriptive statistics

The demographical information of the groups is detailed in table 1. An unrelated t-test revealed there were no differences between the FH + and control ($t(28) = .551, p = .586$) and between the first FH + and control groups ($t[28] = -1.08, p = .291$) in terms of age. There were also no difference in sex between FH + and control groups ($\chi^2(1) = .271, p = .602$) and between first FH + and control groups ($\chi^2(1) = .714, p = .398$), as revealed by a Chi-Square Test for Association. Finally, the FH + and control groups ($U = 110.5, p = 1.00$) and the first FH + and control groups ($U = 82.50, p = .587$) did not differ in PI scores, as revealed by a Mann-Whitney U Test (which was conducted due to the PI-values being skewed).

	OCD FH + n = 13	OCD FH - n = 17	Comparison across groups	Significance
			Statistics	p-value
Age (years)	22.3 ± 3.6	21.8 ± 2.4	t (df = 28) = .551	.586
Sex (Females), n (%)	8 (61.54)	12 (70.59)	χ^2 (df = 1) = .271	.602
PI scores	26.62 ± 16.43	25.00 ± 14.97	U = 110.5	1.00

	OCD First FH + n = 9	OCD First FH - n = 21	Comparison across groups	Significance
			Statistics	p-value
Age (years)	21.2 ± 3.12	22.42 ± 2.8	t(df = 28) = -1.08	.291
Sex (Females), n (%)	5 ± 55.56	15 ± 71.43	χ^2 (df = 1) = .714	.398
PI scores	29.56 ± 19.1	20.05 ± 13.66	U = 82.5	.587

Table 1: Demographic and clinical information.

Data expressed as mean ± standard deviation, unless otherwise stated.

OCD = Obsessive Compulsive Disorder; FH + = Family History Positive; FH - = Family History Negative;

First FH + = First Family History Positive; First FH - = First Family History Negative; PI scores = Padua Inventory Scores.

Neuropsychological performance

Mean performances on tests assessing EF between FH + and FH - are summarised in table 2. Mean EF performance on tests between first FH + and first FH - are summarised in table 3.

	OCD FH + n = 13	OCD FH - n = 17	Unrelated t-test between groups		Significance
			t	df	p-value
Stroop					
C time (sec.)	22.11 ± 2.89	21.4 ± 2.16	.696	28	.492
W time (sec.)	20.53 ± 3.86	21.20 ± 2.97	-.539	28	.594
CW time (sec.)	23.97 ± 4.39	22.74 ± 5.41	.670	28	.508
Rey Osterrieth complex figure test					
Copy score	34.50 ± 2.83	35.53 ± 1.46	-1.196	16.881	.248
Immediate score	18.73 ± 7.88	20.79 ± 6.43	-.790	28	.436
Delayed score	19.54 ± 8.22	20.32 ± 6.68	-.289	28	.775
Cluster Index	12.84 ± 3.99	15.18 ± 3.05	-1.815	28	.080
Tower of London					
Total Scores	10.54 ± 3.76	16.94 ± 4.13	-4.373	28	>.001*
E Score	4.46 ± 1.45	6.24 ± 1.48	-3.281	28	.003*

M Score	2.92 ± 1.61	5.41 ± 1.70	-4.072	28	>.001*
H Score	3.15 ± 2.19	5.29 ± 2.08	-2.725	28	.011*
Time (sec.)	750.82 ± 233.62	814.62 ± 292.78	-.644	28	.525
E Time (sec.)	19.21 ± 9.45	21.47 ± 9.28	-.657	28	.516
M Time (sec.)	26.22 ± 7.79	29.78 ± 12.45	-.905	28	.373
H Time (sec.)	29.66 ± 7.98	30.20 ± 10.31	-.156	28	.877
Initial Time (sec.)	12.65 ± 4.50	16.04 ± 8.62	-1.288	28	.208
E Initial Time (sec.)	10.46 ± 5.75	12.67 ± 8.47	-.808	28	.426
M Initial Time (sec.)	13.22 ± 5.07	18.26 ± 11.19	-1.649	23.494	.113
H Initial Time (sec.)	14.78 ± 5.29	17.22 ± 8.46	-.911	28	.370

Table 2: Neuropsychological test performance between groups with FH of OCD and control (no FH of OCD).

Data expressed as mean ± standard deviation, unless otherwise stated. * = Statistical Significance.

OCD = Obsessive Compulsive Disorder; FH + = Family History Positive; FH - = Family History Negative;

C time = Colour Condition Time; W time = Word Condition Time; CW time = Colour Word Condition Time;

E = Easy Difficulty (4-move solution); M = Medium Difficulty (5-move solution); H = Hard Difficulty (6-move solution).

	OCD First FH + n = 9	OCD First FH - n = 21	Unrelated t-test between groups		Significance p-value
			t	df	
Stroop					
C time (sec.)	21.69 ± 2.29	21.77 ± 2.61	-.084	28	.933
W time (sec.)	20.85 ± 3.44	20.94 ± 3.38	-.069	28	.945
CW time (sec.)	23.71 ± 4.98	23.08 ± 5.04	.315	28	.755
Rey Osterrieth complex figure test					
Copy score	34.78 ± 2.22	35.21 ± 2.21	-.496	28	.624
Immediate score	18.39 ± 8.72	20.55 ± 6.32	-.764	28	.451
Delayed score	19.00 ± 8.59	20.40 ± 6.81	-.479	28	.636
Cluster Index	11.89 ± 3.10	15.14 ± 3.44	-2.441	28	.021*
Tower of London					
Total Score	10.78 ± 3.27	15.62 ± 4.91	-2.63	28	.014*
E Score	4.67 ± 1.66	5.81 ± 1.63	-1.75	28	.091
M Score	3.11 ± 1.76	4.86 ± 1.98	-2.28	28	.030*
H Score	3.00 ± 1.87	4.95 ± 2.33	-2.22	28	.035*
Time (sec.)	705.37 ± 187.52	821.94 ± 290.64	-1.103	28	.279
E Time (sec.)	17.50 ± 6.24	21.78 ± 10.16	-1.166	28	.254
M Time (sec.)	24.59 ± 6.69	29.80 ± 11.77	-1.238	28	.226
H Time (sec.)	28.45 ± 7.51	30.61 ± 9.96	-.582	28	.566
Initial Time (sec.)	13.17 ± 4.89	15.17 ± 8.07	-.687	28	.498
E Initial Time (sec.)	10.41 ± 5.48	12.27 ± 8.12	-.627	28	.536
M Initial Time (sec.)	14.07 ± 5.61	16.93 ± 10.48	-.769	28	.449
H Initial Time (sec.)	15.78 ± 4.58	16.33 ± 8.23	-.187	28	.853

Table 3: Neuropsychological test performance between groups with first FH of OCD and control (no first family history of OCD).

Data expressed as mean ± standard deviation, unless otherwise stated. * = Statistical Significant.

OCD = Obsessive Compulsive Disorder; first FH + = First-Degree Family History Positive; FH - = First-Degree Family History

Negative. C time = Colour Condition Time; W time = Word Condition Time; CW time = Colour Word

Condition Time; E = Easy Difficulty (4-move solution); M = Medium Difficulty (5-move solution); H = Hard Difficulty (6-move solution).

Stroop

With respect to the time taken to complete each trial, there were no significant differences between the groups, revealing inhibition was intact in the OCD FH groups.

Rey-Osterrieth complex figure

In terms of immediate and delayed memory recall score, there were no significant differences between the groups. However, in terms of organisational ability, first FH + significantly scored lower on the cluster index score ($t(28) = -2.441, p = .021$) compared to first FH -. This trend was insignificant in individuals with FH of first and/or second-degree relatives of OCD compared to control. Therefore, it could be inferred, organisational ability was only impaired in individuals with a first FH of OCD.

A linear regression analysis was calculated to predict immediate and delayed memory recall on cluster index scores. In regards to immediate memory recall, a significant regression was found ($F(1,28) = 11.843, p = .002$), with an R^2 of .272. Predicted immediate memory recall is equal to $4.882 + 1.060$ cluster index score. Immediate memory recall score increased 1.060 for each point of cluster index score. For delayed memory recall, a significant regression was also found ($F(2,28) = 9.521, p = .005$), with an R^2 of .254. Predicted delayed memory recall is equal to $5.671 + 1.010$ cluster index score. Delayed memory recall score increased 1.010 for each point of cluster index score. Therefore, organisational strategy - as measured by the cluster index - was a significant predictor on performance in immediate and delayed memory recall.

A multiple regression analysis was then calculated to predict delayed memory recall from cluster index score and immediate memory recall. These variables significantly predicted delayed memory recall ($F(2,27) = 107.785, p < .001$), with an R^2 of .889. Predicted delayed memory recall is equal to $.883 + .980$ (immediate recall) - $.029$ (cluster index score). Delayed memory recall increased .980 points for each immediate recall point ($p < .000$). However, cluster index scores were an insignificant predictor of delayed memory recall ($p = .851$). Therefore, this analysis showed that in regard to delayed memory recall, performance in immediate recall was a stronger significant predictor.

Tower of London

FH + significantly completed less successful trials than FH - on the ToL ($t(28) = -4.373, p > .001$). They performed worse on the easy (4-move solutions) ($t(28) = 3.281, p = .003$), medium (5-move solutions) ($t(28) = -4.072, p > .001$) and hard (6-move solutions) ($t(28) = -2.725, p = .011$) trials compared to control. Similarly, this poorer performance was evident in first FH + individuals compared to first FH - ($t(28) = -2.36, p = .014$), with an inability to successfully complete the medium (5-move solutions) ($t(28) = -2.28, p = .030$) and hard (6-move solutions) ($t(28) = -2.22, p = .035$) trails, in comparison to the control. Regarding motor time and initial thinking time, there were no significant differences between groups.

Obsessive-compulsive symptomology

A Spearman's rank-order correlation was run to determine the relationship between the neuropsychological measures and the clinical measure of OC traits (the PI score). Table 4 shows the correlation coefficients between the PI scores and the neuropsychological measures. There were no significant relationship between PI scores and any of the neuropsychological measures, thus indicating EF is independent of OC symptomology.

	PI	
	r_s	P-value
Stroop		
C time (sec.)	-.022	.906
W time (sec.)	-.062	.745
CW time (sec.)	.153	.419
Rey Osterrieth complex figure test		
Immediate Recall	-.068	.721
Delayed Recall	-.087	.649
Cluster Index	-.242	.199
Tower of London		
Total Score	-.003	.986
E Score	.045	.813
M Score	.177	.350
H Score	-.162	.393
Time (sec.)	-.059	.755
E Time (sec.)	.062	.744
M Time (sec.)	-.119	.530
H Time (sec.)	-.124	.513
Initial Time (sec.)	-.013	.945
E Initial Time (sec.)	.045	.813
M Initial Time (sec.)	-.044	.816
H Initial Time (sec.)	-.158	.404

Table 4: Spearman’s Rho correlations between Neuropsychological measures and clinical measure of obsessive-compulsiveness. C time = Colour Condition Time; W time = Word Condition Time; CW time = Colour Word Condition Time; ToL = Tower of London; E = Easy Difficulty (4-move solution); M = Medium Difficulty (5-move solution); H = Hard Difficulty (6-move solution).

A multiple regression was run to predict cluster index scores based on first FH and PI scores. Analysis revealed a significant regression equation ($F(2,27) = 3.510, p = 0.44$) with an R^2 of .206. Predicted cluster index score is equal to $10.083 + 3.003$ (first FH) - .042 (PI score), where first FH is coded as 1 = FH +, 2 = FH -. First FH + scored 3.033 more than FH - on the cluster index ($p = .033$). PI was an insignificant predictor ($p = .314$).

A multiple regression analysis was run to predict successful trial on the ToL from first FH and PI scores. The regression analysis revealed a significant regression ($F(2,27) = 3.390, p = .049$) with an R^2 of .201. Predicted ToL successful trials is equal to $5.384 + 4.926$ (first FH) + .016 (PI score) where FH is coded as 1 = FH +, 2 = FH -. First FH - completed 4.926 more successful trials than First FH + ($p = .015$). PI was an insignificant predictor on ToL performance ($p = .783$).

And finally, a multiple regression analysis was calculated to predict successful trials on the ToL from first and/or second FH and PI scores. The calculation revealed a significant regression ($F(2,27) = 9.222, p = .001$) with an R^2 of .406. Predicted ToL successful trials is

equal to $4.076 + 6.406$ (FH) and $+ .002$ (PI scores), where FH is coded as 1 = FH + and 2 = FH -. FH - completed 6.406 more successful ToL trials than FH + ($p > .001$). PI was an insignificant predictor ($p = .965$).

Overall, the regression analyses reveals that the significant predictor on the differences in the ToL and ROCF between the groups, is OCD FH. OC symptomatology, as measured by the WSUR PI, was not a significant predictor of poor EF.

Discussion

The primary aim of this study was to investigate the neuropsychological profile of individuals with a FH of OCD. Furthermore, effects of OC traits on EF performance were investigated to establish whether neuropsychological deficits were a trait-like endophenotype of OCD which, to our knowledge, is the first study to do so.

Results revealed that healthy university students with a first-degree FH of OCD were significantly impaired in the ability to strategically organise visual information, compared to students without a first-degree FH. When this EF was assessed in a group of individuals with a first and/or second-degree FH compared to a control, group differences were no longer significant. In terms of planning ability, students with first-degree and second-degree FH of OCD were significantly impaired in their ability to successfully complete the ToL task within the minimum possible moves. However, there were no significant difference in pre-planning time and the motor speed to complete the ToL. There were also no significant impairments in measures of visuospatial memory and inhibition in the students with a FH of OCD compared to those without. A correlational analysis demonstrated neuropsychological performance did not correlate with PI scores, a measure of OC traits. Multiple regression analyses showed OC traits was not a significant predictor of poor performance in organising the ROCF and in the ToL. Presence of a FH of OCD was the only significant predictor of poor planning and organisational strategies. These results support a trait endophenotype hypothesis: impaired EF are not secondary to OC traits [14] and indicate a vulnerability biomarker of OCD [30] mediated by impaired CSTC circuits.

The neuropsychological profile

Results indicated the neuropsychological endophenotype profile of OCD is a deficit in planning abilities and organisational strategies. Inhibition and visuospatial memory were intact. This distinct neuropsychological profile will now be discussed.

Organisational strategy

The significant impairment in organisational strategy is comparable to past findings in unaffected OCD relatives [71]. Furthermore, the significantly poor cluster index score reflects Shin., *et al.* (2014) OCD patient meta-analysis: impairments in organising the ROCF has the largest effect size [74]. Therefore, the results in this study indicates that the significant weakness of organising complex visual stimuli found in OCD patients also exist in unaffected first-degree relatives; hence, visual organisational deficits are a trait endophenotype of OCD. The absence of this impairment in second-degree relatives indicates the susceptibility genes of OCD are likely inherited in an autosomal dominant manner [59].

Visuospatial memory

The absence of impaired visuospatial memory in this study reflects the mixed findings of spared and impaired [71] visuospatial memory in unaffected relatives in the literature. The contradictory findings in the literature may be due to the memory deficit being secondary to poor organisational strategies [74]. Organising the ROCF into meaningful perceptual units enhances recall from memory [75] which can be generalised to effective encoding and retrieval of episodic memories [67]. A linear regression analysis conducted in this study confirmed immediate visuospatial memory performance was secondary to organisational strategies. Therefore, any accounts of impaired memory in prior research may likely be due to the ineffective strategy used when encoding the visual stimuli.

Planning

Individuals with a first FH of OCD were significantly impaired in planning and executing trials of the ToL within the minimum possible moves. Furthermore, this significant trend was evident when including individuals with a second-degree FH in the sample, which provides insight into the trend of heritability of this EF. While motor speed to complete the trials and initial thinking time weren't significantly different to control, the main planning variable of successfully completing the trials indicated planning ability was significantly impaired. These results confirm prior findings of impaired planning ability in unaffected relatives of OCD [27,43]. The planning variable (successfully completing the trials) in OCD patients was reported with a large effect size in a meta-analysis [74] indicating the deficit is an endophenotype due to its evidence in unaffected relatives.

Inhibition

No group differences in Stroop performance was found in this study, indicating inhibition was spared in the FH + group. This finding was surprising due to prior reports of impaired inhibition in unaffected relatives [16]. Furthermore, disinhibition is attributed to common behavioural phenotypes of OCD, such as the inability to suppress compulsive checking [33], symmetry compulsions [33] repetitive behaviours [14] and the helplessness to inhibit intrusive obsessions [14]. However, spared inhibition has also been discovered in previous literature focusing on unaffected relatives [63] which may be attributable to heterogeneity in neuropsychological assessments, participant characteristics and limitations of methodology. Therefore, while students with a FH of OCD had comparable Stroop performance to control in this study, this finding doesn't necessary indicate inhibition was intact and isn't an endophenotype of OCD. Confounding factors in the Stroop task may have accounted for the seemingly intact performance in addition to participant characteristics and methodological limitations. The possible confounding factors and methodological limitations will be discussed in regards to the implications they may have had.

Confounding factors in neuropsychological assessment

EF is an umbrella term for top-down processes that underlie goal-directed responses to novel situations [23] and therefore, the action performed in an EF task must a controlled process [70]. However, a controlled action can effortlessly shift to an automatic process when familiarity of the task increases. Furthermore, since the majority of the participants were psychology students, they may have been more familiar to the tasks than students from other academic disciplines who were naïve. Therefore, there's difficulty in distinguishing whether this neuropsychological tests in this study demanded for controlled or automatic processes and this is a key obstacle in obtaining valid EF measurement. Additionally, since EF describes several processes, the lack of clarity in the definition also prevents accurate measurement of the construct [39]. Completing an EF task usually involves several EF and non-EF processes, therefore, an EF assessment tool is rarely "pure" in measuring one specific domain [34]. For example, good performance on any task relies on testing attitude [52] and attentional and motivational factors [8]. Therefore, poor performance in a task assessing planning, for example, may not equate to planning deficits but could be due to the subject lacking motivation to perform well. Consequently, we can never be sure what an EF task is measuring.

Construct validity of the tower of London

While traditionally a test of planning ability [72], the ToL depends highly on visuospatial memory due to the requirement of mental visualisation when implementing a plan [17], G'Antuono., *et al.* (2017) confirmed this by assessing subjects' visuospatial sketchpad with the Corsi Span and found performance in the Corsi Span correlated with ToL performance [26]. Furthermore, Phillips, Wynn, Hilhooly, Della Sala and Logie (1999) found that a secondary visuospatial memory task negatively affected performance in the ToL [60]. However, a verbal memory task improved it; therefore, implying differences in strategies implemented when carrying out the task, such as verbally guiding oneself, influences performance. Additionally, formulating a successful plan in the ToL require inhibiting inappropriate move selections beforehand [13] and therefore, any inhibitory deficits in the FH + group may have resulted in poor performance. Nevertheless,

G'Antuono, *et al.* (2017) showed that, while Stroop test performance correlated with ToL performance, inhibition did not account for significant amount of variance on the ToL [26]. Finally, performance in the ToL can be predicted by intelligent quotient (IQ) [26]. However, since this study's participant samples were university students, it can be inferred their IQ were similar [20] and therefore, differences in ToL performance is unlikely to be explained by IQ differences.

Construct validity of the Rey-Osterrieth complex figure

Likewise, to the ToL, there are difficulties in establishing what other cognitive processes are involved and influence recall of the ROCF. For example, ROCF recall correlates with the Labyrinth test - a test assessing visual planning [88] - and therefore, ROCF recall may be more indicative of planning ability [21]. Furthermore, the scoring system used to assess memory performance fails to indicate diagnostic importance of including or excluding certain elements [12]. For example, excluding the circle with dots (which almost resemble a smiley face) may indicate a severe deficit due to the relative ease in attaching semantic meaning to the element [19].

Construct validity of stroop

Finally, there's several reasons behind OCD FH + intact performance in the Stroop test that may not be diagnostic of intact inhibition. The task required attention and motor speed [58] and therefore, superior attention and motor speed could have overshadowed any inhibitory deficits. Likewise, deficits in these abilities could have accounted for reported disinhibition in prior studies. Furthermore, since participants in this study were recruited from universities in Edinburgh, where a large percentage of the population are European and International migrants [87], there was a high likelihood of the sample containing several bilingual participants. Bilingual individuals are reported to have superior Stroop performance [6] and a greater control of interference [4], due to constantly managing two languages and inhibiting one language when using another [5]. Therefore, the intact stroop performance in the FH + group could be attributed to bilingualism.

Limitations of the Study

Limited assessment of individual and family medical history

In addition to obvious limitations, such as the small sample size, the methodology in obtaining medical history was inadequate. This study obtained information of medical history through a self-reported questionnaire and FH of OCD was also established this way. However, this contrasts with the extensive screening processes used in past studies on OCD relatives, where clinical assessments with trained professionals were carried out [72]. Past studies clinically assessed participants to rule out any undiagnosed disorders. Furthermore, relatives of OCD patients were recruited by contacting OCD probands and ensuring the OCD probands met a clinical diagnosis of OCD through independent assessment. A self-report questionnaire may have not been enough to confirm a FH of OCD. Employing a methodology similar to this would have ensured the participants' performance on EF was not influenced by an unknown psychopathology, such as depression [51] or trauma [22]. Furthermore, any physical conditions may have influenced poor EF performance, such as chronic pain [3]; history of physical conditions were not investigated in the participants and, therefore, it cannot be established how much this factor confounded the neuropsychological profile.

Furthermore, prior studies assessed medical conditions in the family with validated tools, such as the Family Interview for Genetic Studies [47], to rule out FH of psychiatric/neurological disorders. This study didn't investigate whether there was a FH of other conditions in the sample, hence, it can't be entirely sure whether the EF deficits indicated an endophenotype of OCD or of an entirely different condition. The implications of this is especially important, due to planning impairments having been identified in relatives of Autism Spectrum Disorders (ASD) [82] and Anorexia Nervosa (AN) [27]. Additionally, OCD is often comorbid with ASD and AN [49], therefore, if the students in this study had a relative with comorbid OCD, then how sure can we be that the neuropsychological deficit is an endophenotype of OCD or of the comorbidity?

Limitations in the assessment of obsessive-compulsive symptomology

There are some reported limitations in the accurate measurement of OC symptomology with the WSUR - PI which may have had grave implications on the results. For example, the WSUR - PI is a self-reported measure, which may have not yielded large enough effect sizes as an observer-rated scale does [79]. Furthermore, the tool was originally created to assess healthy students [10] and, while that makes it ideal for the sample population in this study, the reliable application of the assessment tool in clinical OCD is debatable. Gönner, Ecker and Leonhart (2010) explored the psychometric properties of the WSUR PI in a large sample of OCD patient and found that the five-factor structure couldn't be replicated and the items measuring OTAHTSO and OITHSO were unreliable measures, as assessed with a squared multiple correlation [28]. Furthermore, the four items in the OITHSO describe extremely rare OCD symptoms; hence, it would have been even more unlikely for these symptoms to be present in a healthy sample. Therefore, if the WSUR - PI lacked validity to accurately assess OC symptomology in this study, then a higher or a lower PI score may have not actually indicated higher or lower OC traits.

Gönner, *et al.* (2010) devised a new revision, the PI-PR, to address the limitations of the WSUR - PI [28]. The PI-PR excludes the WSUR - PI items measuring rare OCD symptoms and validly assesses a broader range of OC symptoms [28]. This study would have benefitted from using the PI-PR, in addition to other assessments, such as the Y-BOCS. Additionally, OC traits could have been measured in a clinical interview with a clinical psychologist.

Conclusion

Impaired planning and organisational abilities were found in students with a FH of OCD. These significant findings concur with previous reports of deficits in OCD relatives. Furthermore, OC traits did not correlate nor account for significant variance in planning and organisational deficits, suggesting these impairments reflect disrupted CSTC circuits and are a trait endophenotype of OCD. Hence, this finding suggests that EF deficits found in subclinical OC individuals [1,35,40,46,90] may be due to a presence of OCD FH or other confounding factors in EF tasks or participant characteristics. This study also concluded that while visuospatial memory was spared in the OCD FH group, poor organisational deficits affected memory recall in the ROCF, which can account for the mixed reports of visuospatial memory ability in prior studies. And finally, while Stroop performance in the OCD FH groups were comparable to control, this could be attributed to several confounding factors relating to construct validity and participant characteristics. Furthermore, limitation in the methodology means that care must be taken when concluding these results as indicative of an endophenotype of OCD and not another condition entirely.

Future Directions and Implications

Identifying neuropsychological endophenotypes have great implications in discovering underlying etiology of neuropsychiatric disorders. Furthermore, endophenotypes could assist in effective diagnosis on biological basis instead of relying on behavioural presentation, a key criticism of the main psychiatric diagnostic tool, the DSM [48]. Moreover, discovering similar neuropsychological endophenotypes between conditions that are traditionally thought to be categorically separate could lead to a dimensional approach to psychiatry [65]. For example, AN has been argued to belong to the OCD spectrum [27], hence the similar neuropsychological endophenotypes reported in the two conditions. Additionally, OCD symptoms share similarity with impulse control disorders and drug addiction, which are also linked to disrupted CSTC circuits [25] and, consequently, disinhibition is theorised to drive the impulsive and compulsive behaviours in these conditions [65]. If the underlying etiology is discovered to be similar, then similar and effective treatment plans can be devised. Future research should couple the search for neuropsychological endophenotypes with imaging and genomic strategies. Furthermore, future studies should investigate neuroanatomical and chemical endophenotypes.

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Volume 10 Issue 5 May 2021

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