Psychiatry Research

Cognitive deficits and clinical symptoms in patients with treatment-refractory obsessive-compulsive disorder: the role of slowness in information processing.

--Manuscript Draft--

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	Marcos Rios-Lago, PhD
Abstract:	Patients with Obsessive-Compulsive Disorder (OCD) present deficits across different neuropsychological domains, especially in executive functioning and information processing speed. Some studies have even suggested that speed deficits may underlie poor neuropsychological performance. However, this hypothesis remains unanswered in both OCD general population and OCD refractory subgroup. In addition, it is not clear whether such deficits are secondary to clinical symptoms or may constitute a primary deficit. The aim of this study was to explore the speed of processing hypothesis in treatment-refractory OCD patients, and to clarify to what extent slowness is related to psychopathological symptoms . Both clinical and neuropsychological examination was conducted to assess 39 OCD refractory patients candidates for neurosurgery and 39 healthy matched individuals. Principal component analysis revealed a three-component structure in the neuropsychological battery being used, including a speed of processing, working memory, and conflict monitoring components. Group comparisons revealed that OCD patients performed significantly worse than healthy individuals in speed measures, but no differences were found in executive tests not influenced by time . Correlation analyses revealed a lack of association between neuropsychological and clinical measures. The results suggest that treatment-refractory OCD patients exhibit a primary deficit in information processing speed independent of clinical symptoms.
Suggested Reviewers:	Marie Josee Bedard Department of Psychology, Université du Québec à Trois- Rivières, Quebec, Canada bedardma@uqtr.ca She is an expert in cognitive functioning in OCD and has published neuropsychological papers in the OCD area.
	Hannah R Snyder Brandeis University hrsnyder@brandeis.edu Her research seeks to understand the links between executive functions and psychopathology, and published relevant papers about cognitive performance in OCD
	Amitai Abramovitch

	Texas State University abramovitch@txstate.edu Utilizing cognitive neuropsychology, his research aims at gaining insight into cognitive functions associated with psychopathological processes. He has published very relevant articles in OCD cognitive performance.
	Jean Regis Timone Hospital, Marseille (APM), France j.regis@ap-hm.fr He is an expert in severe treatment refractory OCD Patients. As a clinician, we think he would appreciate research in cognitive performance as it could be used to measure clinical outcomes.
	Rosa Ayesa-Arriola Valdecilla Biomedical Research Institute IDIVAL rayesa@idival.org She is an expert in cognitive performance and psychopathology. She has published many papers in this area of expertise
Response to Reviewers:	We thank the anonymous reviewers for their careful reading of our manuscript and their many insightful comments and suggestions. Below we respond to the comments of each reviewer in detail, with reviewer comments in italics. We are also providing a revised manuscript that reflects their suggestions and comments. We feel that this has strengthened the manuscript. Reviewer 1 Q0.-The present study aimed at assessing cognitive function in treatment resistant OCD, with an emphasis on differentiating between tests with a major processing speed component compared to those without. The strength of the study is the subject matter that received little direct attention, the employment of PCA, and the focus on treatment resistant sample. However, unfortunately the study has multiple weaknesses that dampen this readers enthusiasm and bring in to question its potential contribution to the literature. R0.- We first want to thank the Reviewer 1 for his/her positive comments about the novelty of the topic being investigated in a sample not well described yet, and those regarding the innovative methodology being adopted. We also want to thank all the points raised that have helped us improving the quality of our work. Q1.- There are no hypotheses. R1.- Please note that two hypotheses were explicitly formulated in the last paragraph of the Introduction of the original manuscript (p.5). The first one stated that ‘If the deficit in IPS modulates test performance in treatment-refractory OCD patients, then differences between patients and controls would emerge in those scores loading in the IPS factor only’. The second one stated that ‘if slowness of IPS constitutes a primary deficit characterizing treatment-refractory OCD patients, beyond clinical symptoms, then there will be no relations between clinical and neuropsychological speed measures’. Q2.- In addition, the rationale for addressing the issue of processing speed is clear but there is nothing in the introduction about the rationale behind looking at this in a tx resistant sample. Why would that be important, and why would that be different than in common OCD samples? In the discussion the authors note that their results are in line with previous research and meta analysis (conducted on regular OCD samples), but there is nothing addressing this particular type of sample. R2.- Thanks for noting that this point needs further justification in the Introduction. First, the examination of the speed of processing hypothesis in treatment-refractory OCD patients would improve the characterization of their cognitive deficits, and their comparability with the general OCD population. Ultimately, it would justify introducing specific IPS measures in cognitive assessment protocols. Second, it could help enhancing the efficacy of cognitive interventions being developed in OCD (see for instance van Passel et al., 2016), which is a central goal in a subgroup whose response to conventional treatments is minimal or absent. In this regard, clarifying the

modulatory effect of IPS deficits in treatment refractory OCD cognitive functioning could help developing new pathways towards more targeted cognitive interventions for these patients. This information has now being included in the Introduction section of the RM (p.3, second paragraph).

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Q15.- The paper can use a comprehensive proofread by a native English speaker.

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Reviewer 2

Q0.- This is an interesting study that pays attention on relevant aspects of obsessive-compulsive disorder: treatment-refractory patients and the role of information processing. The paper is in general well conducted and well written. However, in reviewing the manuscript, major questions/concerns arose, specifically:

R0.- We first want to thank the Reviewer 2 his/her positive comments regarding the interest of our study, the innovative methodology being used, and the writing stile. We also appreciate the questions being raised since they have contributed to clarify preceding gaps in the description of samples or the justification of the study. A detailed response to all his/her questions is provided below.

Q1.- The information about patients is scarce. Are they in a clinical trial? In this case, you should include study number. What kind of treatments have they received? How long have they received these treatments? Are they similar on the previous treatments received? I would really appreciate to know more about these patients.

R1.- Thank you for noting that the information about patients was scarce. Following your advice, we have improved the description about treatments as well as some other clinical and sociodemographic features of the patients (see new Table 1). Please, note that the patients were not in a clinical trial but in an observational study.

Q2. I find the methodological approach very interesting, but I think that the inclusion of a third group (not treatment resistant) could have enriched very much the paper. Have you considered this approach?

R2.- Thank you very much for this constructive suggestion to enrich our investigation. Note however that the present sample was recruited in the context of a functional neurosurgery unit. In this regard, all patients derived to this unit meet criteria for a treatment-refractory OCD diagnosis. Unfortunately, at the moment, we have no access to “not treatment-refractory” OCD patients. Comparing general OCD and treatment-refractory patients would become important to assess the relevance of the IPS hypothesis in this population and will be considered in future works.

Q3.- The discussion has to be strengthened. What exactly means to be relevant in future research in the field? What roach could represent benefits for the patients?

R3.- Thanks for noting that this point needs further development. Deepen understanding of processing speed deficits in treatment-refractory OCD patients would be relevant at different levels. It will help improving the characterization of their cognitive deficits as compared to the general OCD population. It will ultimately help clarifying the importance of introducing specific IPS measures in assessment protocols. It could also help enhancing the efficacy of cognitive interventions being developed in OCD (van Passel et al., 2016) by introducing IPS as a specific outcome. Also, providing training to improve IPS would complementarily reduce patients’ subjective complaints of psychomotor slowness. These points have been now included in the Discussion section of the RM (P. 15).

Q4.- I can see more limitations than the one that you mention about information on medication, such as the narrow number of subjects in both patients and controls groups, and the lack sociodemographic information such as socioeconomic position, working situation and family history of OCD.

R4.- Thanks for noting that participants’ description should be improved. The revised version of the manuscript now incorporates sociodemographic information regarding: familial situation, and working situation for patients and healthy controls, as well as family history of OCD, and patients’ additional clinical features (see new Table 1).

Regarding the sample size, please note that only one of the four prior investigations describing neuropsychological performance in treatment-refractory OCD samples (Dinn, et al., 2016; Gong et al. 2018, Krámská et al. 2021; and Zhang et al., 2017) has included a larger N than the one used here (with sample sizes of 5, 28, 12, and 107 individuals, respectively). Note also that this study (Zhang et al. 2017) assessed neuropsychological performance by using one single test (i.e., IGT). Considering this information, and the difficulties in recruiting these patients, we believe that our sample size should not be considered narrow.

Authors additional note:

An error in Table 4 was detected when correlation analyses were redone during the review process. Specifically, Pearson and Spearman values from the original Table 4 were inadvertently interchanged. Please, note that the new values included in current Table 4 have not modified the direction of any result or conclusion compared to the original version of the manuscript.

REFERENCES

Rosselli, M., Ardila, A., Salvatierra, J., Marquez, M., Matos, L., & Weekes, V. A. (2002). A cross-linguistic comparison of verbal fluency tests. International Journal of Neuroscience, 112, 759-776. http:// dx.doi.org/10.1080/00207450290025752

Editor-in-Chief Lynn E. DeLisi
Cambridge, Massachusetts,
United States of America

Manuscript ID: PSY-D-21-01161

Title: Cognitive deficits and clinical symptoms in patients with treatment-refractory obsessive-compulsive disorder: the role of slowness in information processing.

Dear Editor,

Thank you for allowing us to prepare a revised manuscript for your consideration.
We highly appreciate the detailed valuable comments of the referees on our manuscript. We have fully addressed each item and hope that this revised manuscript is now acceptable; however, we will be happy to consider any further modifications that may be suggested. Revisions are indicated within the text using colored text. Please find attached our revised paper and a point-by-point summary of the modifications that have been made to the text.

Yours sincerely,

Marcos Ríos-Lago

We thank the anonymous reviewers for their careful reading of our manuscript and their many insightful comments and suggestions. Below we respond to the comments of each reviewer in detail, with reviewer comments in *italics*. We are also providing a revised manuscript that reflects their suggestions and comments. We feel that this has strengthened the manuscript.

Reviewer 1

Q0.-The present study aimed at assessing cognitive function in treatment resistant OCD, with an emphasis on differentiating between tests with a major processing speed component compared to those without. The strength of the study is the subject matter that received little direct attention, the employment of PCA, and the focus on treatment resistant sample. However, unfortunately the study has multiple weaknesses that dampen this readers enthusiasm and bring in to question its potential contribution to the literature.

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R2.- Thank you very much for this constructive suggestion to enrich our investigation. Note however that the present sample was recruited in the context of a functional neurosurgery unit. In this regard, all patients derived to this unit meet criteria for a treatment-refractory OCD diagnosis. Unfortunately, at the moment, we have no access to "not treatment-refractory" OCD patients. Comparing general OCD and treatment-refractory patients would become important to assess the relevance of the IPS hypothesis in this population and will be considered in future works.

Q3.- The discussion has to be strengthened. What exactly means to be relevant in future research in the field? What roach could represent benefits for the patients?

R3.- Thanks for noting that this point needs further development. Deepen understanding of processing speed deficits in treatment-refractory OCD patients would be relevant at different levels. It will help improving the characterization of their cognitive deficits as compared to the general OCD population. It will ultimately help clarifying the importance of introducing specific IPS measures in assessment protocols. It could also help enhancing the efficacy of cognitive interventions being developed in OCD (van Passel et al., 2016) by introducing IPS as a specific outcome. Also, providing training to improve IPS would complementarily reduce patients' subjective complaints of psychomotor slowness. These points have been now included in the Discussion section of the RM (P. 15).

Q4.- I can see more limitations than the one that you mention about information on medication, such as the narrow number of subjects in both patients and controls groups, and the lack sociodemographic information such as socioeconomic position, working situation and family history of OCD.

R4.- Thanks for noting that participants' description should be improved. The revised version of the manuscript now incorporates sociodemographic information regarding:

familial situation, and working situation for patients and healthy controls, as well as family history of OCD, and patients' additional clinical features (see new Table 1).

Regarding the sample size, please note that only one of the four prior investigations describing neuropsychological performance in treatment-refractory OCD samples (Dinn, et al., 2016; Gong et al. 2018, Krámská et al. 2021; and Zhang et al., 2017) has included a larger N than the one used here (with sample sizes of 5, 28, 12, and 107 individuals, respectively). Note also that this study (Zhang et al. 2017) assessed neuropsychological performance by using one single test (i.e., IGT). Considering this information, and the difficulties in recruiting these patients, we believe that our sample size should not be considered narrow.

Authors additional note:

An error in Table 4 was detected when correlation analyses were redone during the review process. Specifically, Pearson and Spearman values from the original Table 4 were inadvertently interchanged. Please, note that the new values included in current Table 4 have not modified the direction of any result or conclusion compared to the original version of the manuscript.

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Highlights

- Differences in cognitive performance of patients with treatment refractory OCD and healthy controls are found in neuropsychological measures affected by speed of information processing only.
- Information processing speed is not related to OCD clinical symptoms.
- There is no association between cognitive and clinical symptoms in patients with treatment refractory OCD.

Cognitive deficits and clinical symptoms in patients with treatment-refractory obsessive-compulsive disorder: the role of slowness in information processing.

Abstract

Patients with Obsessive-Compulsive Disorder (OCD) present neuropsychological deficits across different cognitive domains, especially in executive functioning and information processing speed. Some studies have even suggested that speed deficits may underlie poor neuropsychological performance. However, this hypothesis remains unanswered in both OCD general population and OCD refractory subgroup. In addition, it is not clear whether such deficits are secondary to the clinical symptoms or may constitute a primary deficit. The aim of this study was to explore the speed of processing hypothesis in treatment-refractory OCD patients, and to clarify to what extent slowness is related to psychopathological symptoms. Both clinical and neuropsychological examination was conducted to assess 39 OCD refractory patients candidates for neurosurgery and 39 healthy matched individuals. Principal component analysis revealed a three-component structure in the neuropsychological battery being used, including a speed of processing, working memory, and conflict monitoring components. Group comparisons revealed that OCD patients performed significantly worse than healthy individuals in speed measures, but no differences were found in executive tests not influenced by time. Correlation analyses revealed a lack of association between neuropsychological and clinical measures. The results suggest that treatment-refractory OCD patients exhibit a primary deficit in information processing speed independent of clinical symptoms.

Keywords: Attention, Clinical symptoms, Executive Function, Information Processing Speed, Neuropsychology, Obsessive-Compulsive Disorder, Slowness.

Title: **Cognitive deficits and clinical symptoms in patients with treatment-refractory obsessive-compulsive disorder: the role of slowness in information processing.**

Running Title: **Cognitive and clinical symptoms in refractory OCD.**

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Cognitive deficits and clinical symptoms in patients with treatment-refractory obsessive-compulsive disorder: the role of slowness in information processing.

1. Introduction

Obsessive-compulsive disorder (OCD) is one of the most chronic and disabling psychiatric conditions affecting approximately 2,5% of the population (Ruscio, Stein, Chiu, & Kessler, 2010). It is characterized by repetitive, intrusive, and persistent thoughts and images or obsessions, commonly followed by compulsive behaviours that are rigid, ritualized, time consuming, and repetitive. Compulsive behaviours and mental rituals are intended to relieve the distress caused by obsessive thoughts. OCD may sometimes be very severe and disabling and run a chronic course, being that approximately 40-60% of the patients do not respond to treatment (Pallanti et al., 2002). Moreover, up to 10% of patients with OCD fail to respond to first-line pharmacological and psychotherapeutic treatments and then are considered to have a treatment-refractory OCD (Husted & Shapira, 2004). Criteria for a treatment-refractory OCD has been often defined in terms of a minimal or absent response to an adequate number of trials of selective serotonin reuptake inhibitors (SSRIs; minimum 3 types of SSRI at maximum dosage for at least 12 weeks), and behaviour therapy (minimum 20 hours; Gong et al., 2018). Treatment-refractory patients might be considered a specific OCD subtype (Csigó et al., 2010; O'Connor, 2005) in which more invasive therapies are frequently considered, such as deep brain stimulation or psychosurgery (Woon, Kanapathy, Zakaria, & Alfonso, 2017).

In the last decades an increasing interest in describing cognitive function has emerged in prevailing neuropsychological models of OCD. Three meta-analytic studies have resumed available data regarding neuropsychological correlates of OCD (Abramovitch, Abramowitz, & Mittelman, 2013; Shin, Lee, Kim, & Kwon, 2014; Snyder, Kaiser, Warren, & Heller, 2015). Despite some discrepancies, this large body of literature provides consistent results regarding the statistical size effects described across all cognitive domains. The results indicate a worse neuropsychological performance in OCD adult patients as compared to healthy individuals in different cognitive domains (Abramovitch et al., 2013; Abramovitch, Mittelman, Tankersley, Abramowitz, & Schweiger, 2015; Benzina, Mallet, Burguière, N'Diaye, & Pelissolo, 2016; Shin et al., 2014; Snyder et al., 2015). While there is general consensus identifying deficits in executive functions, verbal and non-verbal memory, attention, or visuo-spatial abilities, different studies have also addressed the presence of information processing speed (IPS) impairments in OCD patients (Abramovitch et al., 2013; Shin et al., 2014; Snyder et al., 2015). In addition, some studies have even suggested that deficits in processing speed could modulate poor performance in executive tasks whose scores are time mediated, that has been called the IPS hypothesis (Abramovitch, Anholt, Raveh-Gottfried, Hamo, & Abramowitz, 2017; Bédard, Joyal, Godbout, & Chantal, 2009; Burdick, Robinson, Malhotra, & Szesko, 2008; Snyder et al., 2015). For instance, while some scores from classical standardized neuropsychological tests of executive functions, like the Trail Making Test, directly reflect the time taken to execute the task, others, like Stroop or verbal fluency (FAS) scores, reflect performance during a specifically limited time frame. This situation makes it difficult to distinguish the extent to which poor performance would reflect a genuine cognitive deficit, a non-specific deficit in IPS, or a mixture of both. However, and despite its relevance, to what extent there is a modulator

effect of IPS in OCD patients' performance in neuropsychological tests of executive function has not been empirically evaluated yet (Snyder et al., 2015). Clarifying the potential modulatory effect of IPS would be relevant in treatment-refractory OCD patients for at least two reasons. First, the examination of the speed of IPS hypothesis in treatment-refractory OCD patients would improve the characterization of their cognitive deficits, and its comparability with the general OCD population. Ultimately, it would justify introducing specific IPS measures in cognitive assessment protocols. Second, it could help enhancing the efficacy of cognitive interventions being developed in OCD (see for instance van Passel et al., 2016), which is a central goal in a subgroup of patients whose response to conventional treatments is minimal or absent. In this regard, clarifying the modulatory effect of IPS deficits in treatment-refractory OCD cognitive functioning could help developing new pathways towards more targeted cognitive assessment and intervention for these patients.

In the general OCD population, the study of slowness of IPS has been traditionally approached in one of the following two ways. On the one hand, some authors have considered slowness as a derived condition of the clinical symptomatology. In fact, it has been suggested that the slower performance of OCD patients may constitute an epiphenomenon related to a meticulous concern for the correct execution of the test, or intrusion of obsessive thoughts which may influence the rate at which cognitive functions are carried out (Galderisi, Mucci, Catapano, D'Amato, & Maj, 1995; Roth, Baribeau, Milovan, & O'Connor, 2004; Veale, 1993). On the other hand, more recent works have suggested that patients with OCD exhibit cognitive slowness relatively independent from those clinical factors. Two main sources of evidence have recently supported this latter explanation. First, there are findings indicating that OCD patients

are more likely to exhibit slowness on tests of executive functions sub served by frontostriatal circuitry, rather than slowness resulting in a generalized deficit on time mediated tests (Galderisi et al., 1995; Roth et al., 2004). In a more recent work, neural responses from paediatric OCD patients and healthy controls were compared in response to a flanker task applied under two conditions, either emphasizing speed or accuracy (Riesel, Kathmann, & Klawohn, 2019). The results revealed that, compared to controls, patients exhibited deficits modulating the Error-related Negativity (ERN; an event-related brain potential associated to error monitoring) when speed was stressed only. Second, most studies have failed to find relations between clinical scales (i.e., Y-BOCS), and IPS indexes (Abramovitch, Dar, Schweiger, & Hermesh, 2011; Bédard et al., 2009; Bucci et al., 2007; Burdick et al., 2008). Importantly, a recent meta-analysis found that when the IPS component was controlled, only a small association with the obsessive symptoms severity was observed (Abramovitch, McCormack, Brunner, Johnson, & Wofford, 2019), thus questioning the symptom-based explanations of slowness in OCD. The study of treatment-refractory OCD has generally omitted the examination of the impact of slowness of IPS in cognitive performance (Gong et al., 2018; Zhang et al., 2017; Krámská, Urgošík, Liščák, Hrešková, & Skopová, 2021). To our knowledge, only one previous investigation has provided specific information about IPS deficits in this group of patients. In the study by Dinn, Aycicegi-Dinn, Göral, Darkal, Yildirim, & Hacioglu, (2016), slower performance in specific neuropsychological measures of processing speed (WAIS-IV) was observed in treatment-refractory OCD patients as compared to healthy controls, being performance in executive functions relatively preserved. Importantly for the aims of the present work, these preliminary evidences suggest that cognitive performance under timed

conditions may have a negative modulatory effect both in the general OCD population as well as in the treatment-refractory subgroup.

In the present study principal component analysis and mean comparisons on neuropsychological performance between patients with treatment-refractory OCD versus healthy participants were conducted (1) to explore the existence of an IPS factor in the test battery being used, and (2) to clarify the presence of differences in performance related to slowness, respectively. It was hypothesized that if the deficit in IPS modulates test performance in patients with treatment-refractory OCD, then differences between patients and controls would emerge in those scores loading in the IPS factor only. Second, we aimed to clarify whether the potential slowness measured in neuropsychological tests could be either an epiphenomenon associated to clinical symptoms (i.e., meticulousness or intrusions during test performance) or a primary deficit. Correlation analyses between clinical and neuropsychological measures were performed to solve this question. It was hypothesized that if slowness of IPS constitutes a primary deficit characterizing patients with treatment-refractory OCD, beyond clinical symptoms, then there will be no relationship between clinical and neuropsychological speed measures. Therefore this study aimed to explore the potential role of information processing speed deficit modulating some cognitive difficulties of patients with treatment-refractory OCD, and to examine its relation to clinical symptoms.

2. Methods

2.1. Participants

The study included 39 patients with treatment-refractory OCD who met the eligibility criteria among 41, as described below. Patients underwent a clinical interview to confirm the diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) OCD criteria (American Psychiatric Association, 2013), and were identified as refractory to all possible treatments stable at least 12 months. Both the diagnosis of OCD and the severity of the disorder were addressed by two independent psychiatrists. Patients received clinical attention at the department of neurosurgery of their reference hospital.

Inclusion criteria for the clinical group were as follows: (1) OCD diagnosis according to DSM-V, (2) candidates for neurosurgery OCD treatment, (3) a 5-year history of obsessive-compulsive symptoms causing substantial suffering and significantly overall reduced functioning (4) having undergone and failure of previous drug therapy or psychological therapy (both drug and psychological therapies) during at least 5 years previous to being considered surgery candidates, (5) an age between 18 and 65 years and (6) disease identified as treatment-refractory by two different psychiatrists. Patients with psychotic spectrum disorder, history of brain injuries, history of drug abuse, or dependence, or any serious concomitant general medical condition were excluded.

For comparison purposes, 39 healthy individuals were recruited from the general population. Each participant underwent a screening interview and provided a self-reported history of medical and psychiatric problems. Exclusion criteria were current or prior: history of psychiatric illness, neurological disease, head injury, stroke, substance abuse (excluding nicotine), learning disabilities, or any other difficulty that could

interfere with testing. All participants had normal or corrected-to-normal vision. The two groups were matched for sex, age, and education. Written informed consent was obtained from each participant after a complete description of the study. This investigation was implemented in compliance with institutional research standards for human research, and in accordance with the Declaration of Helsinki, and received the approval of the ethical committee of the institution.

2.2.Clinical assessment

Clinical participants were assessed with the Spanish version of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989; Vega-Dienstmaier et al., 2002). YBOCS Total score was used as a measure of severity of OCD symptoms. Anxiety symptoms were assessed using the Spanish version of the State-Trait Anxiety Inventory (STAI; Buela-Casal & Guillén-Riquelme, 2017; Spielberger, C.D., Gorsuch, R.L., y Lushene, R., 1982). The severity of depressive symptoms was assessed by means of the Spanish version of the Beck Depression Inventory (BDI-II; Beck, A.T., Steer, R.A., & Brown, G.K., 1996; Fernández, Navarro, & Valverde, 2003).

2.3.Neuropsychological assessment

An experienced neuropsychologist administered a comprehensive neuropsychological battery of tests in a unique session that took approximately 90 minutes to complete. The neuropsychological tests included in the protocol were as follows.

Digit Symbol (WAIS-IV; Wechsler, 2012)*:* The Digit Symbol subtest (DigSym) from the Spanish adaptation of the WAIS-IV (Wechsler, 2012) was used to assess speed of visual search. This score has shown the highest load in the processing speed factor as described in the WAIS-IV construct validity data (Wechsler, 2012). The number of items correctly encoded in two minutes was considered the variable for analyses.

Digit Span subtest (Wechsler Adult Intelligence Scale-IV, WAIS-IV; Wechsler, 2012)*:* This subtest was selected to measure working memory because it shows the highest load in the Working Memory factor as described in the WAIS-IV construct validity data (Wechsler, 2012). Span scores were recorded separately and included in the analyses as the dependent variables.

Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtis, 1993)*:* The test was used as a measure of cognitive control and mental flexibility (Strauss, Sherman, & Spreen, 2006). In this test, individuals were required to sort 128 cards into four reference cards according to one of three changing classification rules unknown to the participant. The percentage of perseverative (WCST % Pers) and non-perseverative errors (WCST % Npers) were considered as the dependent variables for analyses.

Verbal Fluency Test (Strauss, Sherman, & Spreen, 2006)*:* This test was used to assess semantic and phonemic fluency. In the semantic fluency task, subjects were asked to name as many animals as possible within 1 minute (Fluency Animals). On the other hand, in the phonemic fluency task subjects were asked to produce as many words as possible that begin with letters F (FAS-F) and A (FAS-A) within 1 minute for each letter, excluding proper names and derivate words (Strauss, E., Sherman, E., & Spreen, O., 2006). The number of words produced in each task was the dependent variables for analyses.

Stroop Colour-Word Test (Golden, 1978)*:* The Spanish adaptation of the Stroop test was used. The number of correct responses in 45 seconds in the word-reading (SWR), colour-naming (SCN), colour-word (SCW) conditions were considered for analyses, together with a ratio score (Stroop Ratio = SCW divided by SCN). These scores have been previously associated to speed of visual search, working memory, and conflict monitoring to different extents (Periáñez, Lubrini, García-Gutiérrez, & Ríos-Lago, 2021).

Trail Making Test (TMT; Strauss, Sherman, & Spreen, 2006)*:* The time to complete each part of the test (TMT-A and TMT-B) was used to measure speed of visual search, and working memory/cognitive flexibility, respectively. The difference score (TMT B-A) was also calculated as a more specific measure of cognitive flexibility/task-switching abilities (Sánchez-Cubillo et al., 2009).

2.4.Statistical analyses

Kolmogrov-Smirnov test was used to assess normality in the distribution of the variables as a prerequisite for comparison, principal component analysis (PCA), and correlation analyses. PCA on the total sample of 78 individuals was performed to explore the plausibility of an IPS factor subtending the neuropsychological test battery being used. A Varimax rotation method was used, being 0.4 the selected criterion for a meaningful loading. Group comparisons between patients and healthy individuals were performed through Student's *t*-test or Mann-Whitney *U*-test, where appropriated. The association between neuropsychological and clinical measures was explored by means of Pearson correlations or Spearman's rho, were appropriated. A Benjamini-Hochberg procedure was used to control for multiple comparisons, with a false discovery rate set

at $\alpha = 0.05$, across the analyses. This procedure is less restrictive but more sensitive than Family Wise Error corrections (i.e., Bonferroni). Thus, it is appropriate for an exploratory study since it increases statistical power while controlling for type I error. Lastly, the potential confounding effect of the type of pharmacological treatments in the group of patients (i.e., Antidepressant, or Antidepressant + Anxiolytics, or Antidepressant + Antipsychotics, or Antidepressant + Anxiolytics + Antipsychotics) on neuropsychological performance was explored by means of both non-parametric group comparisons (Kruskal-Wallis), and simple linear regression analyses (using type of pharmacological treatment as the predictor variable, and each neuropsychological score as the criteria). All data were analysed using SPSS software (SPSS 20 for Windows, IBM Corp.). Effect sizes (Cohens's d) were calculated for mean comparisons with G*Power software (Faul, Erdfelder, Buchner, & Lang, 2009).

3. Results

Demographic characteristics

Sociodemographic and clinical features of the two groups of participants are displayed in Table 1. There were missing data in both clinical and neuropsychological measures in four patients and in neuropsychological measures of seven healthy individuals. Between-group comparisons revealed an absence of differences in age, gender, or education between treatment-refractory OCD patients and healthy controls (ps> 0.1). Non-parametric comparisons (Kruskal-Wallis) between subgroups of patients according to the type of pharmacological treatment revealed non-significant group effects in any of the 15 cognitive scores being analysed (p> 0.053 in all cases). Simple linear regression analyses using the type of pharmacological treatment as the predictor

variable of each neuropsychological score, revealed a lack of associations between them ($p > 0.062$ in all cases)

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Please, insert Table 1 about here

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Principal component analysis

Individuals with missing scores were discarded from the analysis. A three components structure including the 15 neuropsychological test scores accounted for 65.5% of the variance of data (see Table 2). Particularly, the first factor (33.1% of the variance) included all the scores influenced by time (i.e., Digit Symbol, FAS-F, FAS-A, Fluency Animals, SWR, SCN, SCW, TMT-A, TMT-B, and TMT B-A). The second factor (20.7% of the variance) included Digit Span Forward and Backward, WCST % of perseverative and non-perseverative errors, FAS-A, Fluency Animals, SWR, and SCN. The third factor (11.8% of the variance) included SCW, and Stroop Ratio scores.

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Please, insert Table 2 about here

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Neuropsychological measures

Significant differences between treatment-refractory OCD patients and controls were found in all neuropsychological measures loading in the Speed of Processing Component (i.e., DigSym, FAS-F, FAS Animals, SCN, SCW, TMT A, TMT B, TMT B-A), being SWR marginally significant, and FAS-A non-significant. No between-

group differences were found in the scores loading in the second component (i.e, DigFor, DigBack, WCST % Pers, WCST % NPers) except for those showing a simultaneous meaningful loading in the Speed of Processing component (i.e., FAS-F, FAS Animals, SCW, and SCN). No between-group differences were found in the scores loading in the third component (i.e., Stroop Ratio) except for those showing a simultaneous meaningful loading in the Speed of Processing component (i.e., SCW; See Table 3).

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Please, insert Table 3 about here

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Correlation between neuropsychological performance and clinical symptoms

Individuals with missing scores were discarded from the correlations involving those scores. Results from the exploratory correlation analyses between clinical and neuropsychological variables are displayed in Table 4. No significant correlations between clinical and neuropsychological scores were found.

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Please, insert Table 4 about here

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4. Discussion

The main aim of the present study was to provide a comprehensive description of cognitive performance in treatment-refractory OCD patients, exploring the potential role of IPS deficits underlying patients´ neuropsychological difficulties. In addition, the

association between patients' cognitive performance and their clinical symptoms was explored to clarify the extent to which speed deficits may represent a primary deficit in cognitive processing, or a deficit secondary to clinical symptoms.

Following our first aim, results from the PCA applied to the neuropsychological battery being used revealed a three components latent structure. The first one included all neuropsychological scores influenced by time (DigSym, FAS-F, FAS-A, Fluency Animals, SWR, SCN, SCW, TMT-A, TMT-B, and TMT B-A) and was named *Speed of Processing*. Scores exhibiting a meaningful loading in the second component were, by order of relevance, Digit Span (Backwards, and Forwards), WSCT (% of Perseverative, and % of Non-Perseverative errors), Verbal Fluency (FAS-A, and Fluency An), and two Stroop scores (SWR, and SCN). The most feasible cognitive construct accounting for a portion of the variance of all these scores was *Working Memory*. In this regard, Digit Span scores have shown the highest load in the working memory factor as described in the WAIS-IV construct validity data (Wechsler, 2012). The implication of working memory in Verbal Fluency, Stroop test, and TMT scores has been corroborated in different validation studies (Periáñez et al., 2021, Aita, et al., 2019, and Sánchez-Cubillo et al., 2009, respectively). Also, the role of Working Memory mediating WCST performance has been described in detail in both neuropsychological and neurophysiological studies (Lange, Kröger, Steinke, Seer, Dengler, & Kopp, 2016; Barceló, Periáñez, & Knight, 2002). The third component was named *Conflict Monitoring* as it was the cognitive construct shared by the two scores loading on it (SCW and Stroop Ratio), as suggested in a recent validation study (Periáñez et al., 2021).

Supporting our first hypothesis, the comparison of neuropsychological scores between treatment-refractory OCD patients and healthy individuals revealed differences in performance that emerged in all the scores loading in the *Speed of processing* component of the PCA, except for FAS-A (with SWR being marginally significant after correction for multiple comparisons; See Table 3). It is important to notice that, even when executive functions have been assumed as a key cognitive domain altered in the OCD general population (Snyder et al., 2015), our results from treatment-refractory OCD individuals revealed a lack of differences in those scores from classical neuropsychological tests of executive function not influenced by time. These results are in agreement with existing evidences showing specific IPS deficits in treatment-refractory OCD patients (Dinn, et al., 2016), and also suggest that such speed deficits would be common to both treatment-refractory, and general OCD groups (Bédard et al., 2009; Burdick et al., 2008; Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; Riesel, Kathmann, & Klawohn, 2019). In the present study, time seemed to be a key factor in patients' performance either when performance was directly limited to a specific time frame by instructions (i.e., Digit Symbol, Fluency tasks, and Stroop tests), or when time was assessed as an outcome (i.e., TMT). Taken together, these results respond to the claim of a lack of an empirical validation of the hypothesis about the modulator effect of IPS (Snyder et al., 2015), and bring support to the idea that cognitive slowness may be a core factor underlying some of the treatment-refractory OCD patients' neuropsychological deficits.

The second aim of this study was to explore the association between patients' neuropsychological performance and clinical symptoms. The results revealed a lack of association between clinical and neuropsychological scores, not in the speed-modulated

variables, nor in the remaining neuropsychological scores (see Table 4). It has to be noticed that three recent meta-analyses (Abramovitch et al., 2013; Shin et al., 2014; Snyder et al., 2015) have identified an overall lack of correlation or any moderator effect in the association between cognitive dysfunction and symptoms severity in OCD general population. Consequently, and in agreement with preceding investigations, the current results support the idea of a primary speed deficit in patients with treatment-refractory OCD independently of the severity of obsessive intrusions, or the excessive concern about the accuracy of the answers (Bucci et al., 2007). In the past, understanding the nature of slowness of IPS has involved the identification of deficits in more specific speed components accounting for the observed slow neuropsychological performance. Previous studies using a comprehensive set of reaction time tasks have suggested that the perceptual, cognitive, and motor components can be selectively slowed down in Multiple Sclerosis (Lubrini et al., 2020) or Parkinson disease (Arroyo et al., 2021). As mentioned above, deepen understanding of processing speed deficits in treatment-refractory OCD patients would be relevant at different levels. It will help improving the characterization of their cognitive deficits as compared to the general OCD population. It will ultimately help clarifying the importance of introducing specific IPS measures in assessment protocols. It could also help enhancing the efficacy of cognitive interventions being developed in OCD (van Passel et al., 2016) by introducing IPS as a specific outcome. Also, providing training to improve IPS would complementarily reduce patients' subjective complaints of psychomotor slowness.

Some final considerations should be taken into account regarding the present results. First, the present sample included treatment-refractory OCD patients that were candidates for neurosurgery. Given the potential clinical differences between treatment-

refractory OCD candidates and non-candidates for neurosurgery, caution should be taken generalizing the present results to patients differing in demographic or clinical features regarding the present sample. Second, we cannot exclude the possibility that medication may have contributed to IPS deficits. Clarifying the potential impact of medication on neuropsychological performance exceeds the goals of the present study since it would involve, for instance, between-group comparisons between medicated and non-medicated patients, or within-group comparisons between pre- and post-pharmacological treatment stages. However, analyses were performed to examine the potential confounding effect of the different types of pharmacological treatments on patients' neuropsychological performance. The results of both group comparisons and regressions allowed concludeing that differences in the type of pharmacological treatment should not be considered a confounding factor in the present study. These results are in agreement with evidences suggesting that treatment with SSRIs or atypical antipsychotics, which are frequently prescribed in OCD population, may have no impact on cognitive performance or IPS tasks (de Geus, Denys, & Westenberg, 2007; Keefe et al., 2004). However, and even when the effect of pharmacological treatments seems to be limited in our study, additional evidences are needed to support the lack of impact of medication on IPS within the treatment-refractory OCD subgroup.

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Table 1. Demographic and clinical characteristics of participants.

	N	OCD Patients Mean (SD)	N	Healthy Controls Mean (SD)	Test	p
N (male)	39	39 (27)	39	39 (20)	$\chi 2$	n.s.
Age (years)	39	37.9 (13.6)	39	35.9 (10.9)	*t*	n.s.
Education (years)	39	12.8 (3.5)	39	13.6 (3.1)	*t*	n.s.
Age first diagnosis (years)	38	22.4 (9)	-	-	-	-
Duration of illness (years)	38	15.4 (9.2)	-	-	-	-
STAI state	37	31.1 (12,9)	-	-	-	-
STAI trait	37	42.3 (11.5)	-	-	-	-
Y-BOCSo	36	17.0 (2.6)	-	-	-	-
Y-BOCSc	37	11.8 (6.7)	-	-	-	-
Y-BOCSt	36	28.8 (7.9)	-	-	-	-
BDI-II	38	26.1 (11.7)	-	-	-	-
	N (%)		N (%)			
Working situation						
Employed	10 (26.3)		32 (82.1)			
On sick leave	6 (15.8)		2 (5.1)			
Unemployed	16 (42.1)		5 (12.8)			
Retired	6 (15.8)		0 (0)			
Familial situation						
Single	19 (54.3)		17 (43.6)			
Married	13 (37.1)		20 (51.3)			
Divorced	3 (8.6)		2 (5.1)			
Family history of OCD	7 (18.9)		-			
Comorbidity						
Affective disorder	8 (20.5)		-			
Anxiety	3 (7.7)		-			
Neurodevelopmental disorder	3 (7.7)		-			
Personality disorder	4 (10.3)		-			
Therapy						
Pharmacological	39 (100)		-			
Behavioural	39 (100)		-			
Electroconvulsive	4 (10.3)		-			
Pharmacological treatment						
ADep	5 (13.5)		-			
ADep + Anx	15 (40.5)		-			
ADep + APsych	8 (21.6)		-			
ADep + Anx + APsych	9 (24.3)		-			

Note: STAI: State-Trait Anxiety Inventory; Y-BOCSo: Obsessions in the Yale-Brown Obsessive-Compulsive Scale; Y-BOCSc: Compulsions in the Yale-Brown Obsessive-Compulsive Scale; Y-BOCSt: Total score in the Yale-Brown Obsessive-Compulsive Scale; BDI-II: Beck Depression Inventory; ADep: Antidepressant; Anx: Anxiolytics; APsych: Antipsychotics

Table 2. Loading of neuropsychological scores from principal component analysis.

	Components		
	1	2	3
DigSym	.772	.120	.225
DFor	-.066	.752	.305
DBack	-.030	.812	.147
WCST % Pers	-.315	-.680	.092
WCST % NPers	-.181	-.625	-.026
FAS-F	.679	.012	-.100
FAS-A	.604	.521	-.214
Fluency An	.679	.432	.051
SWR	.590	.439	.273
SCN	.589	.434	.194
SCW	.528	.343	.713
Stroop Ratio	.158	.055	.841
TMT A	-.768	-.017	-.158
TMT B	-.861	-.089	-.290
TMT B-A	-.783	-.125	-.303

Note: DigSym: Digit-Symbol coding test; DFor: Digit Span Forward; DBack: Digit Span Backward; WCST % Pers: WCST Percentage of Perseverative Errors; WCST % NPers: WCST Percentage of Non-Perseverative Errors; FAS-F: Phonemic Verbal Fluency test letter F; FAS-A: phonemic verbal fluency test letter A; Fluency An: Semantic Verbal Fluency test category Animals; SWR: Stroop Word Reading; SCN: Stroop Colour Naming; SCW: Stroop Colour Word; Stroop Ratio: SCW divided by SCN; TMT A: Trail Making Test A; TMT B: Trail Making Test B; TMT B-A: TMT B minus TMT A.

Table 3. Means, standard deviations, significances, and effects size for OCD patient versus healthy control comparisons.

Variable	OCD Patients		Healthy Controls		Test	*p*	Effect Size (Cohen's d)
	N	Mean (SD)	N	Mean (SD)			
DigSym	39	54.9 (21.1)	39	82.4 (16.4)	*t*	0.001*	1.45
DFor	39	6 (1.3)	39	5.7 (1.4)	*U*	0.36	0.23
DBack	39	4.7 (1.4)	39	4.1 (1.6)	*U*	0.12	0.38
WCST % Pers	36	12.1 (7.5)	39	10.3 (5.8)	*U*	0.31	0.27
WCST % NPers	36	9.6 (5.0)	39	9.4 (7.3)	*t*	0.37	0.03
FAS-F	39	11.3 (4.5)	32	13.8 (3.9)	*t*	0.02*	0.58
FAS-A	39	11.8 (5.0)	32	12.7 (3.6)	*t*	0.37	0.22
Fluency An	39	19.5 (6.7)	32	23.7 (5.2)	*t*	0.001*	0.69
SWR	38	107.1 (16.4)	39	115.3 (16.6)	*t*	0.03	0.5
SCN	38	68.2 (15.9)	39	76.5 (11.8)	*t*	0.01*	0.6
SCW	38	40.6 (12.4)	39	48.6 (11.9)	*t*	0.01*	0.65
Stroop Ratio	38	0.6 (0.14)	39	0.63 (0.11)	*t*	0.21	0.24
TMT A	38	51.5 (30.0)	39	28.1 (10.2)	*U*	0.001*	1.04
TMT B	36	118.1 (71.0)	39	62.6 (31.2)	*U*	0.001*	1.01
TMT B-A	36	71.7 (54.7)	39	34.5 (25.2)	*U*	0.001*	0.87

Note: *: Significance level corrected for multiple comparisons set at p< 0.03; DigSym: Digit-Symbol coding test; DFor: Digit Span Forward; DBack: Digit Span Backward; WCST % Pers: WCST Percentage of Perseverative Errors; WCST % Non-Perseverative: WCST Percentage of Non-Perseverative Errors; FAS-A: Phonemic Verbal Fluency letter A; FAS-F: Phonemic Verbal Fluency test letter F; Fluency An: Semantic Verbal Fluency test category animals; SWR: Stroop Word Reading; SCN: Stroop Colour Naming; SCW: Stroop Colour Word; Stroop Ratio: SCW divided by SCN; TMT A: Trail Making Test A; TMT B: Trail Making Test B; TMT B-A: TMT B minus TMT A.

Table 4. Correlation matrix between clinical and neuropsychological measures in OCD patients.

	STAI state	STAI trait	Y-BOCSo	Y-BOCSc	Y-BOCSt	BDI-II
DigSym	-.13	-.12	.07ŧ	-.12ŧ	-.05	-.13
DFor	-.2ŧ	-.15ŧ	.07ŧ	-.01ŧ	.03ŧ	-.18ŧ
DBack	-.29ŧ	-.27ŧ	-.22ŧ	.07ŧ	.05ŧ	-.16ŧ
WCST % Pers	.2ŧ	.14ŧ	-.01ŧ	.02ŧ	.02ŧ	.24ŧ
WCST % NPers	.26	.01	-.06ŧ	-.24ŧ	-.27	.08
FAS-F	.05	.01	.04ŧ	.07ŧ	.09	.01
FAS-A	.06	.07	-.00ŧ	-.14ŧ	-.08	-.02
Fluency An	-.01	.06	.1ŧ	-.00ŧ	.02	-.02
SWR	.24	.15	.08ŧ	-.25ŧ	-.15	.12
SCN	.11	-.08	.07ŧ	-.2ŧ	-.01	.08
SCW	.05	-.06	.01ŧ	-.12ŧ	-.05	-.04
Stroop Ratio	-.03	.03	.00ŧ	.02ŧ	.09	-.12
TMT A	.11ŧ	-.04ŧ	-.1ŧ	-.03ŧ	-.09ŧ	.03ŧ
TMT B	.1ŧ	-.2ŧ	-.16ŧ	.17ŧ	.1ŧ	.23ŧ
TMT B-A	.24ŧ	.34ŧ	.19ŧ	.14ŧ	.09ŧ	.39ŧ

Note: The significance level corrected for multiple comparisons was set at $p < 0.0006$, and revealed no significant correlations. ŧ: Spearman rho correlation; STAI: State-Trait Anxiety Inventory; Y-BOCSo: Obsessions in the Yale-Brown Obsessive-Compulsive Scale; Y-BOCSc: Compulsions in the Yale-Brown Obsessive-Compulsive Scale; Y-BOCSt: Total score in the Yale-Brown Obsessive-Compulsive Scale; BDI-II, Beck Depression Inventory; Digit-Symbol coding test; DFor: Digit Span Forward; DBack: Digit Span Backward; WCST % Pers: WCST Percentage of Perseverative Errors; WCST % NPers: WCST Percentage of Non-Perseverative Errors; FAS-A: Phonemic Verbal Fluency letter A; FAS-F: Phonemic Verbal Fluency test letter F; Fluency An: Semantic Verbal Fluency test category animals; SWR: Stroop Word Reading; SCN: Stroop Colour Naming; SCW: Stroop Colour Word; Stroop Ratio: SCW divided by SCN; TMT A: Trail Making Test A; TMT B: Trail Making Test B; TMT B-A: TMT B minus TMT A.

Conflict of Interest

None declared.

Author statement

Conceptualization: MRL, GL and JAP; Methodology: MRL, GL, and JAP; Formal analyses: VSM, and JAP; Investigation; MRL CVTD, and NMM; Resources: RMA, JAL, CVTD, and NMM; Data curation: VSM and GLZ; Writing-Original draft; VSM and GLZ; Writing-Review and Editing: JAP, MRL, and GL; Visualization: MRL and VSM; Supervision: MRL, GL, and JAP; Funding: RMA, JAL.