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Neuropsychological investigations in obsessive–compulsive disorder: A systematic review of methodological challenges

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ABSTRACT

The inconsistent nature of the neuropsychology literature pertaining to obsessive–compulsive disorder (OCD) has long been recognized. However, individual studies, systematic reviews, and recent meta-analytic reviews were unsuccessful in establishing a consensus regarding a disorder-specific neuropsychological profile. In an attempt to identify methodological factors that may contribute to the inconsistency that is characteristic of this body of research, a systematic review of methodological factors in studies comparing OCD patients and non-psychiatric controls on neuropsychological tests was conducted. This review covered 115 studies that included nearly 3500 patients. Results revealed a range of methodological weaknesses. Some of these weaknesses have been previously noted in the broader neuropsychological literature, while some are more specific to psychiatric disorders, and to OCD. These methodological shortcomings have the potential to hinder the identification of a specific neuropsychological profile associated with OCD as well as to obscure the association between neurocognitive dysfunctions and contemporary neurobiological models. Rectifying these weaknesses may facilitate replicability, and promote our ability to extract cogent, meaningful, and more unified inferences regarding the neuropsychology of OCD. To that end, we present a set of methodological recommendations to facilitate future neuropsychology research in psychiatric disorders in general, and in OCD in particular.

1. Introduction

Obsessive–compulsive disorder (OCD) is a prevalent and often debilitating psychiatric disorder, affecting approximately 2.5% of the population worldwide (Okasha, 2003; Ruscio et al., 2010). The hallmark symptoms of OCD are obsessive thoughts or images that cause significant distress, and/or repetitive compulsive behavioral or mental rituals that the patient performs in order to alleviate distress or to avoid feared events (American Psychiatric Association, 2013). Since the early 1990s, a progressively large body of imaging research has revealed frontostriatal pathophysiology in OCD, with a pronounced hyperactivation in the orbitofrontal cortex, anterior cingulate cortex, and caudate nucleus (Chamberlain et al., 2008; Melloni et al., 2012). These findings received support from studies reporting abnormally increased resting state functional connectivity along the cortico-striato-thalamo-cortical (CSTC) circuits (Harrison et al., 2009; Fitzgerald et al., 2011). As a whole, a positive association between increased activation and OCD symptom severity has been identified at rest (Harrison et al., 2013), during symptom provocation (Breiter et al., 1996; Nakao et al., 2005), and post-treatment (e.g., Schwartz et al., 1996; Saxena et al., 2009). Aberrant brain activity has been further associated with task performance in OCD (e.g., Roth et al., 2007). However, results from these investigations are divergent, with some studies reporting reduced (van den Heuvel et al., 2005), and others increased (Maltby et al., 2005) activation during performance on neuropsychological tasks. Nevertheless, these findings have consistently supported the prevailing CSTC/frontostriatal model of OCD (Saxena and Rauch, 2000; Pauls et al., 2014).

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The growing interest in the neuronal substrates of OCD paralleled an interest in the neuropsychology of OCD, resulting in a large body of literature. However, compared to the robust and consistent nature of results seen in resting state imaging studies, neuropsychological research in OCD has yielded divergent results (Kuelz et al., 2004). The state of the field drove our group to conduct the first systematic meta-analytic review of the entire body of neuropsychological literature in adult OCD (Abramovitch et al., 2013). The result of this meta-analysis, spanning nearly a quarter century of research, revealed an average Cohen's *d* effect size of 0.5 across 10 neuropsychological subdomains. The Random effects model that was employed revealed statistically significant heterogeneity across most subdomains. A subsequent moderator analysis revealed no significant moderators. This has been supported by a second meta-analysis of 88 studies that found only two moderators associated with performance on specific outcome measures from particular tests (Shin et al., 2014). Thus, the persistent inconsistency and between studies heterogeneity remained unexplained and may have been, at least in part, affected by methodological factors.

As a part of the systematic review of the neuropsychological literature of OCD, we recorded methodological factors. Given the scope of the review, the aim of the present investigation is to inform researchers about methodological caveats in order to facilitate replicability and future meta-analytic investigations. For this purpose, we sought to examine methodological factors across three domains: (1) general (e.g., alpha correction for multiple comparisons); (2) clinical (e.g., assessing clinical correlates of neuropsychological test performance); and (3) neuropsychological (e.g., administration of neuropsychological tests that were not validated in non-English speaking populations). We aimed to explore a wide variety of factors ranging from omission of essential information pertaining to a study's methods (e.g., age of OCD onset) – which has a relatively low potential to adversely impact the field – to factors that pose a substantial risk to biasing results (e.g., not performing multiplicity corrections). Notably, some of these factors were addressed in a critical review published a decade ago (Kuelz et al., 2004). However, the number of peer-reviewed papers assessing neuropsychological correlates of OCD has more than doubled in the last decade, justifying a systematic methodological review of the literature.

Some of the aforementioned factors hold specific importance in OCD research, and are grounded in evidence supporting their potential impact on neuropsychological test performance in this population. Other factors are not disorder-specific. Thus, this review may be relevant to researchers conducting neuropsychological investigations of psychiatric disorders in general. Nevertheless, given that these factors were systematically recorded from the body of neuropsychological literature in OCD, this comprehensive review depicts the state of the field of neuropsychological research in OCD in terms of methodological challenges. For each section pertaining to a particular challenge, we provide specific recommendations that may be useful for researchers, reviewers, and editors in this field.

2. Methods

2.1. Systematic literature search and selection criteria

A systematic literature search was conducted via MEDLINE, ISI Web of Knowledge, and PsycINFO databases, as well as by searching publication reference lists and soliciting unpublished data from investigators of the neuropsychology of OCD. Due to the small body of neuropsychological research in pediatric OCD (for a review and meta analysis see Abramovitch et al., 2012b; Abramovitch et al., In-press), this review focuses on adult studies. A total of 207 published research articles were identified through February 2012. Once identified, all studies were evaluated against several inclusion criteria. Studies were included if they: (a) included an adult sample of DSM-diagnosed OCD patients using a structured or semi-structured interview; (b) screened for the presence of psychiatric or neurological conditions; and (c) compared OCD group performance to that of a healthy control group on at least one known and validated standardized neuropsychological test. When a before/after design was employed, studies were included only when a pre-treatment comparison between an OCD and a healthy control group was available. Of the initial 207 studies, 177 studies met these criteria. Of those, 42 studies were excluded due to the use of either highly specific or non-standard neuropsychological tests (e.g., emotional Stroop), the use of tests that were significantly modified from the original version, or the use of tests that are very rarely used (i.e., used in $<1\%$ of studies). Seven excluded studies were duplicates (i.e., they contained information that appeared in studies already included in the meta-analysis). Finally, 13 studies were excluded because they did not provide sufficient information to calculate or estimate effect size. This screening process resulted in a final count of 115 studies published between 1989 and 2012. In terms of geography, the largest number of studies (23) was conducted in the United States, followed by Germany (18), South Korea (13), Spain (8), and the United Kingdom (8).

2.2. Variables recorded

A meta-analytic investigation of differences between OCD and non-psychiatric control samples on neuropsychological tests has been published elsewhere (Abramovitch et al., 2013). The present systematic review focuses on methodological issues. Accordingly, the following general information was recorded from each of the 115 studies: (a) year of publication, (b) publication status, (c) country, (d) number of neuropsychological tests, and (e) percent males in the OCD group. In addition, the following methodological information was recorded: (a) length of testing session, (b) number of sessions (for studies administering 4 or more tests[1]), (c) sample recruitment source for the OCD and control groups, (d) age of onset, and (e) education level. We also noted whether the study: (a) statistically corrected for multiple comparisons (for studies administering 4 or more tests; type of correction was noted); (b) used tests validated in the study's language; (c) controlled for depressive severity; and (d) examined the association between test performance, OCD severity, and depressive severity. The rationale underlying the selection of these factors stemmed from direct evidence reported in the OCD literature wherein these factors had been shown to have an impact on neuropsychological performance in OCD, or on statistical results and their interpretation (e.g., correction for multiple comparison).

3. Results

Fig. 1 depicts the number of studies published by year, demonstrating a steady increase in the number of studies published each year (range 1–17). Descriptive statistics of the methodological factors reviewed are presented in Table 1. With regards to sample characteristics, nearly one in every 10 studies did not report how recruitment for the OCD group was established, and 30% of studies for healthy control samples. Perhaps more importantly, only three quarters of studies reported the education level of their participants—a factor with a known impact on neuropsychological test performance. With regards to statistical corrections, among the studies administering 4 or more neuropsychological tests, only 18% employed some form of alpha correction for multiple comparisons.

In terms of methodological factors pertaining more specifically to neuropsychology research, only 62% of studies reported the number of testing sessions and only 24% reported the average length of the testing sessions. Notably, of the studies employing at least one neuropsychological test requiring understanding of written or spoken English, more than half of those conducted in non-English speaking countries did not report the use of tests validated in the respective country's native language.

Factors that may be more OCD-specific are also presented in Table 1. Among the most prominent findings were that only 54% of

[1] The choice of four tests as a cutoff number for which multiplicity corrections are required is somewhat arbitrary, given that there are no available guidelines or rule of thumb, and since in theory even two tests require adjustment of alpha. In an effort to be more conservative, we chose four. Notably, in most cases each test produces multiple outcome measures and thus 4 tests represent at least 4 comparisons.

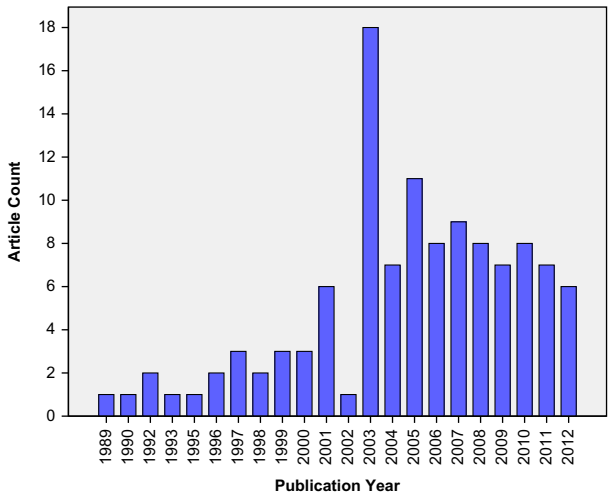

Fig. 1. Number of articles by publication year among 115 included studies.

Table 1
Descriptive statistics of 115 studies reviewed.

Methodological factors	Studies % (*n*)[a]
General	
Reported OCD sample recruitment methodology	88% (101/115)
Reported HC sample recruitment methodology	70% (81/115)
Reported education level	76% (87/115)
Employed statistical correction for multiplicity[b]	18% (12/66)
Neuropsychological	
Reported number of testing sessions[b]	62% (41/66)
Reported length of testing session	24% (28/115)
Reported use of tests validated in different languages[c]	49% (22/45)
OCD-specific	
Reported age of OCD onset	54% (62/115)
Reported % medicated patients	91% (105/115)
Provided detailed medication status[d]	90% (94/105)
Screened for hoarding	27% (31/115)
Screened, but included hoarders	39% (12/31)
Assessed depressive severity	74% (85/115)
Assessed OCD severity	92% (106/115)
Assessed correlation with test performance	53% (56/106)

[a] Numbers in parentheses expresses the number of studies as a fraction of applicable studies.
[b] For studies using 4 or more tests.
[c] For studies conducted in non-English speaking countries that administered at least one test requiring language comprehension.
[d] Detailed medication status was defined as "provided breakdown of types of medications."; OCD=obsessive–compulsive disorder; HC=healthy controls.

studies reported age of OCD onset, and only 27% did screen for hoarding. Importantly, 47% of studies did not attempt to assess the association between test performance and OCD symptoms. Finally, 1 in every 10 studies did not report patients' medication status. Out of those studies that did report medication status, 10% did not provide a breakdown of the types of medication.

4. Discussion

The aim of the present investigation was to systematically review the adult OCD neuropsychological literature in order to identify methodological oversights that may partially account for the inconsistency seen in this field. The results of the present study reveal several methodological shortcomings which may limit our ability to extract cogent inferences regarding an OCD-specific neuropsychological profile.

4.1. General factors

4.1.1. Multiplicity adjustment

At a given significance threshold, the probability of erroneously rejecting a null hypotheses (e.g., identifying group differences when in fact no true difference exists) increases as more hypotheses are tested and more statistical comparisons are conducted. For example, at an alpha level of 0.05, 20 comparisons are expected to yield at least one false discovery of a group's difference. Our review reveal that on average, studies administer 5.2 tests, where most tests yield multiple outcome measures. The literature reviewed in this investigation demonstrated a pervasive failure to correct for family-wise inflation of type I error, resulting from multiple comparisons. Prevalent in an overwhelming 82% of the qualified reviewed studies (studies employing 4 or more neuropsychological tests), this lack of correction poses a well-known concern. In fact, neglecting to correct for multiple comparisons has been identified as a major cause for concern in neuropsychology research in general (Millis, 2003; Schatz et al., 2005), and was specifically noted in a critical review of neuropsychological research in OCD, published a decade ago (Kuelz et al., 2004). However, the vast majority of later studies persisted with the failure to correct for multiple comparisons. In fact, our review indicates only a small non-significant difference between the percent of studies adjusting for multiplicity prior to 2004 (90.9%) and after (82.9%; $p=0.34$). Failure to perform such a correction is particularly problematic when the sample size is small, dependent variables are numerous, and the power is low—as is the case in the majority of the studies reviewed. Moreover, the prevalent phenomenon in which several neuropsychological measures are intercorrelated serves to further amplify the problem of increased probability of type I error. Thus, fortuitous significant results can readily produce inaccurate inferences regarding differences between clinical populations and controls. Notably, in some of the papers reviewed, post-hoc comparisons were confused with correction for multiple comparisons.

Several methods for multiplicity adjustment are available (for a review see Bender and Lange, 2001), with the most common being the Bonferroni correction, which divides the alpha (commonly 0.05) by the number of comparisons within a family of tests (Bland and Altman, 1995). Given the typical large number of comparisons employed in neuropsychological research in OCD, dividing the alpha by the total number of tests is not recommended as this would result in a significant reduction in power (increasing type II errors). We recommend that researchers carefully define clusters of tests or outcome measures and employ the Bonferroni correction separately for each such cluster. Alternatively, we recommend the use of the Holm procedure (Holm, 1979) which is less costly in terms of power and is equally simple to calculate compared to the traditional Bonferroni correction. Notably, half of the studies that adjusted for multiplicity employed the Bonferroni correction, and half of the studies used an overall conservative significant threshold of 0.01 across all comparisons. The latter method is less favorable, and we recommend employing a more theory-driven and statistically sound method that balances the trade-off between type I and type II errors. In fact, rigorous planning of neuropsychological research in OCD is warranted due to the tension between the need to control for potential confounding factors (as detailed in the sections below), and the need to correct for multiplicity due to the high number of comparisons.

It should be noted that the issue of multiplicity adjustment is constantly debated, with some researchers arguing against employment of any type of correction (Rothman, 1990; O'Keefe, 2003). The main argument underlying the objection to adjust for multiplicity is the simultaneous increase of type II error (not identifying a true difference/phenomena), and the overreliance

on null hypothesis testing and less so upon effect sizes. However, as a rule of thumb, studies of more exploratory nature may consider avoiding multiplicity adjustment to facilitate novel discoveries, while studies of confirmatory nature are encouraged to employ corrections. Thus, the study rationale and specific hypotheses serve as important factors in determining whether to implement adjustment for multiplicity (O'Brien, 1983), and the specific design of the study should help researchers to determine which is the appropriate technique (Bender and Lange, 2001). The vast majority of studies reviewed herein were confirmatory, further stressing the need to employ such corrections.

4.1.2. Recruitment

As Table 1 illustrates, many studies did not report recruitment methods for patient and/or control samples. This hinders replicability as well as the reader's ability to make cogent inferences and critical judgments of these studies. Information regarding the sources from which samples were recruited is of importance, especially in light of the phenomenon of selection bias, wherein individuals with multiple diagnoses are frequently more functionally impaired, and subsequently more likely to seek treatment (Galbaud du Fort et al., 1993). This phenomenon results in significant overrepresentation of patients with more complex—and usually more severe—clinical presentations when recruited from specialized clinics, in contrast to community or representative samples (McConaughy and Achenbach, 1994). Thus, we encourage researchers to inform readers as to the recruitment source and procedure for both clinical and control samples, regardless of whether the samples were recruited via convenience sampling or via specialty clinics. For example, among the studies reviewed, some authors reported that their clinical samples were recruited from different sources, including community advertising, private clinics, and specialty clinics. It should be noted that the characteristics of individuals seeking treatment might vary amongst these recruitment pools; nonetheless, rarely did studies provide a detailed breakdown of the sample in terms of recruitment, or attempt to assess potential differences among the subsamples.

4.2. Clinical factors

4.2.1. Clinical correlates

Regardless of each study's specific aim, the ultimate purpose of conducting a neuropsychological investigation into a specific psychiatric condition is to attempt to find disorder-specific neurocognitive markers associated with particular psychopathological mechanisms. Thus, one might expect these studies to examine the association between OCD symptom severity and neuropsychological test performance. However, of the studies that did assess OCD severity (106/115; 92%), 47% did not attempt to assess this association. Moreover, of the studies that did assess the association between OCD severity and neuropsychological indices, only a minority of studies found such an association. Nevertheless, the remarkably high percentage of studies not assessing this association may hinder our ability to conclude whether such an association truly exists, and further impede identification of factors that might mediate such an association. Finally, tests assuming linear association were used by all of the studies that examined this association. Tests of non-linear association were never employed. Therefore, it is entirely possible that different OCD dimensions (or subtypes) may be differentially associated with neuropsychological performance (Kuelz et al., 2004; Abramovitch et al., 2013). Indeed, a recent review and meta-analysis found that the overall neuropsychological test performance of OCD 'checkers' yielded larger effect sizes compared to OCD 'washers' (Leopold and Backenstrass, 2015).

Of further concern, 26% of studies failed to report the severity of associated depression. Depressive disorders and clinical levels of depressive symptoms are prevalent clinical features of OCD (Overbeek et al., 2002), which have been reported to exert a significant impact on neuropsychological performance in OCD (Basso et al., 2001; Moritz et al., 2001). Thus, failure to assess depressive severity (and control for it when testing group differences) in more than a quarter of the reviewed studies limits the inferences that can be made from neuropsychological research in OCD.

Of note, in recent years, there has been an ongoing debate among researchers with regards to the nature of neuropsychological deficits in OCD. Some researchers have argued that underperformance on neuropsychological tests in OCD is an epiphenomenon that may result from an obsessive thoughts-related cognitive overload (Abramovitch et al., 2012a), or from other OCD-related clinical aspects (Moritz et al., 2012). This notion is supported in part by treatment studies indicating improvement in neuropsychological test performance among treatment responders with OCD (e.g., Kuelz et al., 2006; Voderholzer et al., 2013). On the other hand, some authors have suggested that these deficits in OCD may be state-independent (Bannon et al., 2006; Rao et al., 2008). In fact, as outlined by Gottesman and Gould (2003), one of the criteria for endophenotypes in psychiatric research is that these should be state-independent. Thus, candidate neurocognitive endophenotypes of OCD such as response inhibition (Chamberlain et al., 2005), by definition, support the notion of trait deficits. Our ability to weigh the evidence and advance this important debate is hindered by the fact that nearly half of the studies did not examine the clinical correlates of neuropsychological test performance in OCD. In fact, it has been noted that there is a need for more studies focusing on aspects related to the state versus trait controversy (Vandborg et al., 2012). Specifically, it has been argued that too few studies directly examined the evidence for state-dependent neurocognitive functions in OCD (Moritz et al., 2012). Finally, some evidence exists for differential association between neuropsychological test performance in OCD and symptom dimensions such as washing and checking (e.g., Omori et al., 2007; McGuire et al., 2014), emphasizing the need to assess the clinical correlates of cognitive functioning in OCD.

We recommend that researchers make every attempt to examine clinical correlates of neuropsychological test performance in OCD, including OCD severity and depressive severity. In addition, longitudinal studies as well as studies in remitted patients and treatment responders versus non-responders are needed to contribute to the state-trait debate. Whenever possible, researchers are encouraged to assess how symptom dimensions correlate with neurocognitive functioning (see next section for recommended measures).

4.2.2. Hoarding

Formerly conceptualized as a symptom dimension of OCD, hoarding disorder is now a distinct psychiatric disorder in the new DSM-5 (American Psychiatric Association, 2013). However, hoarding disorder may be a common comorbid condition in OCD, and hoarding symptoms are rather prevalent among OCD patients who do not meet criteria for hoarding disorder (18–40%; Pertusa et al., 2008, 2010). In recent years, several investigations reported neuropsychological deficits associated with hoarding (e.g., Tolin et al., 2011). Although preliminary reports suggest that hoarding and OCD may be characterized by distinct pathophysiology (Tolin et al., 2014), it remains unclear whether hoarding disorder, OCD with hoarding symptoms, and OCD without hoarding are

associated with distinct neural substrates or neuropsychological profiles (Grisham and Norberg, 2010). The foregoing issue notwithstanding, these findings as a whole suggest that neuropsychological investigations in OCD should, at the very least, assess/screen for hoarding and control for these aspects statistically. Our results, however, indicate that 73% of studies did not assess hoarding symptoms, and among those that did, 39% did not control for this factor. These high numbers may be explained by the fact that until recently, very little was known about hoarding in general and about the neuropsychology of hoarding in particular. Nevertheless, the lack of control for hoarding may be a potential confounding factor in OCD neuropsychological research.

We recommend that neuropsychological investigations in OCD utilize dimensional measures to assess hoarding, such as the Obsessive–Compulsive Inventory – Revised (OCI-R; Foa et al., 2002) and the Dimensional Obsessive–Compulsive Scale (Abramowitz et al., 2010), in order to examine and control for the impact of hoarding related symptomatology on neuropsychological functions. This may be especially relevant given the establishment of hoarding disorder in the DSM-5, highlighting the need to disentangle comorbid hoarding disorder and hoarding symptoms in OCD that may have different neurocognitive correlates.

4.2.3. Medication status

Our results reveal that 91% of studies reported medication status for OCD samples. While these are positive findings, researchers are encouraged to improve these rates. While there are indications that Selective Serotonin Reuptake Inhibitors (SSRIs; the first line pharmacotherapy for OCD) may not impact neuropsychological performance in healthy controls (Paul et al., 2007) or individuals with OCD (Mataix-Cols et al., 2002), there is anecdotal evidence that Clomipramine, a second-line treatment for OCD, may adversely impact certain cognitive functions (Allen et al., 1991; Serretti et al., 2010). In addition, neuroleptic medication has been demonstrated to negatively impact cognitive functioning in healthy controls (Veselinovic et al., 2013). In fact, there are indications for a potentially similar effect in OCD patients where the percent of patients medicated with neuroleptic agents across samples negatively correlated with effect sizes for performance on tests of executive function ($r = -0.43$; Abramovitch et al., 2013). Indeed, in a recent study, Lewin et al. (2014) found a greater magnitude of cognitive sequelae among a subsample of pediatric OCD patients taking atypical antipsychotics, versus OCD participants that were not taking this type of medication. Nevertheless, our results show that, among the studies that did indicate the percentage of medicated patients, 9% did not report the breakdown of medication types or dosages. Notably, individuals with OCD are usually prescribed relatively small doses of neuroleptic agents, and usually as augmentation agents. Regardless, we recommend that given the potential impact of neuroleptics on cognitive function, future studies should report medication status as well as the breakdown of medications, and specifically assess and control for the impact of neuroleptic agents on test performance when possible.

4.2.4. Age of onset

Age of onset was not reported in almost 50% of the studies surveyed. This often neglected data point may potentially bias inferences based on such studies, especially given findings suggesting different neuropsychological profiles between late-onset and early-onset OCD (Roth et al., 2005; Hwang et al., 2007). Moreover, lack of such information limits moderator analyses in meta-analytic investigations. We encourage researchers conducting neuropsychological research in OCD to routinely collect and present information regarding age of onset, and to assess its impact on neuropsychological test performance.

4.3. Neuropsychological factors

4.3.1. Education

Our results show that only 76% of the studies reported participants' education level. It is well established that education is a major factor in assessing neuropsychological performance, affecting scores on most tests (Lezak et al., 2012). Failure to report and include the education factor in statistical analyses of neuropsychological data may result in potential bias at best and distorted inferences at worst. Moreover, readers as well as researchers conducting meta-analytic investigations should be informed as to the education level of participants, even in cases where patients and controls were matched. This is especially true in cases where studies conducted in different geographical regions report different education levels. For example, one study conducted in Turkey (Kitis et al., 2007) reported that their OCD sample had a mean years of education of 10.3 (S.D.=4.73), while a different study conducted in Germany (Exner et al., 2009) reported a mean years of education of 17.1 (S.D.=3.0). Clearly, this difference is not only quantitatively significant, but moreover, it is reasonable to assume a major baseline difference in neuropsychological performance between a sample of which approximately 50% did not graduate from high school, and a sample of which the majority had at least an undergraduate degree.

We recommend that neuropsychological investigations report education level and address the objective level of education of their samples, regardless of whether a matching procedure has been employed. It is important to consider that while using an IQ estimation may be a sound alternative to education level, cognitive deficits affect performance on a number of IQ subtests. Thus researchers are advised to use 'hold' measures such as Vocabulary, and to a lesser extent tests such as the Block Design, for which scoring involves timely completion of tasks (Lezak et al., 2012).

4.3.2. Validation of tests in non-English speaking countries

When neuropsychological studies are conducted in non-English speaking countries, the issue of neuropsychological test validation in the local language becomes paramount. Of those studies conducted in non-English speaking countries that administered tests including a language comprehension component, 51% did not report the use of measures that were validated in the native language. Consider, for example, verbal fluency tests, and particularly the Controlled Oral Word Association Test (COWAT), where participants are asked to produce as many words as possible starting with the letters F, A, and S (or C, F, L) within the time frame of 1 min (Sumerall et al., 1997). It has long been demonstrated that performance on phonemic verbal fluency tests fluctuates significantly as a function of the choice of letters representing different frequencies of words beginning with these letters in a given language (Borkowski et al., 1967). In some of the reviewed studies, researchers used the letters F, A, and S in non-English speaking samples. While some of those studies were conducted in countries where the native language uses Roman letters, it is reasonable to assume that the frequency of words beginning with these letters differs between languages. Thus, the level of difficulty that has been demonstrated to correlate with the discriminant validity of this test (Borkowski et al., 1967) may be jeopardized, thereby limiting the inferences made from these results.

Research conducted in more than 21 countries has contributed to the vast body of knowledge of neuropsychology of OCD. This commendable international effort may be inherently challenging

when considering language-based neuropsychological tests. We recommend that researchers exercise vigilance with regards to this issue and limit their use of tests to those that were validated in their participants' native language. In cases where researchers decide to translate these measures in lieu of scientifically sound psychometric research, this should be clearly stated in their report, and the method of translation should be detailed.

4.3.3. Use of different tests assessing a single construct

A plethora of assessment tools and tests are available to researchers in neuropsychology, some of which are presumed to measure the same construct, but in a different manner. The variety of instruments presumed to measure 'attention' is a familiar example. However, instrument choice may pose a challenge in neuropsychological research in general, and in the study of OCD in particular (Kuelz et al., 2004), especially when examining a heterogeneous constructs such as response inhibition. While several neuropsychological constructs such as spatial working memory (de Vries et al., 2014) have been suggested as candidate endophenotypic markers for OCD, response inhibition has received the most research support as a marker for OCD (Chamberlain et al., 2005; Cavedini et al., 2010; de Wit et al., 2012). However, response inhibition is not a unified construct (Eagle et al., 2008), and our results reveal that studies that assessed response inhibition administered tests that correspond to four different paradigms: (a) Continuous Performance Test (CPT), (b) Go/No-Go tasks, (c) the Stroop test, and (d) the Stop-Signal Task (SST). The SST was employed in only 6% of the reviewed studies assessing response inhibition, whereas the majority of studies utilized the CPT or Go/No-Go paradigms. However, there is evidence that inhibition of response in Go/No-Go tests is associated with different neural substrates than those implicated in Stop-Signal tests (Rubia et al., 2001). In fact, there is strong neuropharmacological and neuroanatomical evidence that the Go/No-Go and Stop-Signal tests utilize different forms of response inhibition (Eagle et al., 2008); The Go/No-Go task is considered a measure of action suppression, whereas the SST assesses action cancellation. Similarly, studies have suggested that the Stroop task (a measure of interference control) and Go/No-Go task tap different aspects of selective attention and response inhibition (Morooka et al., 2012). These findings are further supported by different pooled effect sizes reported for different tasks of response inhibition in OCD research (Abramovitch et al., 2013).

As previously noted by Kuelz et al. (2004), grouping of partially-related tasks within the context of broader constructs has yielded some conflicting results. For example, our review revealed that the majority of studies utilizing the Go/No-Go task did not find significant differences between OCD and control groups, in contrast to studies utilizing SST where such differences are usually detected. Therefore, neuropsychology researchers are encouraged to treat response inhibition as a heterogeneous construct. Indeed, taking a more careful approach to assessing underlying constructs—such as response inhibition and non-verbal memory—may promote a better understanding of specific neuropsychological correlates of OCD. Furthermore, greater attention to task-specific differences would likely reduce the overall inconsistent and often contradictory findings across studies examining complex constructs such as response inhibition. We further recommend that researchers make an effort to carefully define the construct they wish to investigate, leading to selection of more specific and reliable measures. We would also like to reiterate the longstanding recommendation that researchers should attempt to administer multiple tests to assess neuropsychological constructs within the same study and attend to the pattern of results (Lezak et al., 2012).

4.3.4. Testing sessions

Finally, we have identified two minor shortcomings in a large number of studies: (a) omitting the number of sessions used in test administration; and (b) omitting the length of testing sessions. Although the potential impact of these factors on results is not well-researched, investigators should be aware of the potential impact of these variables on neuropsychological performance, perhaps even more so in OCD research. As is the case with numerous psychiatric disorders, patients with OCD may be prone to cognitive fatigue. For such individuals, it is recommended that testing sessions do not exceed two hours, due to a potential reduction in overall cognitive function after this period of time (Lezak et al., 2012). Indeed, our results demonstrate that an average session's length was two hours. However, some researchers administered up to 24 tests during a single testing session, lasting up to 4.5 h. With regards to multiple-visit testing sessions, 38% of studies did not report the number of testing sessions. In the case of OCD, in which patients' affect can fluctuate and may be partially state-dependent, multiple sessions could impact performance and should be minimized and consistently reported (thus promoting replicability). While these factors may have a lesser impact, one cannot assume that the effect is negligible. We recommend that researchers consider the potential impact of the length and number of sessions on their outcome measures, and provide this information in their reports.

4.4. Additional considerations

Other factors that were not directly reviewed herein are worth mentioning. First, in reviewing this body of literature, it was rare to find studies that report/control for the present status or history of psychological interventions. The literature on neuropsychological correlates associated with psychological treatments in OCD is highly inconsistent (Vandborg et al., 2012). Nevertheless, a number of studies report improved neuropsychological test performance following successful treatment for OCD (e.g., Moritz et al., 1999; Voderholzer et al., 2013). Thus, treatment status and history may potentially impact neuropsychological performance and should be at the very least reported, and when possible controlled for. Secondly, while more common in the recent decade, it is common for studies not to provide a detailed account of the breakdown of comorbidities in their samples. Some comorbidities – such as chronic tics or Tourette's syndrome – that are prevalent among OCD patients may be associated with distinct neuropsychological deficits (Eddy et al., 2009). In fact, it has been indicated that cases of comorbid OCD and Tourette's present with more substantial cognitive deficits, over and above the ones that are thought to characterize each disorder separately (Matsuda et al., 2012). In addition, only a minority of studies assessed and reported the presence of personality disorders, some of which may be associated with a distinct profile of neuropsychological deficits.

A third consideration concerns screening of non-psychiatric controls. There are some indications of underperformance on some neuropsychological tests in first degree relatives of individuals with OCD (e.g., Cavedini et al., 2010), as well as in the context of other disorders (e.g., Gau and Shang, 2010). Thus, we recommend that researchers consider assessing the presence of OCD or other psychiatric conditions amongst relatives of non-psychiatric controls, potentially considering this factor as part of their exclusion criteria or as a measure to be assessed as a confound. A fourth consideration concerns examiners' training. Whereas it is a

common practice among papers reporting clinical trials to report assessors and interviewers' training, it is rare for studies utilizing neuropsychological tasks to report the type of training that test administrators underwent. The importance of examiner/administrator training has been continuously highlighted in the neuropsychological literature, including the need for adequate supervision (Bornstein, 1991). Indeed, numerous aspects of administrator conduct may influence tests' validity, including more subtle dimensions such as the examiner's level of attention to the performance of examinees on computerized tests (Yantz and McCaffrey, 2007). Thus, it is recommended that researchers utilizing neuropsychological tasks adhere to training and supervision guidelines, and subsequently present this information in scholarly publications. Fifth, in the context of neuropsychological testing, maintaining the validity of tests requires investment of effort on behalf of the examinee (Strauss et al., 2006; Lezak et al., 2012). In fact, motivation, effort, and response bias have been repeatedly documented to affect neuropsychological test performance (Iverson, 2010). However, to our knowledge, effort was never assessed using the available validated measures in OCD (e.g., Test of Memory Malingering, Rey 15 Item Test). In one of the only studies to attend specifically to this issue in OCD, Moritz et al. (1999) found that motivation and effort may have an impact on neuropsychological test performance in OCD, but much more research utilizing different measures to assess this effect in OCD is needed. Finally, it is important to note that for some of the factors reviewed herein, it is possible that authors did collect data but did not report it because of word limits placed by journals. Nevertheless, we hope that the present review allows researchers to evaluate their priorities regarding the types of data they deem most important to present.

5. Conclusion

In the present study, we systematically surveyed methodological factors in a substantial body of research exploring neuropsychological test performance between obsessive–compulsive disorder and control samples. We found an array of shortcomings of various degrees—some of which were pervasive—with the potential to affect results and their interpretations. These methodological weaknesses may contribute to the persistent difficulty to form a coherent, clear picture of a neuropsychological profile of OCD. In fact, these shortcomings may have been contributing to the inability of meta-analytic investigation from accounting for the significant heterogeneity found between studies.

The present study is not aimed to dismiss any single study, but rather to promote awareness of the various methodological issues in studies on the neuropsychology of OCD. It may be noted here that these issues are all too prevalent in neuropsychology research in general. We encourage researchers in this field to address the caveats identified herein, and adhere to our specific recommendations such that future studies will facilitate replicability, meta-analytic investigations, and ultimately allow for more reliable inferences. Finally, we believe it is vital to use the accumulated knowledge regarding neurobiological correlates of different neuropsychological tests in the process of constructing neuropsychological batteries. This is especially important when considering tests that assess partially-related aspects of broader constructs, particularly in the domain of response inhibition.

Conflict of interest

All authors declare that they have no conflict of interest pertaining to the present manuscript.

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