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Diagnostic biomarkers for obsessive-compulsive disorder: A reasonable quest or *ignis fatuus*?

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ABSTRACT

Obsessive-compulsive disorder (OCD) has been associated with a wide range of biological and neurocognitive findings, which could assist in the search for biomarkers. We conducted an umbrella review of systematic reviews and meta-analyses to assess and grade the strength of the evidence of the association between OCD and several potential diagnostic biomarkers while controlling for several potential biases. Twenty-four systematic reviews and meta-analyses were included, comprising 352 individual studies, more than 10,000 individuals with OCD, and covering 73 potential biomarkers. OCD was significantly associated with several neurocognitive biomarkers, with varying degrees of evidence, ranging from weak to convincing. A number of biochemical, neurophysiological, and neuroimaging biomarkers also showed statistically significant, albeit weak, associations with OCD. Analyses in unmedicated samples (123 studies) weakened the strength of the evidence for most biomarkers or rendered them non-significant. None of the biomarkers seem to have sufficient sensitivity and specificity to

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become a diagnostic biomarker. A more promising avenue for future biomarker research in OCD might be the prediction of clinical outcomes rather than diagnosis.

1. Introduction

The development of clinically useful biomarkers has been heralded as a top priority in contemporary mental health research (Abi-Dargham and Horga, 2016; Kapur et al., 2012). Although advances in basic neuroscience have generated hope in identifying such biomarkers, they are not yet a reality (Venkatasubramanian and Keshavan, 2016). The identification of biomarkers (including diagnostic biomarkers) for psychiatric disorders is faced with numerous challenges, chief amongst which is the fact that these conditions are "*practical kinds*", rather than "*natural kinds*" (Kendler et al., 2011). Indeed, psychiatric diagnoses are currently based on sets of signs and symptoms (American Psychiatric Association, 2013), and do not require a biological test (Prata et al., 2014). The expectation is that further understanding of the biological underpinnings of psychiatric disorders will lead to a more rational classification system based on biomarkers, rather than clinical signs and symptoms (Insel, 2014; Kapur et al., 2012; Perlis, 2011). Obsessive-compulsive disorder (OCD) is a common and disabling disorder that has been associated with a wide range of biological and neurocognitive findings (Bandelow et al., 2017; Stein et al., 2019), which could potentially assist in the quest for diagnostic biomarkers. However, the existing literature is vast, has differing levels of quality, and is likely affected by a number of reporting biases. Umbrella reviews (a quantiative review of individual studies included in systematic reviews and meta-analyses) are ideally suited to critically appraise the literature and uncover such biases and have an increasingly important role in evidence-based mental health care (Ioannidis, 2009). Here we report the results of an umbrella review to summarize and grade the quality of evidence regarding potential, non-genetic diagnostic biomarkers for OCD. We then discuss the merits of such work and future directions in the field.

2. Methods

We conducted an umbrella review (Ioannidis, 2009) of potential diagnostic biomarkers for OCD. The study protocol was pre-registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42018081199).

2.1. Search strategy and eligibility criteria

Two researchers systematically and independently searched *PubMed*, *Web of Science*, and *Scopus* through January 6th, 2020 to identify systematic reviews and meta-analyses of studies examining potential diagnostic biomarkers for OCD. Reference lists of the systematic reviews and meta-analyses reaching full-text review were also reviewed. Eligibility criteria included: 1) a systematic review or meta-analysis of potential diagnostic biomarkers for OCD – diagnosed via the International Classification of Diseases (ICD) manual or the Diagnostic and Statistical Manual of Mental Disorders (DSM); 2) inclusion of a healthy control group; and 3) studies reporting sufficient data to perform the analyses (or where data were retrievable from the authors). We did not apply any language restrictions. Further information about the search strategy can be found in the supplementary material. For a complete list of the excluded systematic reviews/meta-analyses, see https://www.umbrellaevidence.com/anxiety/diagnosticbiomarkers/OCD.xlsx.

2.2. Definition of biomarker

We used the following accepted definition of biomarker (Atkinson et al., 2001, p 91): "*Acharacteristic that is objectively measured and evaluated as an indicator of normal biological processes or pathogenic processes.*" In keeping with recent research, our definition of the term 'biomarker' was broader than previous definitions (based only on biospecimens) and included objective markers of any modality, including behavioral and neurocognitive biomarkers (Bandelow et al., 2017; Ioannidis and Bossuyt, 2017; Perlis, 2011). We did not include potential genetic biomarkers because different analytical methods are required for umbrella reviews of genetic variables (Ioannidis et al., 2008). Neither did we include potential biomarkers from whole-brain voxel-based neuroimaging studies (although we did include other types of neuroimaging data), because we would need to treat each voxel as a biomarker. We refer the reader to existing meta-analyses of whole-brain imaging studies in OCD (e.g., Picó-Pérez et al., 2020; *Radua et al., 2014; Thorsen et al., 2018).

We used the definition for each biomarker provided in the corresponding systematic review or meta-analysis, but for reporting purposes, we classified biomarkers into the following categories: behavioral, biochemical, neurocognitive (i.e., neuropsychological), neuroimaging, and neurophysiological.

2.3. Data extraction and selection

Two investigators conducted the following steps independently. First, we identified the potential biomarkers assessed in each of the selected systematic review or meta-analysis. Second, we confirmed that each individual article included in the systematic review or meta-analysis met our eligibility criteria for the umbrella review. Third, we extracted the following data (from the respective systematic review or meta-analysis or, otherwise, from the individual study): 1) first author and year of publication, 2) number of cases and controls and number of cases receiving pharmacological treatment, 3) effect size measure (standardized mean difference [SMD] for continuous biomarkers, odds ratio [OR] for binary biomarkers) and corresponding 95 % confidence interval (CI), 4) means and standard deviations for cases and controls for continuous biomarkers, and number of cases and controls with and without the biomarker for binary biomarkers. Fourth, we rated the quality of the systematic review or meta-analysis using the Assessment of Multiple Systematic Reviews (AMSTAR) tool (Shea et al., 2007), with high interrater agreement (both weighted Cohen's kappa and intraclass correlation $K = 0.82$). For further information on the data extraction, selection, and quality assessment, see the Appendix Asupplementary material. For a list of the included and excluded individual studies, see https://www.umbrellaevidence.com/anxiety/diagnosticbiomarkers/OCD.xlsx.

2.4. Statistical analyses

For each potential biomarker being assessed in more than one individual study, we conducted a separate random-effects meta-analysis, estimating the variance as the inverse of the sum of the weights of the studies and assuming a normal distribution (DerSimonian and Laird, 1986). The outcomes of the meta-analyses were the effect sizes with their corresponding CIs and *p*-values, as well as the statistics required to assess the level of evidence (see below). We used the measure of effect size reported in each original meta-analysis.

We assessed between-study heterogeneity with the I^2 statistic. I^2 values above 50 % are conventionally understood as indicating large heterogeneity (Ioannidis et al., 2007). We also estimated the 95 % prediction intervals, within which the results of 95 % new studies should lie. Therefore, when these intervals exclude the null value (0 for SMDs, 1 for ORs), it is likely that such association remains significant in new

studies. We assessed whether there was evidence of small-study effects using the Egger test (Stuck et al., 1998), where statistical significance would indicate potential reporting or publication bias in the smaller studies or other reasons why small studies differ from larger ones (Sterne et al., 2011). Excess significance (i.e., a relative excess of studies reporting statistically significant findings) was assessed with a binomial test comparing the observed *vs.* the expected number of studies yielding statistically significant results (Ioannidis and Trikalinos, 2007).

We classified the levels of evidence of the significant associations between each biomarker and OCD into *convincing* (class I), *highly suggestive* (class II), *suggestive* (class III), or *weak* (class IV) (Fusar-Poli and Radua, 2018; Ioannidis, 2009). *Convincing* evidence required a number of cases n>1000, a highly statistically significant association ($p<10^{-6}$), $I^2<50$ %, a 95 % prediction interval excluding the null value, and the absence of signals of small-study effects and excess significance. *Highly suggestive* evidence required $n>1000$, a highly statistically significant

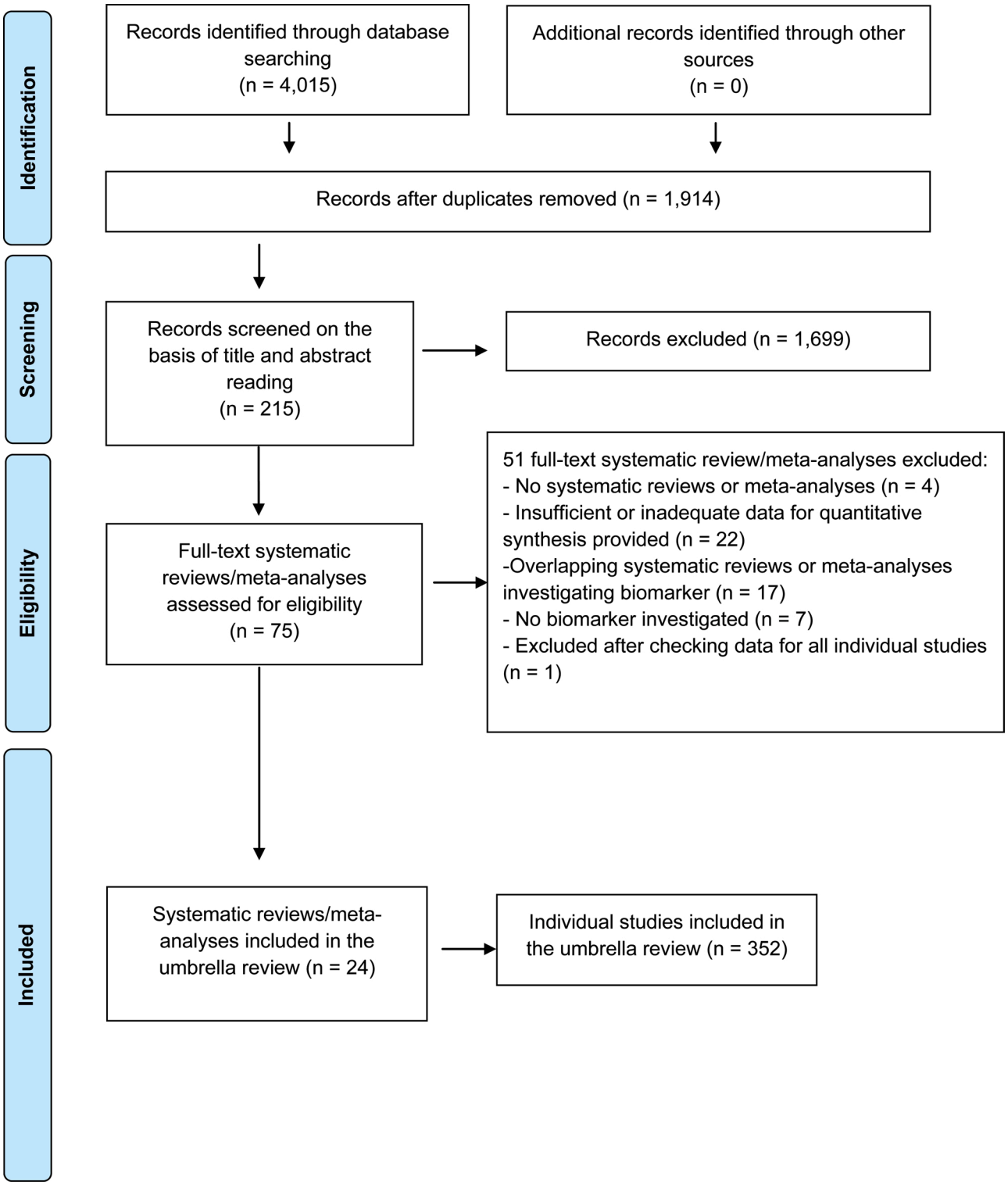

Fig. 1. Flowchart of the literature search.

association ($p<10^{-6}$), and that the largest study had a statistically significant effect. *Suggestive evidence* required $n>1000$ and $p<10^{-3}$. *Weak evidence* required no specific number of cases and $p < 0.05$.

In light of the potential effects of psychopharmacological treatments on biomarkers (Heuvel et al., 2020), and of potential differences between pediatric and adult OCD (Kalra and Swedo, 2009), we conducted two sensitivity analyses: one including only studies that recruited unmedicated patients and another including only studies conducted in adults.

3. Results

All extracted data and results are available from https://www.umbrellaevidence.com/anxiety/diagnosticbiomarkers/OCD.xlsx.

We included 24 systematic reviews and meta-analyses encompassing data from 352 individual studies (Fig. 1). These studies covered 73 potential biomarkers and were based on data from 10,196 OCD patients and 10,456 healthy controls. Fourteen (58%) of the included systematic reviews/meta-analyses were classified as high quality, 9 (38%) as moderate quality, and 1 (4%) as low quality, according to the AMSTAR tool. The main characteristics of the selected systematic reviews/meta-analyses are presented in Table 1.

Forty-three of the 73 biomarkers (58.9%) showed statistically significant evidence of an association with OCD at $p < 0.05$ under the random-effects model, 35 (47.9%) had a $p < 0.005$, and 15 (20.5%) reached $p<10^{-6}$. The number of OCD cases was greater than 1000 for 8 (10.9%) biomarkers. For 6 biomarkers (8.2%), the 95% prediction interval did not include the null, and 25 biomarkers (34.2%) showed large (i.e., $I^2>50\%$) heterogeneity. Evidence for excess significance bias was found for 17 (23.2%) biomarkers and evidence for small-study effects was found for 12 (16.4%) biomarkers (see https://www.umbrellaevidence.com/anxiety/diagnosticbiomarkers/OCD.xlsx).

3.1. Associations according to the level of evidence

Biomarkers that showed a significant association with OCD in the main analysis are presented in Table 2. Only the associations with neurocognitive biomarkers achieved class I-II evidence. One neurocognitive biomarker (visuospatial abilities) showed convincing (class I) evidence of association with OCD. Another four neurocognitive biomarkers showed highly suggestive (class II) evidence of association with OCD: non-verbal memory, processing speed, inhibition, and verbal fluency. Moreover, flexibility, planning, and verbal working memory had class III (suggestive) evidence. For all neurocognitive variables, significant biomarkers indicated decreased performance in OCD patients in comparison to healthy controls.

A number of biomarkers achieved class IV (weak) evidence. These included several biochemical biomarkers (e.g., increased levels of cortisol, anti-basal ganglia antibodies [ABGA] positivity, levels of several oxidants and antioxidants); neurocognitive biomarkers (e.g., decreased sustained attention, non-verbal working memory, verbal memory); neuroimaging biomarkers (e.g., increased fractional anisotropy of the anterior limb of the internal capsule, decreased fractional anisotropy of the genu of the corpus callosum); and several neurophysiological biomarkers (e.g., increased error-related negativity [ERN] as measured with conflict tasks, increased neurological soft signs [NSS], and several polysomnographic measures). Class IV biomarkers based on at least three individual studies are reported in Table 2 (see also https://www.umbrellaevidence.com/anxiety/diagnosticbiomarkers/OCD.xlsx).

3.2. Sensitivity analyses

Sensitivity analyses using only studies of unmedicated patients included 63 biomarkers, of which 35 remained significant at $p < 0.05$. All biomarkers that were class I-III in the main analysis either became class IV or non-significant, except flexibility, which went from class III to class II. These analyses included far fewer individual studies overall ($n = 123$) and for each biomarker than the main analysis.

Sensitivity analyses including only studies in adults ($n = 314$) did not substantially alter the main results. All class I, II, and III and most class IV biomarkers retained the same level of evidence. ABGA positivity (class IV in the main analyses) became non-significant, partly because it had only been investigated in one adult study.

3.3. Post-hoc analyses

Given that only 10% of the biomarkers investigated included more than 1000 cases, and to obtain a better perspective on the potential of several factors as diagnostic biomarkers, we also examined the levels of evidence removing the requirement of $n>1000$ (Fullana et al., 2019). In this analysis, the only biomarker that achieved class I was still visuospatial abilities, but several biochemical (cortisol and levels of different oxidants) and one behavioral biomarker (automatic emotional facial expression) became class II (i.e., showed highly suggestive evidence of association with OCD). Removing the $n>1000$ criteria also upgraded the level of evidence to class III for several biochemical, neuroimaging, and neurophysiological biomarkers that in the main analysis were class IV (see https://www.umbrellaevidence.com/anxiety/diagnosticbiomarkers/OCD.xlsx). These results should be interpreted with caution because they are based on a limited number of studies/cases.

4. Discussion

We have summarized the evidence from 24 systematic reviews or meta-analyses including 352 individual studies with information on more than 10,000 individuals with OCD and a similar number of controls to provide a state-of-the art classification of potential diagnostic biomarkers for OCD, based on the robustness of the associations with the disorder, and after controlling for several biases.

In our main analysis, more than 60 % of the investigated biomarkers showed a significant association with OCD. The evidence for the association of one neurocognitive biomarker with OCD was convincing (class I) and for several other neurocognitive biomarkers was highly suggestive (class II). A number of biochemical, neurophysiological, and neuroimaging biomarkers, also showed significant (albeit weak) associations with OCD. Removing the $n>1000$ cases criterion upgraded the evidence for several biomarkers that were class IV in the main analysis to class II or class III. Notably, the strength of the evidence for almost all biomarkers identified in our main analysis became weak (class IV) or non-significant when only studies of unmedicated samples were analyzed.

Our finding of several biomarkers associated with OCD with strong evidence is in contrast with recent umbrella reviews in autism spectrum disorder (Kim et al., 2019), bipolar disorder (Carvalho et al., 2016b), and depression (Carvalho André et al., 2016a), were no robust biomarkers were identified, although these works did not include neurocognitive biomarkers. However, most effect sizes found in our umbrella review were small or medium in magnitude (Cohen, 1988), which limits their clinical utility. Regardless, it is important to assess whether the biomarkers found here meet the definition of valid “diagnostic biomarkers”. There are several issues surrounding the concept of “diagnostic biomarker” that deserve discussion.

First, the diagnostic specificity of the biomarkers for OCD identified in this umbrella review is questionable. By definition, a diagnostic biomarker should have little overlap with other disorders, i.e., be highly specific (Davis et al., 2015). It is unlikely that any of the neurocognitive biomarkers that we identified as robustly associated with OCD possesses such specificity. Indeed, deficits in visuospatial abilities (our class I factor) have been associated with multiple disorders including, but not limited to, schizophrenia (Schaefer et al., 2013) and anxiety-related disorders (O'Sullivan and Newman, 2014; Scott et al., 2015).

Table 1
Characteristics of the systematic reviews and meta-analyses included in the umbrella review of diagnostic biomarkers of obsessive-compulsive disorder.

Systematic review or meta-analysis	Type of biomarker	Method of assessment	Biomarker	Number of individual studies included
Abramovitch et al., 2013	Neurocognitive	Neuropsychological testing	Flexibility	15
			Inhibition	17
			Nonverbal memory	38
			Nonverbal working memory	7
			Planning	2
			Processing speed	49
			Sustained attention	6
			Verbal memory	25
			Visuospatial abilities	42
			Verbal working memory	16
*Abramovitch et al., 2015	Neurocognitive	Neuropsychological testing	Flexibility	7
			Inhibition	6
			Nonverbal memory	5
			Planning	3
			Processing speed	7
			Verbal memory	4
			Verbal working memory	3
			Visuospatial abilities	7
Aoki et al., 2012	Neuroimaging	^{1}H-spectroscopy MRI	nAA concentration in basal ganglia	8
			nAA concentration in dlPFC	3
			nAA concentration in mPFC	12
			nAA concentration in thalamus	3
Bey et al., 2018	Neurophysiological	Video-oculography or electrooculography	Antisaccade error rates	11
			Antisaccade latencies	10
Chalmers et al., 2014	Neurophysiological	Electrocardiogram	High frequency HRV	2
Cosco et al., 2019	Biochemical	Blood analysis	IL-6 levels	7
			IL-6# levels	4
			IL-1β levels	5
			IL-4 levels	4
			IL-10 levels	4
			IFN-ϒ levels	3
			TNF-α levels	8
			TNF-α# levels	4
Davies et al., 2016	Behavioral	Visual induction system	Automatic emotional facial expression	2
Díaz-Román et al., 2015	Neurophysiological	Polysomnography	Sleep efficiency	6
			Sleep latency	3
			Stage 2 sleep	6
Fradkin et al., 2018	Neurocognitive	Neuropsychological testing	Flexibility	72
Jaafari et al., 2013	Neurophysiological	Physical examination	Neurological soft signs	15
Lipszyc and Schachar, 2010	Neurocognitive	Neuropsychological testing	Inhibition	2
Maia et al., 2019	Biochemical	Blood analysis	8-hydroxy-20 –deoxyguanosine levels	2
			Catalase levels	2
			Glutathione levels	2
			Glutathione peroxidase levels	2
			Malondialdehyde levels	5
			Nitric oxide levels	2
			Superoxide dismutase levels	3
			Thiobarbituric acid reactive substances	3
			Total antioxidant status	3
			Total oxidant status	3
			Vitamin C levels	3
			Vitamin E levels	2
Nota et al., 2015	Neurophysiological	Polysomnography	Awakening after sleep onset	6
			Sleep duration	6
			Proportion of REM sleep	6
			Proportion of slow wake sleep	6
			Sleep onset latency	6
Pearlman et al., 2014	Biochemical	Blood analysis	ABGA positivity	4
Piras et al., 2013	Neuroimaging	Diffusion tensor imaging MRI	FA anterior limb internal capsule	3
			FA genu corpus callosum	3
			FA splenium corpus callosum	2
Radua and Mataix-Cols, 2009	Neuroimaging	Structural MRI	Global GMV	8
Radua et al., 2010	Neuroimaging	Structural MRI	Global GMV	2
Radua et al., 2014	Neuroimaging	Structural MRI	Global WMV	7
Riesel, 2019	Neurophysiological	Electroencephalography	ERN (conflict tasks)	26
			ERN (other tasks)	4
Rutigliano et al., 2016	Biochemical	CSF analysis	Oxytocin levels	2
			Vasopressin levels	2
Snyder et al., 2015	Neurocognitive	Neuropsychological testing	Flexibility	33
			Inhibition	46
			Non-verbal working memory	23
			Planning	25
			Processing speed	9
			Verbal fluency	38

(*continued on next page*)

Table 1 (*continued*)

Systematic review or meta-analysis	Type of biomarker	Method of assessment	Biomarker	Number of individual studies included
			Verbal working memory	22
Sousa-Lima et al., 2019	Biochemical	Blood analysis	Cortisol levels	18
Suliman et al., 2013	Biochemical	Blood analysis	BDNF levels	3
Wright et al., 2014	Neurocognitive	Neuropsychological testing	Inhibition	3

Note: Only biomarkers assessed in more than one individual study are shown. AMSTAR scores ranged between 5 and 11 (see www.umbrellaevidence.com/OCDbiomakers.xlsx). *Included only studies in children/adolescents.

Abbreviations: ABGAanti basal ganglia antibodies; ADHantidiuretic hormone/vasopressin; BDNFbrain-derived neurotrophic factor; CSFcerebrospinal fluid; dlPFC-dorsolateral prefrontal cortex; ERNerror-related negativity; FAfractional anisotropy; GMVgray matter volume; HRVheart rate variability; ILinterleukin; mPFCmedial prefrontal cortex; MRImagnetic resonance imaging; nAAN-acetylaspartate; OT-oxytocyn; REMrapid eye movement; TNF = tumor necrosis factor.

Moreover, in one study that directly examined its specificity, visuospatial abilities could not differentiate OCD from other mental disorders (Moritz et al., 2005). In a similar vein, many of the neuroimaging findings summarized in voxel-based morphometric meta-analyses are not specific to OCD (Patel, 2020). It has been suggested that deficits in cognitive function -assessed here by neurocognitive biomarkers- could be an integral part of the vulnerability to "all" psychiatric disorders, i.e., the *p* factor (Caspi et al., 2014; see below).

Similarly, the biochemical or neurophysiological biomarkers found to be associated with OCD in our study are also unlikely to be diagnosis-specific. For example, both high levels of cortisol and high levels of oxidants are known to be increased by stress and have been associated with psychotic (Flatow et al., 2013), bipolar (Andreazza et al., 2008; Carvalho et al., 2016b), and depressive (Black et al., 2015; Kennis et al., 2020) disorders. This suggests that they might be related to the allostatic load associated with psychiatric disorders in general, rather than to specific conditions (Pinto et al., 2017). Increased rates of neurological soft signs have also been associated with psychotic and bipolar disorders (Bora et al., 2018), and polysomnographic measures seem to have little diagnostic specificity (McGorry et al., 2014). Finally, increased ERN could be a more specific marker for OCD, since *decreased* ERN has been found in other psychiatric disorders such as schizophrenia, autism spectrum disorder, and substance use disorders (*Riesel, 2019). However, increased ERN seems also to characterize a number of other disorders that often co-occur with OCD, such as anxiety-related disorders and depression (Gillan et al., 2017; *Riesel, 2019).

Another important criterion for evaluating diagnostic biomarkers should be their incremental validity (Abi-Dargham and Horga, 2016; Ioannidis, 2011), i.e., to what extent the biomarker will add critical information for diagnosing the disorder in comparison to, for example, a clinical interview. This is important because identification of biomarkers in a given individual can be costly and time consuming. To our knowledge, none of the potential biomarkers found here has shown to be incrementally valid in diagnosing OCD. Similarly, recent work from the ENIGMA OCD work group has shown that neuroimaging data alone cannot reliable discriminate OCD patients from healthy controls (Heuvel et al., 2020).

The fact that the strength of the evidence for all biomarkers -except flexibility- became weaker/non-significant in our sensitivity analyses of unmedicated samples could be related to the smaller sample size available for these analyses (123 vs.352 studies) but highlights the role of medication as a potentially important confounder in much of the literature reviewed herein. Interestingly, in the above-mentioned ENIGMA OCD meta-analysis (Heuvel et al., 2020), machine-learning algorithms were much better at classifying medicated *vs.* unmedicated patients than OCD cases *vs.* controls. Unmedicated patients may be inherently different from those on medication (e.g., less severe) and, therefore, whether these potential differences on biomarkers are due to the use of medication *per se* or to the fact that this group has different characteristics should be discerned in future research.

Taken together, and in line with previous research (Boksa, 2013; Kapur et al., 2012), our results suggest that there is currently no single specific or incrementally valid diagnostic biomarker for OCD. Some authors have suggested that it is unlikely that we will ever find a single diagnostic biomarker in mental health (Boksa, 2013; Caspi and Moffitt, 2018; Prata et al., 2014; Venkatasubramanian and Keshavan, 2016). There are several methodological and conceptual reasons for this. First, the 'catch-22′ situation between current diagnoses and biomarkers (Prata et al., 2014). That is, psychiatric diagnoses are "practical" rather than "natural" kinds, and thus the ability to identify valid biomarkers is inherently limited (Deacon, 2013). In addition, biomarkers identified for other (non-psychiatric) disorders have not yet proven useful for psychiatric diagnoses. Second, most research on potential diagnostic biomarkers in mental health (including the studies reviewed here) is based on comparisons between patients and healthy controls, limiting the search for specific biomarkers between different psychiatric disorders (Kapur et al., 2012; Scarr et al., 2015). Another reason is clinical heterogeneity: the different expressions of (the same) mental disorders -including OCD (Mataix-Cols et al., 2005)- and the plurality of diagnostic profiles for a single disorder inherent in current classification systems, make it unlikely that we find a single diagnostic biomarker that fits all these expressions. Furthermore, if part of what we observe in mental disorders is an adaptive response rather than an underlying dysfunction, it is unlikely that we can find diagnostic biomarkers. New methodological and conceptual approaches have been proposed to deal with these limitations in the quest for diagnostic biomarkers. These include the use of within-subject designs (Le-Niculescu et al., 2019), the use of systems-biology (Venkatasubramanian and Keshavan, 2016), moving to "digital biomarkers" (Insel, 2018), or the integration of biomarkers in clinical staging models (Kalanthroff et al., 2017; McGorry et al., 2014). Some researchers have proposed abandoning the search of "diagnostic" biomarkers in mental health and focusing instead on "transdiagnostic" biomarkers for several (Kapur et al., 2012) or for one unique psychopathological dimension (the *p* factor; Caspi and Moffitt, 2018). Others have proposed that the search for biomarkers focuses on early detection of disorders or prediction of clinical outcomes rather than on diagnosis/classification (Boksa, 2013; Davis et al., 2015).

Our study has several strengths. We used systematic methods for data search, extraction, and selection and followed best practice approaches for conducting umbrella reviews (Fusar-Poli and Radua, 2018). We also used standard methods to assess the quality of the included systematic reviews/meta-analyses, and most of them were at least of moderate quality. In addition, this umbrella review is also the first to include neurocognitive biomarkers. Finally, to facilitate replication and contribute to a database of potential biomarkers for OCD that may be expanded in the future, we are making all the collected data publicly available (https://www.umbrellaevidence.com/anxiety/diagnosticbiomarkers/OCD.xlsx).

We also note several limitations. First, for methodological reasons, we could not include genetic or whole-brain neuroimaging studies in our umbrella review. However, OCD genetics research is very much in its infancy and no genome-wide significant loci have been identified (Mattheisen et al., 2014; Stewart et al., 2013). Moreover, it is clear from the ENIGMA consortium data that whole-brain neuroimaging data do not currently represent viable diagnostic biomarkers for OCD (Heuvel et al., 2020; McKay et al., 2017). Second, umbrella reviews entail loss of

Table 2
Biomarkers showing convincing (class I), highly suggestive (class II), suggestive (class III), or weak (class IV) evidence of association with obsessive-compulsive disorder.

2Type of biomarker	Biomarker	Number of studies	Number of cases	Measure	ES (95 % CI)*	*p*	95 % PI	I^2 (%)	SSE *p*	ESB *p*	LS 95 % CI	Class of evidence
Neurocognitive	Visuospatial abilities	49	1617	SMD	−0.34 (-0.42, -0.26)	2.5×10^{-16}	(-0.59,-0.09)	16.8	0.66	0.26	(-0.61, -0.1)	I
	Nonverbal memory	43	1408	SMD	−0.68 (-0.81, -0.56)	3.3×10^{-26}	(-1.32, -0.04)	57.3	0.36	0.0055	(-1.04, -0.52)	II
	Processing speed	65	1791	SMD	−0.44 (-0.53, -0.35)	2.4×10^{-21}	(-0.89, 0.02)	37.7	0.57	0.0032	(-0.93, -0.41)	II
	Inhibition	74	1980	SMD	−0.4 (-0.52, -0.29)	6.7×10^{-12}	(-1.2, 0.39)	65.5	0.56	0.032	(-0.68, -0.18)	II
	Verbal fluency	38	1252	SMD	−0.37 (-0.48, -0.26)	8.9×10^{-11}	(-0.82, 0.09)	41.4	0.32	0.027	(-0.62, -0.08)	II
	Flexibility	127	3946	SMD	−0.5 (-0.58, -0.26)	1.3×10^{-29}	(-1.29, 0.3)	68.7	0.015	3.1×10^{-27}	(-0.36, 0.06)	III
	Planning	30	1079	SMD	−0.41 (-0.53, -0.29)	5.8×10^{-11}	(-0.9, 0.07)	46.6	0.1	9.4×10^{-09}	(-0.26, 0.24)	III
	Verbal working memory	41	1375	SMD	−0.29 (-0.42, -0.17)	4.7×10^{-6}	(-0.92, 0.33)	56.5	0.018	0.2	(-0.56, 0.05)	III
	Sustained attention	7	241	SMD	−0.49 (-0.72, -0.27)	1.6×10^{-05}	(-0.98, -0.01)	25	0.85	1	(-0.78, -0.24)	IV
	Non-verbal working memory	30	974	SMD	−0.46 (-0,6, -0.33)	4.3×10^{-12}	(-0.96, 0.03)	41.8	0.78	0.00034	(-0.97, -0.42)	IV
	Verbal memory	29	996	SMD	−0.31 (-0.44, -0.17)	7.9×10^{-06}	(-0.84, 0.23)	48.8	0.25	0.0042	(0, 0.5)	IV
Biochemical	Malondialdehyde	5	236	SMD	2.57 (1.54, 3.6)	9.8×10^{-07}	(-1.38, 6.51)	93.5	0.37	1	(3.28, 4.17)	IV
	Vitamin C	3	117	SMD	−1.41 (-2.38, -0.44)	0.0045	(-13.54, 10.72)	90.5	0.96	1	(-2.56, -1.56)	IV
	Cortisol	18	327	SMD	0.73 (0.45,1.01)	2.8×10^{-07}	(-0.32, 1.79)	66.8	0.01	0.032	(0.2, 1.05)	IV
	Total antioxidant status	3	74	SMD	−0.72 (-1.16, -0.29)	0.001	(-4.78, 3.33)	35.7	0.7	0.29	(-0.89, -0.01)	IV
	ABGA positivity	4	97	OR	3.25 (1.53, 6.92)	0.0022	(0.62, 17.06)	0	0.86	0.34	(1.75, 21.58)	IV
Neurophysiological	Neurological soft signs	15	498	SMD	1.31(0.65, 1.97)	9.8×10^{-05}	(-1.52, 4.14)	95.5	0	0.0058	(1.14, 1.98)	IV
	Awakening after sleep onset	6	126	SMD	0.56 (0.31, 0.81)	1.2×10^{-05}	(0.2, 0.91)	0	0.71	1	(0.28, 0.99)	IV
	ERN (conflict tasks)	26	735	SMD	−0.55 (-0.65, -0.45)	7.9×10^{-26}	(-0.65, -0.44)	0	0	9.3×10^{-10}	(-0.61, 0.07)	IV
	Sleep duration	6	126	SMD	−0.53 (-0.89,-0.18)	0.0035	(-1.44, 0.37)	38.6	0.83	0.42	(-1.14, -0.39)	IV
	Sleep onset latency	3	30	SMD	−0.5 (-0.99, -0.01)	0.044	(-3.66, 2.66)	0	0.57	1	(-1.31, 0.41)	IV
	Antisaccade latencies	10	347	SMD	0.47(0.02, 0.91)	0.039	(-1.07, 2.01)	84.3	0.02	0.047	(0.01, 0.43)	IV
	Antisaccade error rates	11	358	SMD	0.45 (0.24, 0.67)	4.5×10^{-05}	(-0.08, 0.99)	36.5	0.21	0.014	(0.01, 0.43)	IV
	Stage 2 sleep	6	111	SMD	−0.38 (-0.64, -0.12)	0.004	(-0.74, -0.01)	0	0.75	1	(-0.79, -0.08)	IV
	Sleep efficiency	6	111	SMD	−0.37 (-0.73, -0.02)	0.037	(-1.23, 0.48)	32.4	0.39	1	(-1.02, -0.29)	IV
Neuroimaging	FA anterior limb internal capsule	3	32	SMD	0.88 (0.37, 1.38)	0.0007	(-2.41, 4.16)	0	0.51	0.58	(0.07, 1.52)	IV
	FA genu corpus callosum	3	45	SMD	−0.56 (-1.1, -0.02)	0.042	(-5.56, 4.44)	34.7	0.87	0.19	(-1.65, -0.35)	IV

Note: Classes of evidence are classified into I, convincing; II, highly suggestive; III, suggestive; IV, weak. Only biomarkers including 3 or more individual studies are shown. * Positive effect sizes indicate increased values in individuals with obsessive-compulsive disorder, in comparison to healthy controls. Negative effect sizes indicate decreased values in individuals with obsessive-compulsive disorder, in comparison to healthy controls. Note that because ERN is negative, a negative effect size indicates increased ERN.

Abbreviations: ABGA, anti-basal ganglia antibodies; CI, confidence interval; ERN, Error-related negativity; ES, effect size; ESB, excess significance bias; I^2, heterogeneity; LS, largest study; OR, odds ratio; SMD, standardized mean differences; PI, prediction interval; SSE, small study effect.

granularity and we must note that there are meaningful differences in the methods used to quantify and interpret most of the biomarkers included in our review. Third, since only 10% of the studied biomarkers included samples larger than 1000 individuals, a major criteria of class I evidence, we repeated the analyses by removing the n>1000 cases criterion. Results from these additional analyses should be interpreted with caution since they are based on relatively limited observations.

In sum, we identified 27 biomarkers that showed convincing (n = 1), highly suggestive (n = 4), suggestive (n = 3) or weak (n = 19) evidence of association with OCD. The biomarkers with the strongest evidence were neurocognitive variables. Based on our results, use of medication for OCD is likely to be an important confounder in the search for biomarkers and should be further explored. The fact that all the identified biomarkers show little specificity or incremental validity limits their diagnostic utility. It is still theoretically possible that a combination of some of the biomarkers identified here, or a combination of biomarkers plus additional information (e.g., clinical data), could have diagnostic validity in OCD. Nevertheless, no combinations of biomarkers or of biomarkers plus clinical data have yet been found that hold sufficient specificity to correctly classify or diagnose any psychiatric disorder. A more promising avenue for future biomarker research in OCD might be the prediction of clinical outcomes rather than diagnosis.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.08.008.

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