JOURNAL OF PSYCHOPATHOLOGY 2024;30:8-19
DOI: 10.36148/2284-0249-N452

Review

The Compulsive Obsessive Disorder: many clues, still little evidence

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SUMMARY

The Obsessive-Compulsive Disorder (OCD) is a debilitating psychiatric condition characterized by intrusive, distressing obsessions and repetitive, ritualistic compulsions. Despite its relatively high prevalence, elucidating its pathogenesis remains a significant challenge. The present study aims to review the current understanding of OCD's pathophysiological mechanisms focusing on the role of cortical and subcortical structures and their connections, proposing that obsessions may be a consequence, rather than a trigger, of compulsions. For this reason, the syndrome might be rebadged as the Compulsive Obsessive Disorder (COD). This will be explored, from a neurocognitive point of view, as an imbalance between goal-directed and habitual behaviour. Moreover, the issue of refractoriness will be addressed – with emphasis on the complex mechanisms that underlie refractory OCD and the cruciality of developing targeted interventions. This review discusses the potential contributors to treatment resistance, including neurobiological alterations, comorbid psychiatric conditions and the duration of untreated illness, a potential modifiable parameter which influences clinical outcomes. Innovative interventions offer hope for individuals with refractory OCD. The evolving landscape of OCD treatment will be overviewed, ranging from pharmacology to neurostimulation and novel psychotherapeutic techniques tailored to refractory cases which have shown promise in ameliorating symptoms when traditional approaches fall short.

Key words: Obsessive Compulsive Disorder, habit, goal directs behaviour, pathophysiology, refractoriness, duration of untreated illness, glutamate

Towards a new paradigm?

The Obsessive Compulsive Disorder (OCD) is the epicenter of a spectrum of related conditions identified as obsessive-compulsive spectrum disorders (OCSDs) sharing obsessions and compulsive behaviours as their defining characteristics. Currently, it is estimated that lifetime prevalence of OCD is 2.3%, however, more than 25% of the general population has reported obsessions or compulsions at some point in their lives, suggesting that the OCSDs, including subclinical OCD, may be more prevalent than previously expected [1].

Obsessions are intrusive and repetitive thoughts, images, impulses or urges that are persistent and unwanted, and are commonly associated with anxiety. Compulsions are repetitive behaviors or mental acts that the subject feels driven to perform to achieve a sense of 'completeness' [2]. These clinical features are associated with modifications of normal neurocognitive mechanisms moderating behavioural inhibition (motor inhibition, cognitive inflexibility), reversal learning and habit formation (shift from goal-directed to habitual responding) with fronto-striatal neural connections that contribute toward obsessive compulsive symptoms in both OCD and OCSD [3].

The knowledge about pathophysiological and neurobiological basis of OCD is increasing and over the last years we are witnessing a revolution in OCD's phenomenological paradigm that sets compulsions as

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How to cite this article: Maraone A, Panfili M, Wilson Jones G, et al. The Compulsive Obsessive Disorder: many clues, still little evidence. Journal of Psychopathology 2024;30:8-19. https://doi.org/10.36148/2284-0249-N452

behaviors performed to reduce the anxiety evoked by obsessions [4]. Moving away from the traditional 'anxiety-based' theory, which views OCD as a disorder driven by pathological sensitivity and anxiety-inducing suggestions that may arise from obsessions, the role of 'compulsivity' has reached a greater significance: compulsions are designed to reduce harm, but they can also lead to a profound experience of 'lack of control' [5]. The fact that compulsions themselves may induce anxiety prompts the idea that OCD could even be rebadged as "Compulsive Obsessive Disorder" ("COD") calling into question the causal relationship between obsessive and compulsive symptoms [6].

Gillian and colleagues formed the opinion that compulsions are a manifestation of a disarray in the neurobiological balance between goal directed action and automatic habits and that excessive habit learning and deficits in goal-directed control systems are an adequate model of compulsive behaviour [7]. Compulsive-like habits in OCD seems to be valence independent and obsession independent, therefore compulsions are not epiphenomenal but rather a core component of OCD. They also argue that obsessions might arise because of compulsive behaviour: OCD patiens are poorly capable of reverse inference, wrongly deducing that if they felt driven to perform an act of avoidance they must have something to fear [8].

From this point of view compulsions seem to have a primary role in OCD: they are identified as repetitive behaviors pathologically invested with reward values and as the substantial perseverative phenomena, while obsessions are eventually seen as consequential cognitive conceptions defined by patients to assimilate the intrusive behavioral schedules back in the self [9].

Compulsions might emerge from habit dysregulation and excessive habit formation, which may be heighten by anxiety or stress [10], and they could lead to a subjective post hoc rationalization that could in turn further sustain obsessions. Proposing that the intrusive thoughts (obsessions) characteristic of OCD may be a consequence, rather than an instigator, of compulsive behaviour in these patients [8].

The pathophysiology of OCD

The neurophysiopathology of OCD is not yet consistently determined. Findings from several structural and functional neuroimaging studies agree on the involvement of cortico-fronto-striatal circuits and their limbic connections in the pathophysiology of OCD [11-13]. Cortico-striatal-thalamo-cortical (CSTC) circuits are responsible for regulating fundamental cognitive and motor functions, including decision-making, habit learning and goal directed behaviour based on reinforcement and reward. Physiologically, synchronization and oscillations in different domains of this pathway play a crucial role in the successful execution of habitual actions [14].

From a functional point of view, different prefrontal cortical regions serve different neurocognitive functions [15]. The orbitofrontal cortex (OFC), is implied in decision making, behavioural planning and extinction recall integrating affective implications and warning some types of reward [16]. The anterior cingulate cortex (ACC), and its connections with the limbic system, are involved in motivation, attention, error detection, fear conditioning, inhibitory control and action planning [17]. The dorsolateral prefrontal cortex (dlPFC) is believed to mediate executive functions and working memory [18]. The striatum's function is to perform an information processing, contributing to higher-order cognitive functions such as thought inhibition and memory retrieval g [19]. Integrating inputs arriving from the cortex and sending efferences to the thalamus through direct and indirect pathways, subcortical structures could reduce "sparse cortical information" reinforcing learning rules and signals [20]

Two main models of OCD pathophysiology have been identified so far: a "cortical model" [21,22] that attributes OCD to a prefrontal cortex dysfunction and a "subcortical model" [23], centered on basal ganglia dysfunction and on their cortical connections.

The first model suggests an imbalance between the activity of different prefrontal regions: dlPFC hypoactivity, ACC hyperactivity and OFC hyperactivity seem to be responsible for the impaired action-outcome monitoring, lack of sense of completeness, egodystonic beahvioural commands and enhanced error-related signals [6,22,24,25]. According to this model an unsuccessful sensory and limbic feedback to the error signal provides behavioural perseveration, verification, stereotyped repetition, ruminations and pathological doubt, attempting to reduce uncertainty typical of OCD [26,27]. The involvement of the limbic system, especially the amygdala and the nucleus accumbens, modulated by reciprocal connections with the ACC and OFC, appears to play an important role in the apprehension and the anxiety characteristic of OCD [20].

The second model, proposed by Modell in 1989 [23], is focused on the pallidal dysfunction to inhibit mediodorsal thalamic nucleus and its connections to the prefrontal cortex. An abnormal reverberation of CSTC circuits is thought to contribute to the development of repetitive and intrusive thoughts, as well as compulsive behaviours. These circuits may contribute to rigid thoughts and behaviors in turn serving to promulgate OCD symptoms [28]. Recent reviews underline the role of CSTC in the pathophysiology of OCD and how the dysfunction of monoamines in these circuits may underpin symptom [29].

The CSTC circuit is made up of direct and indirect path-

ways: the direct pathway is mainly excitatory and promotes behaviour, while the indirect pathway is largely inhibitory and restricts behaviour. It is hypothesized that OCD is associated with excessive activity of the direct pathway, due to a primary a dysfunction of the indirect pathway, resulting in reduced inhibition of the thalamus. Consequently, the thalamus becomes disinhibited and increases its excitatory influence on the cortex, leading to the clinical features of OCD [30]. CTSC dysfunction may derive from an unbalance between the midbrain afferents to the striatum: the serotonergic inhibitory ones from the raphe nuclei and the dopaminergic excitatory ones coming from the ventral tegmental area [20,26]. From a neurochemical viewpoint, this could also provide a therapeutic rationale for the pharmacological strategies to treat OCD [31].

More recently, authors have tended to avoid the dichotomy between cortical and subcortical models [28,32-34] focusing on the CSTC loops and their parallel and interconnected nature. The hyperactivity of orbitofrontal corticobasal circuits gets worse due to the hypoactivity of dlPFC and its projections to neurons in the striatum (that in normal conditions should enhance the indirect pathway, participating in the interruption of automatic behaviours). The consequence is that direct pathway becomes predominant maintaining the hyperactivity of the OFC and ACC [32], activating behaviours and impairing cognitive flexibility, sustaining the compulsive dimension of OCD [28].

Milad and Rauch [34] point out that the cortico-striato-thalamo-cortical circuits can be functionally divided into three broad networks involving different domains:

- The affective circuit (Anterior cingulate cortex (ACC)/ Ventromedial prefrontal cortex (vmPFC) - Nucleus Accumbens - Thalamus): responsible for affective and reward processing.
- The dorsal cognitive circuit (dorsolateral prefrontal cortex (dlPFC) - dorsal caudate - thalamus): responsible for working memory and executive functions.
- The ventral cognitive circuit (orbitofrontal cortex (OFC)/ - putamen - thalamus): responsible for motor programming and response inhibition.

Impaired neural activity among these circuits is implicated in the maintenance of automatic and stereotyped behavioural and cognitive patterns characteristic of OCD, explaining the inefficiency in suppressing automatic behaviours and intrusive thoughts. Some evidence also suggests a role of the Pre-Supplementary Motor Area (pre-SMA) and of the Supplementary Motor Area (SMA) in the inhibitory control impairment perceived in OCD patients, which could be linked to their lack of control over compulsions [35-37].

Regarding the lack of control, Gillian et al., proposed that compulsions are the core feature of the disorder and obsessions are a troublesome by-product. They suggest that the feeling of being driven to enact compulsions may derive from the impairment of the goal-directed control (which protects against habits) relaying on the integrity of the caudate nucleus and medial orbitofrontal cortex [38]. Obsessions may be a consequence of dysfunction in fear conditioning processes [8], impairment in extinction recall are tangible in OCD, and the neural correlates of this cognitive functions overlaps on regions thought to be involved in the pathophysiology of the disorder [38].

Literature-based meta-analyses suggest that a reduction in white and grey matter ACC volume, medial frontal gyrus and OFC and a relative age-related preservation of grey matter volume in the putamen, insula, and OFC, combined with a more rapid age-related decrease of volume in bilateral temporal cortex that may result from impaired neuroplasticity associated with cognitive dysfunction and chronic compulsive behaviour [36]. Fouche et al. confirm the previous findings underlining lower cortical thickness (but not surface area) in ventrolateral and dorsomedial prefrontal cortex, as well as greater age-related decline in parietal-temporal cortical thickness. Overall hippocampal volume was found to be smaller in OCD [39].

Recent findings from the ENIGMA-OCD working group also demonstrate the implication of the parietal cortex in both adults and children with OCD. They highlight lower cortical thickness of the inferior parietal cortex [40], indicating possible neurodevelopmental abnormalities resulting in thinner parietal cortex in childhood that persist into adulthood.

The parietal cortex is involved in the processing of cognitive functions that are impaired in OCD such as set shifting, attention, planning and response inhibition [41], reflecting a deficiency of cognitive flexibility probably related to the repetitive nature of OCD symptoms and behaviours [42]. The same group has also studied subcortical structures, finding that adult patients with OCD had significantly larger pallidum volumes and smaller hippocampal volumes compared to healthy subjects, whereas pediatric patients had larger thalamic volumes, suggesting the potential importance of neurodevelopmental alterations in OCD [43].

The dysfunctional habit learning and goal-directed systems

The word compulsion derives from the latin term “compellere”, meaning “to drive” or “to force”. Over time, the meaning of the word has evolved to include the sense of an irresistible urge or impulse to do something, often against one’s will. Compulsions have been recognized in various forms throughout history, with early descrip-

tions of compulsive behaviours in ancient texts from different cultuRes In modern psychiatry, compulsivity is a term that can be used to describe the repetitive and uncontrollable nature of a broad range of maladaptive behaviours such as gambling, binge eating, tics in Tourette's syndrome and compulsions in OCD [8]. Yin et al interestingly state "actions become compulsive when they are no longer controlled by their consequences" [44], effectively, in the case of compulsive behaviours, the link between behaviour and its consequences becomes distorted. Individuals with compulsions feel forced to engage in repetitive actions or rituals, even if they don't result in desirable outcomes. Moreover, despite the total lack of positive reinforcement, these behaviours persist and may even increase in frequency and intensity.

But what is the neural basis of compulsivity? Many studies have explored this hypothesis on the quest to pinpoint the exact neural basis of pathological habits. In neurocognitive terms, compulsivity has been described as the manifestation of an imbalance between the brain's habit-learning and goal directed systems [45]. Therefore, to tackle this question, it is important to introduce these two systems that are the cognitive processes which determine decision making, working in tandem to achieve normal behaviour.

A habit can be defined as a pattern of behaviour or routine that originates spontaneously but is subsequently repeated quasi-automatically due to prior experience. It is based on the concept that the brain creates links between cues, such as a time of day or a location, and specific behaviours. These links are reinforced each time the behaviour is repeated, thus leading to the formation of a habit. The main neuroanatomical pathway involved in habit formation is the corticostriatal sensorimotor loop that links the sensorimotor cortex to the dorsolateral striatum [46].

The goal directed system, on the other hand, is involved in the selection and execution of actions that are necessary to achieve a specific goal or outcome. It is opposed to the habit learning system as it requires greater cognitive engagement – it is less reflexive and automated because it is performed based on a desired outcome. The main neuroanatomical pathway involved in this system is encoded in the corticostriatal associative loop linking the prefrontal and orbitofrontal cortex with the dorsomedial striatum [46].

During the last decade researchers in the neurocognitive field have hypothesized that OCD symptomatology could be the result of an imbalance between the habitual versus the goal directed neural systems as normal behaviour ideally relies on the flexible integration of both [47]. Emerging evidence converges in the understanding that when the when the habitual system supersedes the goal-directed system this could give rise to OCD, in fact, recent experiments have demonstrated that OCD sufferers show an impairment in goal-directed behaviour and an overreliance on habits [7]. Experimentally, this has been tested using an outcome devaluation-based task probing whether actions are habitual or goal- directed. It was observed that OCD patients were less likely than healthy participants to respond to devaluation by modulating their performance, suggesting an overreliance on habits. Moreover, the authors noted that OCD patients demonstrated decreased understanding of the consequentiality between actions and outcomes. However, some authors that have not found the same results asserting that habitual model is still incomplete, as it does not explain how the repetitive idiosyncratic behavioural rituals are maintained in OCD stating that more studies are required [48].

Gillian et al., advance a paradigm in which compulsions are the core feature of the disorder and obsessions are a troublesome by-product – effectively challenging the 'cognitive' status quo by placing compulsions as the primum movens of OCD and obsessions as consequential, continuing the debate on whether obsessions cause compulsions or vice versa.

Refractoriness as an indicator of insufficient treatment options

Refractoriness refers to the lack of response to conventional care, the term can be used to describe a disease which does not improve despite receiving appropriate treatment according to established guidelines. When a disease displays refractoriness, it serves as a signal to healthcare professionals that novel approaches may be necessary, prompting the re-evaluation of existing treatment and the exploration of new therapeutic interventions, whilst calling for a better understanding of the underlying disease mechanisms.

In the realm of OCD, refractoriness represents a challenge as a significant number of patients do not sufficiently benefit from available treatment. Although controlled trials have shown that selective serotonin reuptake inhibitors (SSRIs) have efficacy in treating OCD, a substantial proportion of patients, ranging from 40% to 60%, do not show a satisfactory response, leading them to experience considerable disability and morbidity [49].

But how exactly is response to treatment measured? This is another factor contributing to the complexity of the challenge – historically there isn't a precise definition of response and non-response. This, coupled with the coexistence of terms which are used interchangeably such as "non-responder", "treatment-resistant" and "treatment-refractory" [49], has lead studies investigating "non-response" to lack generalizability due to the absence of a clear operational definition [50]. For such rea-

son, Pallanti et al., proposed a nosological system of classification based on "stages of response", whereas Piccinelli et al., defined treatment refractory OCD as the absence of improvement after undergoing three to six months of treatment with three different antidepressant medications, and attempting at least two additional trials with atypical antipsychotics as augmentation strategies [51]. Presently, the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [52] provides a standardized measure to assess the seriousness of symptoms, monitor treatment progress, and compare results across different studies. Complete treatment response has been defined as a decrease of at least 35% in Y-BOCS score, while a partial response is considered a reduction between 25% and 35%. A lack of response is characterized by a decrease of less than 25% in Y-BOCS score [53].

What exactly causes patients to display refractoriness remains elusive, however, some clinical features are more highly correlated with resistance to treatment. For instance, factors such as the presence of more severe symptoms, an early age of onset, a longer duration of illness, and a longer duration of untreated illness have been linked to a diminished response to pharmacotherapy with SRIs. Interestingly, also the content of the obsessions can be a predictor of treatment response, in fact, those with contamination or cleaning obsessions are less likely to respond compared to those with sexual, religious, or harm-based obsessions [54].

The treatment of OCD typically follows a stepwise approach; first line treatment is represented by SSRIs and/or cognitive behavioural therapy (CBT) with exposure and response prevention (E/RP). NICE guidelines recommend combining treatments for adults experiencing severe functional impairment due to their OCD symptoms or for those who do not respond adequately to either an SSRI alone within 12 weeks or CBT (including ERP) alone after more than 10 therapist hours per patient [55]. If this fails, the implementation of second-line treatments becomes necessary. This is represented by different psychopharmacological approaches, such as the tricyclic antidepressant clomipramine, and serotonin and norepinephrine reuptake inhibitors (SNRIs). Additionally, there are a plethora of add on treatments and strategies, such as antidepressant combination (clomipramine in combination with an SSRI), switch to intravenous administration, antipsychotics, antiepileptics and glutamatergic agents [56]. Finally, there are interventional techniques, such as deep brain stimulation (DBS), transcranial magnetic stimulation (TMS) and stereotactic ablation [30,57].

For over fifty years, stereotactic neurosurgery has been a treatment option for individuals with severe and debilitating OCD, who have failed to respond adequately to extensive pharmacological and psychological interventions [58]. Recently, McLaughlin et al., have conducted statistical analysis investigating what is thought to be one the most effective neurosurgical options: gamma knife capsulotomy (GKC). A GKC involves creating lesions in the white matter pathways located in the anterior limb of the internal capsule (ALIC) which connect the prefrontal cortex to the thalamus and basal ganglia. The therapeutic rationale is rooted in the interruption of abnormal activity observed within the prefrontal-subcortical circuitry demonstrated by neuroimaging studies [59]. The observed responder rate in their analysis was 69%, however, this kind of intervention is not free from side effects, which range from mild, such as headache, hypomania, weight gain, to severe, such as radiation-induced frontal lobe edema, which in turn is associated with apathy, fatigue, disinhibition, memory loss, and delirium.

Alternatively, another interventional technique that has recently been approved for intractable severe OCD is neurostimulation, which has emerged as a reversible option with more potential to target specific networks compared to neurosurgery [60]. Neurostimulation involves the modification of neural activity through the application of electrical stimulation to precise areas of the brain. This can be achieved using invasive techniques like deep brain (DBS), which utilizes microelectrodes, or non-invasive methods such as transcranial magnetic stimulation (TMS). Also Gamma-knife Ventral Capsulotomy (GVC) seems to be an effective radiosurgical procedure for many treatment-refractory OCD patients [61].

Beyond serotonin: the limits of serotonergic drugs in OCD treatment

As discussed in the previous section, it is well known that OCD is a complex multifactorial disease with varied aetiology. When talking about the neurotransmitters involved, serotonin emerges unanimously as the most cited, in fact, OCD has long been regarded as a disorder of serotonergic dysfunction [62]. The 'serotonin hypothesis' was first formulated in 1975 [63], upon the observation that clomipramine (a robust serotonin transporter inhibitor) had an anti-obsessional action. This neurobiological theory suggests that abnormalities in serotonergic neurotransmission underlie OCD symptomatology. More studies confirmed that clomipramine demonstrated greater efficacy in treating OCD when compared to desipramine, a TCA primarily targeting norepinephrine reuptake [64]. Later, with the development of newer SSRIs like fluoxetine, fluvoxamine and sertraline, the greater efficacy of serotonergic agents compared to TCAs was confirmed by large randomized clinical trials (RCTs) - establishing them as the primary choice for the treatment of OCD. The pharmacological observation of SRI's and SSRI's efficacy

led researchers to hypothesize that the malfunction in the brain's serotonergic systems and serotonin deficiency could be the underlying cause of OCD. In turn, this led to a substantial number of studies performed in the 80s and 90s that tried to elucidate serotonin function in OCD; however, to this day concrete evidence for serotonergic abnormalities remains elusive [30].

Of course, SRIs have a broad spectrum of action in psychiatric conditions, including depression and anxiety disorders, so what makes them so specific to OCD? The key distinction is that SRIs are specifically effective in treating OCD, whereas other antidepressants that do not strongly bind to the serotonin transporter are generally ineffective.

Neuroimaging studies have aimed to identify potential brain alterations observed in individuals with OCD characterizing the neural circuitry underlying the disease, pointing to a dysfunction in CSTC loop. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies have delved into distinct aspects of serotonergic neurotransmission within CSTC circuitry, measuring 5-HT transporter (5-HTT) and receptor binding using specific tracers, however, due to considerable variability in the results, a consensus regarding the exact pathomechanism of serotonin has not yet been reached [65]. Nonetheless, these studies do provide evidence of regional 5-HT abnormalities, such as decreased 5-HT transporter availability within thalamus and midbrain regions, increased 5-HT2A receptor availability within caudate and decreased 5-HT2A receptor availability in prefrontal regions [66]. Interestingly, more recently, Lissemore et al. [65], have used PET and α-[11C] methyl-L-tryptophan tracer to investigate alterations in brain regional serotonin synthesis capacity in OCD patients after undergoing either CBT or SSRI treatment, concluding that the alleviation of OCD symptoms might be linked to an increase in serotonergic activity and more specifically to whole-brain 5-HT synthesis capacity.

It is also important to underline the concept that it is not the sole neurotransmitter involved in OCD. While the serotoninergic system has long been implicated in OCD pathophysiology, research has also unveiled the involvement of other neurotransmitter systems, involving dopamine, glutamate, and gamma-aminobutyric acid (GABA). This expanding understanding challenges the traditional monoamine hypothesis, highlighting the intricate interplay of various neurochemical pathways and calling for an integrated neurotransmitter model of OCD [66]. The notion that OCD may arise from the dysregulation in a network of interconnected neurotransmitter systems rather than a specific dysregulation in the serotonergic system offers a rationale to why in a substantial proportion SRI and SSRI treatments do not achieve a satisfactory response.

The current challenge in OCD research lies in translating cognitive neuroscience and neuroimaging discoveries into effective treatments that address the neurobiological changes underlying symptoms - integrating a multi-neurotransmitter perspective opens potential avenues for pharmacological interventions beyond traditional serotonergic drugs. Whereas serotoninergic drugs have been widely used in treating OCD it should be noted that they are not universally effective. In fact, about 40% patients doesn't show symptom improvement to a treatment with a first-line SSRI [67]. This has led to the ideation and actualization of the various augmentation and modification strategies discussed in the previous section concerning refractoriness. However, the problem of refractoriness and the limits of serotonergic agents are still central topics surrounding the discourse regarding OCD treatment and management. For this reason, recently, researchers have begun to more thoroughly explore the therapeutic possibilities of tackling pathways that don't directly involve serotonin. Importantly, the glutamatergic system is receiving growing attention, as will be discussed in the following section.

Antiglutamatergic agents

During the last decades, different studies addressed the role of the glutamatergic system in obsessive compulsive pathology [68]. Glutamate is the principal neurotransmitter involved in CSTC models of OCD and appears to be implicated in its pathogenesis. Some authors suggested the presence of a glutamatergic signal dysregulation within the CSTC loop, with a reduction in glutamate concentration in the anterior cingulate cortex and an increase in the striatum and OFC [69]. CSTC loop hyperactivity implies a high level of glutamate and a consequent dysregulation of GABAergic transmission in the cortical-striatal pathways [62,70]. Glutamate receptors (ionotropic and metabotropic) are in the candidate brain circuits of OCD and seem to be involved in habit learning. Genetic studies identified a polymorphism encoding the N-methyl-D-aspartic acid receptor (NMDAR) in families with OCD [71]. Additionally, an increase in glutamate in the cerebrospinal fluid of OCD patients compared to controls has been recorded[1]. Biria M. and collegues [72], in a study using 7-Tesla proton magnetic resonance spectroscopy (H-MRS), detected an altered excitatory/inhibitory balance between the neurometabolites, Glutamate and GABA, in anterior cingulate cortex and supplementary motor area demonstrated that compulsivity and clinical compulsive symptoms are related to neurochemical imbalance in these regions.

In some cases, glutamate can act as a neurotoxin, its excess or dysregulation coupled with receptor hyperactivity can lead to neurotoxicity [73]. This aligns clinically with the imperative of early intervention, prolonged

glutamatergic dysregulation corresponds to an escalation in neurotoxic damage, resulting in heightened disease chronicity and concomitant treatment challenges, thereby contributing to refractoriness [74]. If the hypothesis that glutamate related neurotoxicity is one of the drivers of OCD pathogenesis is confirmed, tackling this neurotransmitter system may represent a stepping-stone for novel treatment strategies. Glutamate-modulating drugs have been proposed as candidates for the augmentation strategy of OCD treatment. For instance, randomized controlled trials with memantine, riluzole, *N*-acetylcysteine (NAC) or glycine reported promising results [75,76]. However, the presence of contradictory findings signals the need for more randomized placebo-controlled trials on larger population samples [77]. In the hypothesis of glutamate-neurotoxicity the early intervention for OCD will be the most important variable and the role of glutamate-modulating drugs may represent an auspicious treatment.

Duration of untreated illness and the patient's perspective

Typically manifesting early in life, OCD follows a chronic and debilitating course [78]. Almost 76% of the cases have early onset and there are two peaks of incidence: one in the pre-adolescent period (mean age 11 years) and one in early adulthood (mean age 23 years) [79]. The burden of OCD is influenced significantly by delayed initiation or lack of intervention. Patients may spend almost half the duration of their illness either receiving ineffective treatment or receiving no treatment at all [80,81]. Several studies have highlighted that SSRIs, clomipramine, CBT or a combination of these are evidence-based treatments for OCD [82]. Many authors agree that the longer OCD is left untreated, the higher functional impairment and clinical comorbidity [83-85]. The duration of untreated illness (DUI) is defined as the period between the onset of symptomatology and the administration of the first appropriate pharmacological treatment at the correct dosage and for adequate duration [86]. In OCD the DUI is one of the longest for major psychiatric disorders ranging between seven and ten years [83,84,87,88].

Micali et al. found that in children and adolescents "technical treatment failure" constitutes a common cause of refractoriness and a predictor of disease persistence [89]. In terms of treatment outcomes some authors also found that a DUI above 24 months was linked to a worse response to pharmacological treatment [84,86]. A longer DUI could also contribute to the disorder burden growth due to the associated medical or psychiatric comorbidities [90], critical in increasing severity, chronicity, and refractoriness of the disorder with consequent suffering both for the patients themselves and for families [91]. Moreover, longer DUI is also associated with increased family accommodation of symptoms, which is in turn related to treatment resistance and to the impairment of family relationships [92] impacting the quality of life (QOL) and increasing the risk of comorbid depression and anxiety disorders [93]. Van Oudheusen and colleagues observed the presence of depressive symptoms in 56.6% of OCD patients. This association was found in both infancy and adulthood [94]. The presence of depressive symptoms seems to negatively influence treatment outcome [95]. Patients with OCD, similarly to those affected by schizophrenia, show a poorer QOL than healthy controls, especially in social domains, demonstrating substantial emotional and psychological difficulties [96]

Regarding DUI length, Viswanath et al found that family history of OCD is associated with a longer DUI, earlier age at onset, greater comorbidity (especially depression and anxiety) and worse treatment response [80]. Dell'Osso et al. found that DUI duration and severity of illness resulted significantly higher in the aggressive/checking subgroup [81]. Some of the factors implied in DUI duration are stigma related attitude; secretiveness [88], poor access to psychiatric services and the belief that OCD symptoms do not represent illness [87] are associated with a longer DUI. Often, due to the ego dystonic features and poor insight typical of the disorder, OCD sufferers may be reluctant to seek specialized medical assistance, thus extending intervention time, lengthening the DUI and worsening the prognosis. It is important to underline that to optimize intervention strategies and to improve clinical outcomes, the DUI represents a key variable: early diagnosis, increasing recognition of obsessions and compulsions, evidence-based practice, a link between child and adult psychiatrists could reduce the latency between the onset and the adequate treatment [97].

Cognitive behavioural therapy techniques for refractoriness

CBT is a widely recognized and effective psychological treatment for OCD. Over time, CBT has evolved into an amalgamation of methods designed to alter both thought processes and behaviours. Classically, the primary focus is addressing erroneous thoughts and beliefs, whereas in ERP, individuals are exposed to stimuli that trigger their obsessions and are guided through diverse techniques to abstain from enacting the compulsions [98]. CBT can be carried out as a monotherapy or combined with pharmaceuticals [99]; the combinatory approach has shown higher effectiveness compared to either medication or CBT alone in numerous research studies [100]. The American Psychiatry Association (APA) suggests combined therapy for patients with severe OCD, sufferers of comorbid conditions such as anxiety and depression and

for patients who prefer to restrict the duration of pharmacological treatment. To address patients who are not responsive to standard treatment, it is essential to contemplate a combined approach as well as methods aimed at augmenting the effectiveness of CBT-ERP. Overall, only about 50% to 60% of patients who successfully undergo ERP treatment demonstrate alleviation of symptoms; therefore, alternative, or novel psychological approaches are currently being explored [101]. Moreover Wheaton and Gallina [102], illustrated how depression symptoms can interfere in ERP for OCD and how treatment could be modified to address these patterns. They suggested a sequential treatment (first treating the depression) rather than a parallel treatment that incorporate treatment for both OCD and depression together.

There are several methods aimed at augmenting the effectiveness of CBT-ERP for refractory cases. For instance, technology-assisted therapies, referring to the integration of digital tools and technology into the therapeutic process. Some individuals may benefit from the use of digital tools such as video conferencing, internet-based treatments, and virtual reality (VR) smartphone apps designed to complement CBT-ERP. For instance, internet-based treatments and apps are useful in order to improve access to CBT-ERP in countries lacking clinical support.

Family and couple-based interventions have emerged as a valid adjunct to CBT-ERP. Involving family members, partners or participating in group therapy sessions with others who have OCD can provide valuable support and a sense of community, improve symptom reduction and decrease dropouts. In a recent metanalysis, it was observed that patients partaking in family therapy experienced reduced depression and anxiety together with enhanced functional well-being [103]. Additionally, family members expressed greater relationship satisfaction resulting in a better family dynamic and harmony.

An alternative method to address refractoriness could be represented by mindfulness-based and acceptance-based programmes. So far, CBT-ERP is considered as the as the 'gold standard' treatment for OCD, however, for some patients who experience refusal and drop out the problem could be the intrinsically aversive and triggering nature of the intervention, the repeated exposure to the feared stimuli could be perceived as particularly challenging [104]. The readiness to encounter uncomfortable thoughts, emotions, and physical sensations in a receptive, accepting, and non-critical manner seems to be an indicator of effective ERP [105]. As a result, methods that foster acceptance of distressing thoughts and emotions may help overcome the shortcomings of traditional treatment. For such reason, incorporating mindfulness-based techniques and acceptance strategies can help individuals tolerate the distress and uncertainty associated with OCD. Moreover, mindfulness exercises can teach individuals to observe their thoughts and feelings without judgment and to let go of the need to control them.

Metacognitive therapy (MCT), is a psychological therapeutic approach that focuses on modifying a person's patterns of thinking about their thoughts and cognitive processes, rather than directly challenging their content. MCT has been recently implemented in the treatment of OCD, based on the hypothesis that it is the belief about the meaning and significance of obsessive thoughts and compulsions rather than the obsessions and compulsions themselves that are that are crucial for the development of OCD [106]. Recently, a handful of studies have suggested that MCT may be even more effective than CBT-ERP, especially because it could be better tolerated by patients, as it doesn't involve extended exposure to anxiety-inducing stimuli. However, evidence is still sparse and requires to be verified by a RCT.

Conclusion

In this review, we highlighted the new findings rising from neuropathophysiology of OCD. More, we collected converging evidences on the primary role of compulsions rather than obsession on the etiology of OCD. Obviously is still untimely to redefine the syndrome as COD, but this is not a simple academic provocation. However, the new data coming from neurophysiopathology, neuroimaging, pharmacological and CBT therapy limits posit several clues on the traditional explanation of OCD.

Conflict of interest statement

The Authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

A. Maraone and M. Pasquini contributed to the conception and design of the research; M. Panfili, G. Wilson Jones and I. Pinucci contributed to the acquisition and analysis of the data; A. Maraone M. Panfili and M. Pasquini contributed to the interpretation of the data; A. Maraone, M. Panfili and G. Wilson Jones drafted the manuscript; M. Pasquini collaborated as a consultant in every phase of the research; AM supervised the final version of the manuscript; M. Pasquini and M. Biondi supervised in each phase of the research and contributed to the final version of the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Ethical consideration

Not applicable.

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