

Role of Glutamatergic System in Obsessive-Compulsive Disorder with Possible Therapeutic Implications

Authors

Přemysl Vlček^{1, 2}, Jakub Polák¹, Martin Brunovský^{1, 2}, Jiří Horáček^{1, 2}

Affiliations

- 1 National Institute of Mental Health, Topolová 748, 250 67 Klecany, Czech Republic
- 2 Third Faculty of Medicine, Charles University, Ruská 87, 100 00 Prague 10, Czech Republic

Key words

amygdala-hippocampus complex, checking obsession, CSTC circuitry, glutamatergic agent, OCD, temporal lobe

received 26.06.2017

revised 07.08.2017

accepted 11.08.2017

Bibliography

DOI <https://doi.org/10.1055/s-0043-118665>

Published online: 26.9.2017

Pharmacopsychiatry 2018; 51: 229–242

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ISSN 0176-3679

Correspondence

Přemysl Vlček

National Institute of Mental Health

Applied Brain Electroencephalography

Topolova 748

25067, Klecany

Czech Republic

premysl.vlcek@nudz.cz

ABSTRACT

Obsessive-compulsive disorder (OCD) is a chronic psychiatric illness and 1 of the most common anxiety disorders with the prevalence of 3%. Although its pathogenesis remains unclear, the traditional model focused on alternations in the serotonin system. Selective serotonin reuptake inhibitors provide the most effective treatment; however, as much as 40–60% of patients do not respond to antidepressants therapy. Thus, attention has shifted towards other neurotransmitter systems and related neuroanatomical structures. Recently, there is extensive evidence showing a key role of glutamate pathways abnormalities within the cortico-striatal-thalamo-cortical circuitry and temporal lobes in OCD pathogenesis. In this review, we link together the existent neuroanatomical, neurophysiological, and neuropsychological evidence to argue for potential benefits of adjuvant treatment with glutamatergic agents, especially memantine. By a targeted de-excitation effect on the glutamatergic system in the temporal lobes and connected brain regions, memantine might further alleviate OCD symptoms. This effect should be even more pronounced in certain subtypes of patients with specific cognitive deficits and maladaptive compensatory memory processes (e.g., checkers).

Introduction

Obsessive-compulsive disorder (OCD) is a common and debilitating psychiatric illness with the high prevalence of 1–3%, which makes it the fourth most common mental disorder [1, 2]. Apart from the public health impact, it also presents a considerable economic burden; while €2.72 billion were estimated to be spent in 2010 for the treatment and management of OCD in Europe [3], data from the United States show striking \$14.6 billion spent in 1990 [4]. The most effective first-line treatment (up to 70% of cases) involves cognitive-behavioral therapy (CBT) in combination with pharmacological treatment [5]. Especially serotonergic agents including selective serotonin reuptake inhibitors (SSRIs) and clomipramine have provided the mainstay of OCD medication management for decades and are still considered the primary pharmacological treatment avenue [6]. Despite the efficacy of serotoner-

gic compounds in the treatment of OCD, treatment-resistant symptoms remaining in 40–60% of patients present a clinical problem [7]. In this case, a medication switch for another SSRI or augmentation with atypical antipsychotics (e.g., aripiprazole) is necessary [8] and may be beneficial for another 40% of patients nonresponsive to the first selected drug [9, 10].

Neuroanatomical and Neurophysiological Structure of OCD

CSTC circuit and glutamatergic system

So far, specific causes of OCD have remained unclear. It was historically considered to be exclusively of psychogenic origins; howev-

er, current neuropsychological, electrophysiological, and neuroimaging data strongly suggest the existence of a neurobiological basis for OCD [11–14]. Based on the effectiveness of SSRIs, the mainstream hypothesis of OCD etiology largely focused on the serotonin (5-HT) system [15, 16]. However, due to a high proportion of patients resistant to SSRI treatment [17], the focus has shifted towards the cortico-striatal-thalamo-cortical (CSTC) brain circuit. Neural and pathophysiological mechanisms linking the OCD with structures of the CSTC circuit have been further studied and some modifications to the model were recently proposed in the prominent Baxter's model [18], which is largely based on neuroimaging data. According to prevailing concepts, the CSTC circuit involves direct and indirect pathways that work in balance.

Glutamatergic excitatory signals from the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) to the striatum lead through the direct pathway to increased inhibitory GABAergic signals to the globus pallidus interna (GPi) and substantia nigra (SNr). This, in turn, produces decreased inhibitory γ -aminobutyric acid (GABA) output from GPi and SNr to the thalamus resulting in increased thalamic stimulation of the cortex. In the normally functioning CSTC, the excitatory glutamatergic pathway is modulated by an inhibitory function of the indirect GABAergic projections. Through this indirect pathway, the striatal inhibition of the globus pallidus externa disinhibits the subthalamic nucleus, which then excites the GPi and SNr, leading to thalamic inhibition [19].

However, according to the aforementioned Baxter's model, an imbalance between the direct and indirect pathway may cause OCD symptoms. Human and animal research has shown that excessive hyperactivation of the orbitofrontal-subcortical direct pathway together with hypoactivation of the basal ganglia indirect pathway generates increased anxiety and fear about one's safety. Through reinforcement, behavioral patterns relieving such constantly perceived threat become repetitive and are no longer under control of the will [19]. Multiple lines of evidence have shown an integral role of glutamate as the key neurotransmitter within the CSTC circuit [20]. Glutamatergic synaptic dysfunction within this area might, therefore, be implicated in the pathogenesis of OCD and related disorders [16, 21, 22] as shown above for the CSTC's direct pathway that is glutamatergic.

Pathophysiology of OCD studied at the molecular level has focused on synaptic and extrasynaptic N-methyl-D-aspartate (NMDA) receptors [23]. The striatum, the major nucleus of the basal ganglia and 1 of the CSTC circuitry components, receives a large glutamatergic excitatory input carrying information about movements and associated sensory stimulation. This results in a large extracellular concentration of glutamate that can overcome neuronal and glial uptake homeostatic systems, hence allowing stimulation of extrasynaptic glutamate receptors.

Significant associations with OCD have been identified for genes including the glutamate receptor, ionotropic kainate 2 (GRIK2) [24] and glutamate transporter (SLC1A1) gene [25, 26]. Mice with a deactivated SAPAP3 gene coding for a postsynaptic scaffolding protein at corticostriatal glutamatergic excitatory synapses developed facial lesions, repetitive grooming behaviors, and anxiety that could be reversed by SSRIs [27]. Glutamate also plays a significant role in the ACC, where high concentrations of glutamate receptors compared to other neurotransmitter binding sites can be found [28]. It

is noteworthy that genetic research on OCD pathology has not stopped here; for example, a regulation of intracellular Ca^{2+} (RYR3), RNA-editing/protein modification (ADAR3), and immune response linked to microglial function (pre-B-cell leukemia homeobox) are recently studied areas [22].

The primal role of glutamatergic signaling system abnormalities in OCD pathogenesis has been supported by studies using proton magnetic resonance spectroscopy (1H-MRS) [29–31]. Rosenberg et al. [32] found higher striatal glutamate + glutamine (Glx) concentrations in pediatric OCD patients than in healthy controls. Interestingly, the increased levels normalized after treatment with SSRIs but not CBT despite its comparative effectiveness in symptoms reduction. In contrast to that, lower Glx concentrations were found in the ACC of both children [33] and female adult OCD patients [34] where the Glx levels correlated with symptoms severity. Moreover, reduced ACC Glx and increased caudate Glx in children with OCD is consistent with a previous report of inverse correlations between ACC and striatal volume [21]. It has been suggested that it is glutamate hyperactivity in the OFC that constitutes the substrate upon which SSRIs act to decrease such hyperactivity [35] (see also [13]).

Another piece of evidence came from a study of the relationship between polymorphism in genes involved in the pathophysiology of OCD (specifically, genes for serotonergic and glutamatergic pathways) and concentrations of neurometabolites in the ACC [36]. Significant associations between variations in 5 genes and concentrations of inositol, glutamate, glutamine, and choline in the ACC were found in children with OCD. The authors interpret this finding as a demonstration of the interaction between serotonin and glutamate pathways in OCD pathology. Conversely, Simpson et al. [37] reported no significant differences in glutamate levels in any of the 3 striatal regions (dorsal caudate, dorsal putamen, and ventral striatum) between OCD patients and matched healthy control subjects. It is noteworthy that the authors found negative results using a 1H-MRS imaging technique with a relatively high spatial resolution at 3.0 T, while MRS at 1.5 T in another study revealed significant elevations in glutamatergic compounds. Therefore, at least some of these contradicting findings might be caused by differences in methodology [37].

Despite existing discrepancies in the previous studies of the association between the glutamatergic system dysfunction and OCD, it has been concluded that tonic-phasic dysregulation of Glx within the corticostriatal circuitry in OCD is plausible [30]. All this evidence has thus prompted increased effort to develop and evaluate agents modulating glutamatergic neurotransmission for more effective OCD treatment, although no controlled studies of such agents for standard OCD pharmacotherapy have yet been reported.

Finally, an interesting link between abnormalities of the glutamatergic system and OCD was proposed in a glutamate-based genetic immune hypothesis by Rotge et al. [25]. Genetic variability in gene SLC1A1 leads to functional alterations of the glutamate transporter excitatory amino-acid carrier 1 (EAAC-1), which results in increased (toxic) glutamate activity. Moreover, these functional alterations of EAAC-1 are also responsible for immunopathological reactions after the exposure to Borna virus that consequently lead to structural and functional changes in thalamic nuclei that send glutamatergic projections to the ACC and OFC. The neurotoxicity

effect of glutamate in these predisposed cortical areas is then responsible for the cognitive disruptions characteristic of OCD.

Role of temporal lobe in OCD pathogenesis

There is some evidence suggesting that apart from the CSTC circuitry an important role in the brain pathogenesis of OCD is played by the temporal lobe (TL), which has attracted increased research attention in the past few years [38–40]. Different neuroimaging methods, e.g., magnetic resonance imaging (MRI) or single-photon emission computed tomography (SPECT), have already shown bilateral cortical abnormalities in the prefrontal and anterior-temporal regions together with perfusion deficits in frontotemporal regions and anterior striatum a few months after the onset of OCD. Moreover, clinical progress 6 months later was reflected by visible improvements of brain perfusion in the striatum area [41].

In a study comparing OCD twins with their healthy co-twins, the former scored higher for OCD symptoms and had increased fractional anisotropy in multiple regions of the right TL [42]. Furthermore, drug-naïve OCD patients showed increased values of fractional anisotropy in the corpus callosum and associated areas of white matter in the bilateral superior temporal region [43]. The superior temporal region itself is connected with other structures implicated in OCD, such as the orbitomedial frontal areas, putamen, and nucleus caudate [44, 45]. This leads to the conclusion that white matter of the TL might play an important role in OCD neuropathology [46]. In a follow-up twin study, a significant interaction effect of sex and OCD symptoms on the grey matter volume was found [47]. While larger grey matter volume in the right middle temporal gyrus was revealed in males scoring high on OCD symptoms, it was reduced in high-scoring females. Interestingly, exactly the opposite sex-related pattern was observed for the right precuneus volume. Thus, the authors argue that the differences in OCD brain-related changes for males and females may hide the main effect of OCD symptoms on the brain volume.

Another study focused on a potential relationship between morphological abnormalities of the superior temporal gyrus (STG), which may be involved in OCD pathophysiology, visuospatial function, and clinical symptoms [48]. A significant volume reduction in the grey matter of the anterior STG in patients compared with healthy volunteers was observed, but this reduction did not correlate with cognitive impairment and clinical symptoms assessed by a psychometric battery. Therefore, the link between a reduction in brain volume in specific areas and cognitive impairment observed in OCD patients warrants further research (see also [49]).

Based on a few neuroimaging studies, abnormalities in the amygdala-hippocampus complex (AHC), a specific region of the TL, seem to be implicated in the pathophysiology of pharmacoresistant OCD [50]. This is not so much surprising since the AHC has strong connections with the OFC [51] and together are thought of as structures connecting the brain regions that modulate information involved in the initiation of behavioral responses without conscious awareness [48]. As demonstrated by Atmaca [52], the mean left and right hippocampal and amygdala volumes were smaller in OCD refractory patients than in healthy controls, and even more, the severity of their symptoms was correlated with the left hippocampus volume. Interestingly, pharmacological agents effective in OCD treatment (e.g., SSRIs) exert their effects on amygdala re-

ceptors [53]. Furthermore, a network-based statistical analysis has recently revealed decreased structural connectivity among orbitofrontal, striatal, insula, and temporolimbic areas with important local alternations for the amygdala and temporal pole in patients with OCD as indicated by graph theoretical measures [54].

An intriguing association between abnormalities in TLEs and OCD symptoms has been demonstrated in a study focusing on the prevalence and severity of clinically significant obsessions and compulsions in a large sample of patients with temporal lobe epilepsy (TLE) [55]. Compared with the general population, the TLE patients reported OCD symptoms at a higher prevalence rate. Specifically, 22% of the patients scored in the clinical range on the Obsessive Compulsive Inventory, which is considerably higher than 2.5% observed in the general population. This was further corroborated by Monaco et al. [56], who found that 14.5% of TLE patients also had a diagnosis of OCD. Moreover, it has been argued that brain structures and neurobiological mechanisms responsible for compulsions are different from those associated with obsessions and are particularly vulnerable in TLE patients [55]. It is noteworthy that a complete remission of OCD symptoms after epilepsy surgery has been observed [57, 58].

Based on evidence from quantitative electroencephalography (QEEG), the existence of 2 subtypes of OCD patients meeting the DSM-III-R diagnostic criteria has been suggested [17]. While cluster 1 was characterized by excess relative power in theta (especially in the frontal and frontotemporal regions), cluster 2 could be described by increased relative power in alpha within bipolar temporal and frontotemporal regions. Furthermore, 80% of patients from cluster 1 were found to be nonresponders to drug treatment by SSRIs, but exactly the opposite pattern was found in cluster 2, where 82.4% of members responded well to medication. Thus, the author, later supported by others [59], argues that despite common symptoms at least 2 pathophysiological subgroups showing a differential response to treatment with SSRIs exist within the OCD population.

The neurophysiological abnormality of TL activity in OCD patients was later confirmed in another study [60]. During TL activation by olfactory stimulation, a power increase was detectable in the slower beta frequencies in healthy subjects. In contrast to that, the OCD patients' EEGs showed no change or even a slight decrease. Moreover, increase in delta-1 and decrease in alpha-2 power at rest was evident when comparing OCD patients with healthy controls.

Structural and functional changes within the TL in OCD patients are also reflected in cognitive, or more precisely, memory deficits. One of the cognitive theories conceptualized OCD as a fundamental disorder of implicit (frontostriatal) information-processing systems that is compensated by aberrant recruitment of limbic structures centrally involved in explicit information processing (hippocampal hyperfunction vs. striatum hypofunction). These failures in implicit (nonconscious) processing may, therefore, lead to the clinical expression of OCD symptoms such as intrusive repetitive cognitions and associated cognitive anxiety that healthy subjects are able to put to rest [61]. As predicted by the theory, significant implicit sequence learning deficits in OCD versus healthy subjects were demonstrated in a behavioral experiment adopting a serial reaction time paradigm [62]. The authors conclude that in order to mask the implicit information-processing deficit (frontostriatal

dysfunction) in OCD patients, explicit information-processing networks including medial temporal structures are engaged in a compensatory fashion (see also [63]).

The switch between different memory processes used as a compensatory mechanism in a range of impairments across neurodevelopmental disorders including OCD has been recently demonstrated by Ullman and Pullman [64], who based their concept on an extensive review of existing behavioral, electrophysiological, and neuroimaging evidence. Since OCD symptoms might be partly explained by impairments in procedural memory, they hypothesize that patients might use declarative memory to fully or partly compensate the impairment in procedural learning tasks. This is supported by positron emission tomography (PET) studies that report more activation in declarative memory brain substrates in OCD patients [61, 62]. Moreover, a negative correlation has been found between the volume of hippocampal and medial TL regions and the intensity of obsessive thoughts and actions [65].

However, others have challenged the model suggesting that deficiencies of striatal recruitment or thalamic gating in the context of implicit learning are not necessarily present in OCD [40]. Instead, they stress the aberrant hippocampal activation that can be consistently observed in the absence of deficient striatal recruitment across samples and symptom types of OCD. Thus, instead of the view that hippocampal involvement is attributable to striatal deficiency, it is possible that the aberrant hippocampal function itself has a principal role in OCD. In regards to the evidence of dysbalance between frontostriatal (implicit) and frontohippocampal (explicit) information-processing systems in OCD, some authors call for larger-scale human neuroimaging studies to support functional connectivity analyses [66] that are already well-established in nonhuman research [67].

The neuropsychological model of OCD is well-extended by a hypothesis of a potentially close relationship between checking rituals and neuropsychological dysfunction related to memory. Interesting results have come from the comparison of different OCD subtypes showing that more severe memory deficits were experienced by people with obsessions/checking than people with cleanliness/washing rituals [13]. One of the proposed etiologies for checking behavior is the inability to accurately recall whether an activity has been completed correctly [68]. Paradoxically, repeating checking behaviors bring even more distrust in one's own memory [69–71]. Therefore, it is self-confidence in memory rather than memory per se that seems to be more impaired [72]. Checkers demonstrate poor general memory compared to washers, which is related inhibition deficits [73]. On the other hand, washers perform significantly better than checkers on a pattern of recognition task and show a faster motoric response during a planning task [74].

Finally, an association between checking symptoms and spatial memory dysfunction has been found in several studies [75, 76]. In line with this evidence, an intriguing hypothesis linking anxiety and spatial memory deficits with specific TL regions in patients with checking symptoms has been proposed [77]. It is suggested that lower performance on spatial working memory tests in those patients might be explained by higher anxiety levels that can subsequently worsen the symptoms. At the neural level, the authors hypothesize interactions between the cortico-basal ganglia circuits and the amygdala and/or ventral hippocampal node, which fits with

the above-mentioned CSTC model extended to temporal regions. Furthermore, this concept makes a comprehensive connection between anxiety, repetitive behaviors, and cognitive deficits.

In this perspective, it is noteworthy that the neural circuit going from the prefrontal cortex (PFC) to the hippocampus, as well as connections between the hippocampus and amygdala, are, among others, glutamatergic. It may, therefore, be speculated that pharmacological agents affecting the glutamatergic system (e.g., memantine as an NMDA antagonist) could lower the initially increased excitation potential of these neural pathways that would eventually lower the symptoms of OCD.

Do Different OCD Subtypes have Specific Neural Correlates?

Neuroimaging research on brain structural changes in OCD patients has mostly provided consistent results [78]. Compared to a control group, OCD patients show alternations of grey matter volume in several brain regions, including the medial frontal gyrus, medial OFC, ventral putamen, and the anterior cerebellum [38]. Moreover, intriguing neuroanatomical alternations have been observed for individual subtypes as well, which confirms the hypothesis that each OCD subtype with specific symptomatic dimensions has its own neural signature. While significant associations were found between contamination/cleaning symptoms and the reduced dorsal caudate, scores on harm/checking obsessions were, on the other side, negatively correlated with the grey and white matter volume in anterior parts of TLs [79]. These regions including the amygdala and parahippocampal cortices are known to have connections with the hippocampus and associated areas.

Such findings are interesting in the context of the hypothesized important role of TL abnormalities in OCD neuropathology. It is especially the amygdala, a structure predominantly involved in fear and anxiety processing, whose functional alternations seems to contribute to observed differences between specific OCD subtypes. A significant correlation was found between the severity of aggression/checking symptoms of OCD patients and the amygdala activation representing an abnormal fear reaction in response to fearful faces [80]. Corroborating results were reported in another study of patients with prominent aggressive/checking symptoms who showed reduced volume in the right amygdala [38]. However, others have localized brain structural changes associated with these symptoms to other regions (e.g., the insula and putamen [81] or the right posterior cingulate and medial occipital cortices [82]).

Although several different approaches were taken to categorize a clinically heterogeneous presentation of OCD, research has recently focused on a classification separating OCD subjects in 2 specific groups: those with autogenous and reactive obsessions [83]. According to this conceptualization based on symptomatology, autogenous obsessions are relatively independent on perceived external triggers and/or come abruptly into consciousness without any link to the environmental context of present stimuli. Based on their content (mainly immoral, sexual, aggressive, etc.) the autogenous obsessions are ego-dystonic and perceived as aversive. In contrast, reactive obsessions are triggered by external objects or clues in the environment. The evoking stimuli are perceived as realistic, therefore less ego-dystonic, leading to rational coping

mechanisms. Thoughts about contamination, accident, asymmetry, or loss are among the most common reactive obsessions. Moreover, following studies have shown that a distinction between the 2 subtypes exists not only in the clinical variables but also in a sociodemographic and neurobiological profile.

Specifically, autogenous obsessions were associated with decreased N-acetyl-aspartate levels in the limbic medial TL [84] and other TL structural alternations. This is in line with a study exploring neural correlates of dysfunctional beliefs associated with OCD [85]. In normal subjects, the authors observed significant negative correlations between anterior temporal lobe (ATL) volume and scores on the over importance/need to control thoughts domain of the Obsessive Beliefs Questionnaire-44, which can be attributed to autogenous obsessions. Moreover, ATL volume was bilaterally smaller in OCD patients than in the controls, especially those from a low-belief group. Corroborating results from another study showed that autogenous OCD patients had a smaller left anterior TL than healthy controls, while bilaterally larger volumes in the putamen were observed in reactive patients [39]. Moreover, both patients subgroups compared to control subjects were observed to have a smaller right middle temporal gyrus. The authors consider these results as a neurobiological support for the above-mentioned OCD classification [83] and suggest that the 2 types of obsessions have a distinct neural substrate.

Nevertheless, autogenous and reactive obsessions are not mutually exclusive categories as patients with a mixture of obsessions can be found as well. For example, the harm/checking thoughts that were found to negatively correlate with the grey matter of the ATL [79] also partially overlap with autogenous obsessions [39].

Glutamatergic agents in OCD therapy

Several studies have already provided evidence showing the effectiveness of medication acting on the glutamatergic system in the treatment of pharmacoresistant OCD [86–88]; for a review, see ► **Table 1**. First, there is riluzole, which exerts a neuroprotective effect, inhibits the glutamate release, and blocks GABA reuptake [89]. It has also proven a therapeutic effect when added to SSRIs [88, 90]. Moreover, riluzole action through neuroglial systems is noteworthy, as it apparently decreases the activity of glutamatergic transporters GLAST, GLT1, or EAAC1, which may possess a specific effect in OCD [91–93].

Ketamine, which is a noncompetitive antagonist of the NMDA receptor, is primarily tested for its rapid antidepressant effect within 40 min following an intravenous infusion [94, 95]. Moreover, there are sporadic studies demonstrating an anti-obsessional effect of ketamine infusion in unmedicated OCD individuals that is as rapid as in depression and can last for a few days [96]. This rapid effect was also confirmed in some patients with intrusive thoughts in a randomized controlled crossover trial on 15 adults with OCD [97, 98]. Finally, Bloch et al. [99] found statistically significant improvement in OCD symptoms over 1–3 days following ketamine infusion compared with baseline.

Similarly, another drug with a potential benefit for OCD patients is topiramate, an anticonvulsant and antagonist of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors [100]. However, very few double-blinded placebo-con-

trolled studies have been conducted on this drug. Nevertheless, promising results were reported by Berlin et al. [101], who found its predominantly anticomulsive activity. Therefore, topiramate may potentially be used in reactive forms of OCD, while the therapeutic effect of memantine is expected mostly in autogenous OCD. An explanation for positive outcomes after treatment with topiramate can be potentially rooted in its anti-epileptogenic action, which is mainly due to the impact it has on glutamatergic receptors, but also its capacity to alternate the function of sodium and calcium channels and GABA-A receptors.

Another anti-epileptic drug with a positive effect, when used as an adjuvant medication to treatment with SSRIs and clomipramine, is lamotrigine. Several case studies [102–104] and 1 double-blinded placebo-controlled study has already reported encouraging therapy outcomes from treatment of pharmacoresistant OCD with lamotrigine [105]. This drug can influence OCD symptoms through the glutamatergic system indirectly as it decreases the glutamate release by acting on presynaptic voltage-gated sodium channels in the hippocampus, amygdala, and striatum [106, 107]. In addition, other authors argue that release of glutamate is in the case of lamotrigine caused by other pharmacodynamic mechanisms [108, 109]. Thus, more double-blinded studies need to be done in order to gain full understanding.

It has been suggested that damage to glial cells by oxidative stress is at the root of various neuropsychiatric disorders including OCD [110–112]. Decreasing the levels of glutamate N-acetylcysteine (NAC) helps keep glutathione within glial cells, which decreases their vulnerability to oxidative damage [112]. Furthermore, NAC increases the level of cystine in the brain, which leads to an exchange of intracellular glutamate with cystine due to activation of cystine-glutamate antiporter. Increased levels of extracellular glutamate then activate inhibitory metabotropic glutamate receptors (mGluR2/3) on presynaptic neurons, which results in a decrease of glutamatergic excitation neurotransmission [113]. In association with CSTC pathology in OCD, there is an important finding that NAC increases dopaminergic neurotransmission in the striatum by facilitating the release of vesicular dopamine in striatal neurons [114]. This ability to alternate dopamine levels, together with the finding that NAC restores extracellular glutamate homeostasis in the nucleus accumbens [115], might explain the positive effect of NAC in OCD, but also in addictive and impulse control disorder (e.g., trichotillomania) [116].

Antibiotic used to treat tuberculosis, D-cycloserine (DCS), also acts as a partial agonist of NMDA receptors. In the case of low glycine levels, DCS is able to facilitate NMDA receptors functioning, but when glycine levels are sufficient, DCS acts as their antagonist [117, 118]. Animal studies of conditioned fear have demonstrated that stimulating the NMDA receptor at the glycine site in the amygdala by DCS plays a significant role in fear extinction. In compliance with the partially agonistic action of DCS, its effect on the psychotherapeutic process might be understood through increasing neuroplasticity (enhancing the NMDA receptor functioning) or fear memories reconsolidation (reducing the NMDA receptor functioning) [117, 119]. However, as shown in ► **Table 1**, clinical studies failed to show significant differences between the experimental and placebo group, which may be due to the fact that the exposure and response prevention therapy (ERP) that was used in both con-

► **Table 1** Review of studies testing the effect of augmentation drugs in pharmacoresistant OCD.

Augmentation drug	Dose	Duration	Target/ control group size	Main effect	Notes	Refer- ence
D-cycloserine	125 mg/ERP	10 ERP 2 ERP/week	14/11	DCS = PLA	Obsession-related fear ratings declined more rapidly in the target group ($p < 0.02$)	[123]
	250 mg/ERP	12 ERP 1 ERP/week	12/12	DCS = PLA		[154]
	100 mg/ERP	10 ERP 2 ERP/week	10/13	DCS > PLA * * *		[121]
	125 mg/ERP	10 ERP 2 ERP/week	10/12	DCS > PLA * * *	The target group recovered 2.3 times faster	[122]
	weight-adjusted 25 or 50 mg/ERP	7 ERP 1 ERP/week	15/15	DCS = PLA	The effect for CY-BOCS	[155]
	weight-adjusted 25 or 50 mg/ERP	7 ERP 1 ERP/week	15/15	DCS = PLA	The effect for CY-BOCS	[156]
	50 mg/day	5 ERP 1 ERP/week	64/64	DCS = PLA	Significantly greater proportion of antidepressant-free patients in the target group achieved remission ($p = 0.008$)	[124]
	50 mg/ERP	10 ERP 1 ERP/week	13/14	DCS > PLA * *	The effect for CY-BOCS: homework compliance not associated with treatment outcome in the placebo conversely to treatment group	[157]
	weight-adjusted 25 or 50 mg/ERP	7 ERP 1 ERP at least every 5 days	70/72	DCS = PLA		[120]
	125 mg/day	6 ERP 1 ERP/week	19/20	DCS = PLA	Significant effect found only for contamination/cleaning subgroup ($p = 0.033$)	[125]
Glycine	60 g/day	12 weeks	5/9	GLY = PLA	Close-to-significant effect ($p = 0.053$)	[126]
Ketamine (infusion)	0.5 mg/kg (no other medica- tion)	1 week	8/7	KET > PLA *	Full response ^b in 50% of the target group vs 0% of the placebo group	[97]
Lamotrigine	100 mg/day	16 weeks	17/16	LAM > PLA * * *	Improvement in affective symptoms (HRSD) too	[105]
Memantine	mean final dose 18.0 mg/day	62 days (mean)	22/22	MEM > PLA ^a	Clinical improvement in the target group 27.0% (vs. 16.5% in the placebo group)	[131]
	20 mg/day	8 weeks	19/19	MEM > PLA * * *	More patients in the target group achieved remission	[133]
	5–10 mg/day	12 weeks	14/15	MEM > PLA *	Full response ^b more likely in the target group	[132]
N-acetylcysteine	2.4 g/day	12 weeks	19/20	NAC > PLA * * *		[158]
	3 g/day	16 weeks	20/15	NAC = PLA	Significant effect observed for the compulsions subscale ($p = 0.013$)	[159]
	2 g/day	10 weeks	22/22	NAC > PLA *		[160]
	3 g/day	16 weeks	16/19	NAC = PLA	NAC superior to placebo in reducing anxiety symptoms ($p = 0.02$)	[161]
	2.4 g/day	10 weeks	18/11	NAC > PLA *		[162]
Riluzole	100 mg/day	12 weeks	29/30	RIL = PLA	Effect for CY-BOCS	[163]

► **Table 1** Review of studies testing the effect of augmentation drugs in pharmacoresistant OCD.

Augmentation drug	Dose	Duration	Target/control group size	Main effect	Notes	Reference
	100 mg/day	12 weeks	19/18	RIL = PLA	Close-to-significant improvement of obsessions in the outpatient subsample (p = 0.056)	[90]
Topiramate	mean dose 180.15 mg/day	12 weeks	20/21	TOP > PLA * * *		[164]
	mean dose 177.8 mg/day	12 weeks	13/14	TOP = PLA	Treatment effect on the compulsions (p = 0.014), but not obsessions (p = 0.99)	[101]
	mean dose 137.5 mg/day	12 weeks	13/14	TOP = PLA	Significant effect observed for the first 2 months (p = 0.01)	[165]
<p>The level of statistical significance: * p < 0.05, ** p < 0.01, *** p < 0.001; ^a single-blinded case-control study, no statistical significance was reported; ^b full-response: ≥ 35% Y-BOCS reduction; CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale (i.e., used in studies conducted on children patients); ERP: exposure with response prevention; HRSD: Hamilton Rating Scale for Depression.</p>						
<p>Only the studies on glutamatergic agents using a control group were included in the table. Unless otherwise specified, these are double-blinded placebo-controlled studies on adult OCD patients that employed the Y-BOCS to measure the effect of augmentation pharmacotherapy on obsessive-compulsive symptoms. The target/control group size column reports the number of participants in either of the groups at the end of the study. The main effect shows whether the Y-BOCS score was significantly higher in the treatment group than in the placebo group and the level of statistical significance</p>						

ditions leads most likely alone to substantial decrease in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score [120]. Nevertheless, a few studies have shown that DCS considerably accelerates the onset of the ERP effect and lowers distress associated with exposures [121–123].

Based on the literature on DCS, there are many unresolved questions that remain. For instance, how is the therapeutic effect of fear memory extinction alternated by adding antidepressants to DCS medication [124]? Additionally, how is the effect on distress differentiated from the own memory effect depending on the dose level? These pharmacokinetic questions ought to be resolved considering different dosing schemes, which have been until recently below the lower dose in antibiotic therapy (see ► **Table 1**). Another interesting point is the potential effect of adjuvant therapy (antidepressant + DCS) in patients with a cleaning/contamination OCD subtype [125].

An alternative approach to influence the glutamatergic system in OCD therapy is to medicate with glycine. This amino acid has been shown to be active in forebrain structures, where it activates NMDA receptors function. Besides that, it also possesses a neuro-modulating effect in the hippocampus, hence its plausible role in learning and memory functions. Currently, there is just 1 placebo-controlled study that proves clinical efficacy of glycine [126].

There is also bitopertine (glycine transporter 1 inhibitor), an experimental drug, currently in the third stage of clinical testing [127], which is a glycine reuptake inhibitor (i.e., the glycine levels increase upon administration of bitopertine). Therefore, bitopertine is another drug that might potentially reduce OCD symptoms through its impact on the glutamatergic system. Although the exact pharmacodynamic effect of both glycine and bitopertine remains unclear, an activity similar to memantine might be expected.

Finally, among several other drugs affecting the glutamatergic system, which are tested for their therapeutic effect in OCD, should

be mentioned rapastinel. It is a partial agonist at the glycine functional site of the NMDA receptor [128]. Most recently, there has been a study on a negative allosteric modulator of mglu5 receptors, mavoglurant [129].

Treatment potential of memantine—drug of choice for checkers?

There is an extensive line of evidence showing benefits of adjuvant medication with memantine in the treatment of OCD resistant to other drugs [22, 87, 88, 130–132]. For example, when memantine was added to fluvoxamine treatment in a randomized double-blinded study, significantly more patients from the combined medication group than from the placebo group (17 vs. 6) achieved remission, while the frequency of side effects was comparable between the 2 groups [133]. These results clearly show that memantine addition significantly improved the treatment outcomes in moderate to severe OCD subjects, which was corroborated in a similar study reporting a significant decrease in both symptoms and illness severity in a group of OCD patients co-medicated with memantine compared to placebo [132].

Pharmacodynamics of this agent may be explained in light of the aforementioned findings that are in support of the original CSTC model extended of the glutamatergic system [35, 134–136]. Furthermore, another piece of evidence coming from the research of intractable OCD also points to the TL [52], which is also linked to the glutamatergic system and sensitive to its functional changes [137].

Besides the potential of memantine as an antagonist of the NMDA receptor to improve excitability of glutamatergic neurons connected in the CSTC circuitry, also noteworthy is its capacity to impact on several structures of the TL and their glutamatergic internal connections and inputs/outputs to other regions involved in OCD and related neuropsychological symptoms. Considering both

the structural and functional abnormalities localized in the TL that are characteristic for OCD, and particularly some of its subtypes (e.g., checkers), here we propose a novel hypothesis that use of memantine with a glutamatergic or, more specifically, de-excitation impact on these structures may have a significant therapeutic outcome (see ► Fig. 1). The rationale for that may be found when cognitive (a compensation of implicit memory by the explicit one; impaired spatial working memory), neurochemical, and neuroanatomical aspects of the illness are linked together into 1 theoretical model (see description for figure).

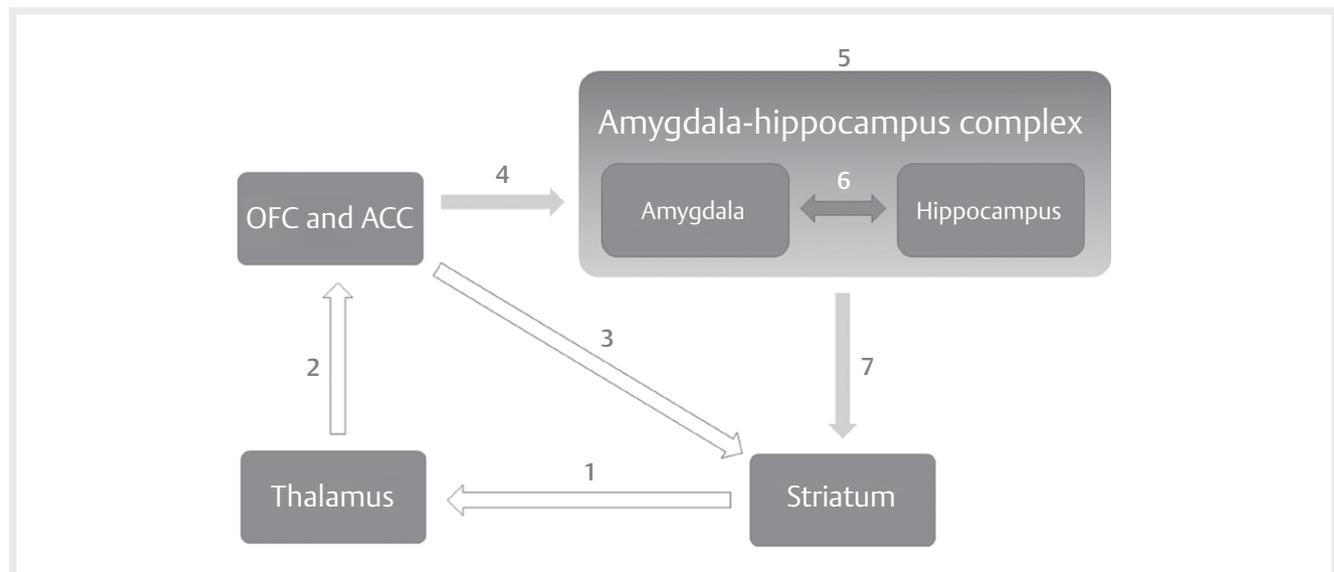
Moreover, it can be supported by evidence coming from research focusing on connectivity between different brain regions after administration of memantine. For example, resting state functional MRI (fMRI) following subchronic treatment by memantine revealed significant decreases in functional connectivity among the hippocampal and frontal cortical structures (prelimbic, cingulate) indicating a loss of connectivity. Besides that, memantine also caused functional and ultrastructural alterations in these regions, and moreover, induced behavioral effects comparable to other NMDA antagonists [138].

A study of changes in cerebral glucose metabolism after memantine therapy of patients suffering from post-traumatic cognitive impairment found significantly decreased glucose metabolism in several brain structures including the cerebellum, left thalamus, left olfactory and right middle temporal gyrus, and the right amygdala and insula [139]. On the other hand, increased glucose metabolism was detected in the inferior and middle frontal gyri and the inferior parietal lobule of the left hemisphere. This is an interesting finding because it confirms the de-excitation effect of memantine on specific regions of the TL that are associated with in-

creased activity of explicit memory. Although more studies would be necessary to confirm the findings mentioned above, it can be preliminarily stated that memantine is able to regulate increased activity in the regions that form a neural substrate of pharmacoresistance in OCD and also interlink neuropsychological and symptomatological (checking rituals, autogenous obsessions) aspects of OCD.

In regards to the above-mentioned relation between TLE and OCD, the effect of memantine on the reduction of experimentally induced epileptogenic activity of the TL is worthy of interest [140, 141]. Besides that, memantine was also found to improve cognitive deficits (spatial memory) associated with TLE [142, 143]. Moreover, other studies have reported an even more pronounced effect of substance IEM-1913 (1-amino-4-(1-adamantane-amino)-butane dihydrochloride), which, apart from being an antagonist of NMDA receptors as memantine, also acts antagonistically on AMPA receptors [144]. Thus, it might be promising in future research of experimental models of OCD to extend the focus from memantine to other drugs affecting the glutamatergic excitation-inhibition balance of the temporal neural structures.

Another region that is worth focusing on in regards to memantine therapy is the anterior part of the TL. As stated above, ATL volume has been found to be bilaterally smaller in autogenous as well as harm/checking obsessions [39, 79]. The temporal pole that is a part of the ATL has strong connections with the amygdala and orbital PFC and plays a crucial role in a multimodal analysis of social and emotional processes. Specifically, the right temporal pole is related to socially relevant, personal, and episodic memories [145–149]. Thus, it is possible that the emotionally charged content of autogenous obsessions that are incongruent with the actual context may



► **Fig. 1.** Potential effect of memantine. By its de-excitation effect memantine decreases the activity of direct pathway of the CSTC circuit (1, 2, 3), which results in lower pathological activity of the orbitofrontal cortex (OFC). Memantine might also probably modulate connectivity between the OFC, anterior cingulate cortex (ACC), and amygdala-hippocampus complex (AHC) (4). Direct action of memantine on the temporal lobe structures, especially the AHC might also be expected (5). Within the AHC, memantine could alternate the dysbalanced activity between the amygdala and hippocampus, which would explain the positive changes in anxiety, as well as in the impaired or alternated cognitive performance characteristic of OCD (6). Another expected effect of memantine in OCD is removal of disturbing interference between the AHC and striatum that could improve performance of implicit memory. Besides that, memantine may improve functioning of the striatal memory system by decreasing levels of extracellular glutamate which disrupts functioning of the striatum (7).

be co-created by disinhibition of the temporal pole through a dysfunctional connection with the PFC and amygdala (i.e., the regions involved in OCD pathogenesis). We suggest that future studies testing this hypothesis would be required. Using a connectivity matrix, this research could also demonstrate whether eventually pathological circuits of the mentioned brain regions may be affected by memantine. In addition, OCD, both reactive and autogenous, is associated with a smaller right temporal gyrus, where memantine decreases the glucose metabolic rate, as shown above [139]. In this perspective, future pharmaco-fMRI and pharmaco-EEG studies of memantine impact on interconnections between the TL and associated neuroanatomical structures could be promising.

The reported evidence that memantine causes frontohippocampal disconnectivity is in line with its hypothesized higher effectiveness in pharmaco-resistant checkers characterized by frontohippocampal compensation (explicit memory) of otherwise impaired frontostriatal connection (implicit memory), impaired spatial working memory, and higher intractable anxiety. More precisely, this combined treatment would benefit especially those cases where OCD is linked to a cognitive deficit caused by dysfunction of the TL regions. This is supported by several anecdotal reports of benefits of memantine treatment for patients with checking rituals, both children [130] and adults [150, 151].

Furthermore, we may assume that a positive response to memantine should be followed by changes in QEEG parameters in terms of a lower proportion of slow-wave activity in the TL. Finally, the weakest effect of memantine adjuvant therapy may be expected in washers. This is based on a premise that people with hygiene-linked obsessions and associated cleanliness/washing rituals probably differ in the extent of specific cognitive functions impairment as compared to checkers. Besides, as it follows from this review, washing rituals belong to reactive obsessions that are related to alternations in different brain structures (e.g., the putamen) compared to autogenous obsessions.

In this perspective, we find it essential to study further the structural, functional, and effective connectivity between the ventral hippocampus and PFC together with other crucial neural structures related to OCD pathology. Detailed neuroanatomical and neuropharmacological research in this area ought to explain, among others, the co-occurrence of increased use of explicit memory in checkers that mainly originates in the dorsal hippocampus. It would be of high interest to focus on the question of whether memantine affects the associated structures of the TL (i.e., amygdale-hippocampal complex) directly and/or through the CSTC circuit. In fact, memantine could have a de-excitation effect on the increased activity of the direct pathway in the CSTC circuit, which projects into the cortex that would subsequently alternate connectivity between the PFC and TL.

Conclusion

In this review, we focused on specific neuroanatomical and neuropsychological mechanisms, which would complete the classic CSTC model of OCD. The dysfunction of TL regions could explain both the OCD pharmaco-resistance to standard monoaminergic antidepressants and certain symptomatic manifestations of this illness. We suggest that when in connection with the glutamatergic

system and its own role in OCD neuropathology, our perspective may provide an explanation for a potential benefit of NMDA antagonist memantine in a treatment of intractable OCD. We argue that the effect of memantine may be understood through functional disconnection of crucial frontal regions with the hippocampus (i.e., structures that are associated with OCD pathogenesis) (see ► **Fig. 1**). Connections within these structures can be better evaluated in the context of a compensational mechanism substituting implicit memory impairments with the higher engagement of explicit memory. These functional abnormalities together with the effect on the amygdala may clarify the decrease of anxiety associated with doubts over activities that are controlled by implicit memory (checking rituals).

We suggest that future research might focus on a closer inspection of the AHC complex (a region affected by memantine activity) involvement in pharmaco-resistant OCD. In this context, it is noteworthy that key structures of the TL memory system (i.e., hippocampal and parahippocampal regions) are interconnected predominantly by glutamatergic projection neurons [152]. Further neuroanatomical and electrophysiological evidence shows that projections connecting these regions with the amygdala are mainly mediated by glutamatergic pyramidal neurons (for a review see [153]). Based on the current knowledge it is mainly the ventral hippocampus that is responsible for anxiety and affects the amygdala (basolateral nucleus) response during the occurrence of a threatening stimulus (leading to avoidance behavior). The amygdala thus represents an anatomical structure that may substantially contribute to pharmaco-resistance related to the hyperactivity of the ventral hippocampus. Through this mechanism, the activation of avoidance behavior is facilitated, which itself poses a barrier to effective treatment of OCD.

Acknowledgements

We would like to thank two anonymous reviewers for their valuable comments which greatly helped improve the manuscript.

Funding

This work was supported by the grants AZV MHCR no. 15-34524A and 15-29370A, the project “NPU4NUDZ” no. LO1611, with a financial support from the MEYS under the NPU I program, by the Charles University research program PROGRES Q35, 260388/SVV/2017.

Conflict of Interest

No conflict of interest has been declared by the author(s).

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