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Evaluating the Efficacy of Deep Brain Stimulation and Selective Serotonin Reuptake Inhibitors as Treatments for Obsessive Compulsive Disorder

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Obsessive-compulsive disorder (OCD) is defined through persistent obsessions and compulsions that can have debilitating impacts on the individual. The biological underpinnings have been linked to genetics, the serotonin system, and specific neural regions such as the Cortico-striatal-thalamic circuit. Various treatments have emerged to address this condition. Selective serotonin reuptake inhibitors and deep brain stimulation have shown promising results in terms of effectively treating obsessive-compulsive disorder; however, both are not without their limitations. The purpose of this article is to compare selective serotonin reuptake inhibitors and deep brain stimulation to determine the optimal treatment for OCD patients. As such the findings may be used to guide clinical procedures in future cases of OCD and may influence the treatment of other mental health conditions beyond OCD, paving the way for personalised interventions tailored to individual patients' needs.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a mental health condition characterised by obsessions and compulsions — core symptoms which can severely impact an individual and their ability to function in everyday life (Steuber & McGuire, 2023). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) defines obsessions as urges, images, or thoughts that are recurrent and persistent, often causing intense distress or anxiety. Compulsions are characterised as repetitive mental acts (e.g., repeating words, counting, praying) or behaviours (e.g., hand washing, checking, ordering) that the individual feels compelled to perform in an attempt to reduce the anxiety produced by their obsessive thoughts. Although, such behaviours and mental acts are often excessive or are not rationally linked to the obsessions that they are meant to neutralise. The majority of people with OCD have both obsessions and compulsions (Shavitt et al., 2014) however, due to the internal nature of the symptoms, OCD is often misidentified or unrecognised (Hirschtritt et al., 2017).

The treatment of OCD is a highly important area of research because, despite the various different methods of treatments available, not all are suitable for each individual. The condition is phenotypically heterogeneous (Bloch et al., 2008) meaning that there are a multitude of different obsessions and compulsions, therefore this could result in the efficacy of treatments being impacted by individual differences. For example, compulsions and obsessions in OCD can relate to concerns regarding contamination (resulting in washing and cleaning compulsions), concerns about symmetry (ordering and counting compulsions), concerns with potential harm to others or themself (checking compulsions, such as checking five times that a door is locked), and intrusive sexual or aggressive thoughts (resulting in mental rituals such as repetition; Stein et al., 2019). Approximately 0.8–2% of the global population have an OCD diagnosis (Ruscio et al., 2010) — at least 10–40% of these individuals will not experience symptom improvement after a full course of standard treatment, and will then develop treatment refractory OCD (TROCD) meaning their symptoms are resistant to treatment (Xu et al., 2022); however, a large proportion of people do improve with the implementation of different behavioural therapies and/or pharmacotherapy (Raviv et al., 2020; Hirschtritt et al., 2017). Hence, research into the treatment of OCD is crucial for determining the treatments with the best patient outcomes and tailoring treatments to ensure the care of all OCD patients.

At present, the most common treatment pathways for OCD consists of cognitive behavioural therapy, exposure and prevention therapy, and the prescription of selective serotonin reuptake inhibitors (SSRIs). More experimental methods include ketamine, transcranial magnetic stimulation, transcranial direct current stimulation, and, if there are no symptom improvements aftering exploring the above methods, ablative brain surgery and deep brain stimulation (DBS; Krzyszkowiak et al., 2019). The central focus of this article will be on SSRIs and DBS, ultimately aiming to determine the treatment that is most effective for OCD patients.

GENETICS AND NEUROCHEMICALS IN OCD

There have been several attempts to explain the cause of OCD through the use of biological, cognitive, and behavioural models (Krzyszkowiak et al., 2019); however, there are many theories with biological basis which will be discussed, specifically: the role of genetics, the role of serotonin, and implicated brain regions in OCD.

Twin studies have provided robust evidence regarding genetics and their contribution to OCD (Rosario-Campos et al., 2005). Twin studies have shown that monozygotic twins (MZ, i.e. identical twins) have higher concordance rates (the probability that both individuals will have a specific trait) than dizygotic twins (DZ, i.e. fraternal twins); 80–87% compared to 47–50% (McCoy et al., 2013). MZ twins have greater genetic similarity as they share 100% of their genetic variance, whereas DZ twins share only 50% of their genetic variance. Therefore, we can assume that genetics play a crucial role in the development of OCD due to the fact that MZ twins are more likely to both have OCD than it is for both DZ

twins. It should be noted that because the concordance rate for MZ twins is not 100%, it suggests that there may be environmental factors that contribute to the development of OCD. Regardless, these risk factors are beyond the scope of this essay (for further information see: Wang et al., 2023 and Yilmaz et al., 2022). Additionally, much of this research relies on the equal environments assumption (EEA) which implies that MZ and DZ twins are exposed to shared environmental factors and that twins do not experience different treatment based on their degree of genetic relatedness (Hagenbeek et al., 2023). In reality, it is likely that MZ twins may share more similar environments than DZ twins, and the higher concordance rates of MZs found in heritability studies may be caused by the higher similarity of the environment in addition to genetic similarity (Harrop et al., 2013). Therefore, violations of EEA in twin research could lead to the genetic risk being overestimated.

In addition to genetic research, there has been a significant focus on the role of serotonin in the onset of OCD symptoms. Serotonin (5-HT) is a monoamine neurotransmitter which plays a crucial role in the central nervous system as it underlies a variety of important functions such as mood regulation, behaviour, cognition, and sleep (Vanhoutte, 1990; Murphy et al., 2008). It has been proposed that OCD symptoms may be the result of a disruption in the functioning of the brain's serotonin system (Sinopoli et al., 2017; Stein et al., 2019). Individuals may inherit a dysfunction in the genetic coding for serotonergic transporters and receptors resulting in an excess of serotonin being reabsorbed into the presynaptic neuron. Maia and Cano-Colino (2015) put forward the idea that low levels of serotonin (potentially caused by dysfunctional SERT) leads to continuous neuronal activity which traps the network in a specific state, and obsessions (trends in network activity that are hard to break free from) are then caused as a result. Further support for this theory comes from the high response rates to selective serotonin reuptake inhibitors (SSRIs), which inhibits the reabsorption of serotonin in the presynaptic neuron. This has led many researchers to focus on irregular serotonergic systems as the basis of the pathophysiology of OCD (Goodman et al., 1990).

SELECTIVE SEROTONIN REPUTAKE INHIBITORS

SSRIs are the dominant choice of pharmacological treatment for OCD (Skapinakis et al., 2016). They can be effective in reducing obsessive-compulsive symptoms, are not toxic if overdosed, and have side effects that are more tolerable than other pharmacological treatments available, for example, tricyclic antidepressants (Blier & de Montigny, 1999). The mechanism underlying SSRIs is their serotonin-agonistic effect, meaning they have the opposite effect of serotonin on the synapse — blocking the reuptake of serotonin in the synaptic cleft, consequently increasing the level of serotonin activity (Xue et al., 2016). The action of SSRIs is not completely understood; however researchers have postulated a potential effect on the myelination of axons which will ultimately impact the volume of white matter in the brain (Bracco et al., 2023). Research by Koch et al. (2012) suggests differences in the integrity of white matter is correlated to the severity of ordering, and obsessing symptoms are influenced by decreased myelination; as such increased symptom severity is related to higher abnormalities in myelin. The use of SSRI treatment increases extracellular serotonin which results in the desensitisation of serotonin receptors, ultimately enhancing serotonin transmission (Sinopoli et al., 2017). Interestingly, SSRIs have an almost immediate biochemical effect at the synapse, however there is an observed delay of approximately two weeks (Marazziti et al., 2019) between the administration of the medication before the therapeutic effects are visible (Blier & de Montigny, 1999). Furthermore, despite being the initial choice of treatment for OCD, various pieces of research have highlighted that roughly one third of patients do not have any response to the medication (Blier & de Montigny, 1999), thus highlighting a need for further research and potentially the development of alternative modes of therapy. Additionally, SSRIs appear to have potential side effects which may cause individuals to stop taking them before they have had a full course of treatment or may deter individuals from taking them entirely. Side effects can include emotional blunting (also known as "reduced affect" (Marazziti et al., 2019, p. 76), essentially meaning they have reduced emotional reactivity), cognitive impairment, proneness to bone fractures, and proneness to bleeding. Cognitive side effects can include impairment of memory, attention, motivation, concentration, and emotional response to external stimuli.

There is a vast amount of research demonstrating the clinical efficacy of SSRIs, for example there are numerous randomised controlled trials (RCTs) that have shown treatments based on SSRIs are significantly more effective in reducing OCD symptoms compared to placebo treatments (Katz et al., 1990; Pittenger & Bloch, 2014). Additionally, in the study conducted by Ahmari et al. (2013), whereby mice were used to demonstrate the hyperactivation of the cortico-striatal-thalamic circuit (CSTC) and its resulting effect of heightened grooming behaviour, the researchers found that the abnormal grooming behaviours were successfully inhibited through the implementation of SSRIs, therefore demonstrating its ability to potentially reduce compulsive behaviours. Although, it is worth mentioning that long-term effectiveness of SSRIs treatment can be impacted by the presence of co-occurring disorders. Jakubovski et al. (2013) found that the addition of at least one other psychiatric diagnosis was associated with a worse treatment outcome. The lower response rates in OCD with a co-occuring disorder could be due to depressive symptoms and avoidance behaviours (both of which are common symptoms in anxiety and mood disorders, which were the most commonly co-occurring conditions in Jakubovski et al.'s sample) which may impact adherence behaviour; however this is a speculative conclusion. The prevalence of co-occurring disorders in OCD varies substantially. Research from the United States shows that co-morbid rates of major depressive disorder range from 19%–67% in adults with a primary diagnosis of OCD, with similar variation in the prevalence of other mental illnesses, such as anxiety disorders (22%–56%; Sharma et al., 2021).

In addition, a very recent review compiled brain imaging (diffusion tensor imaging, structural magnetic resonance imaging, and functional magnetic imaging) data from 7 studies and was able to identify the neural regions implicated in the reduction of OCD symptoms (Bracco et al., 2023). They established that brain differences between healthy controls and OCD patients were significantly reduced after a round of SSRI treatment (daily doses in the data ranged from 60–200 mg), specifically atypical WM volume in the region of the CSTC, corpus callosum, temporoparietal lobe, and occipital lobe appeared to normalise as a result. This evidence clearly supports the use of SSRIs and provides some explanation for the underlying mechanisms of the drugs, however there are some flaws in the research that should be acknowledged. Namely, the comparison groups used to determine the effectiveness of SSRIs were not appropriately comparable due to the use of healthy controls who had no OC symptoms, therefore preventing us from seeing the neural effects on OCD patients who didn't receive medication (Bracco et al., 2023). Therefore, precaution may be needed when considering the results of this study as it is currently unclear whether the observed improvements are the result of the SSRIs or other factors that have not been measured. A better approach may be by the use of a double-blind trial with exclusively OCD patients, wherein the symptom reduction and cortical changes could be more critically examined.

While SSRIs are the favoured treatment choice for OCD (Bracco et al., 2023), a recent meta-analysis looking into the rates of withdrawal effects from SSRIs found an average rate of 40–60% (Horowitz & Taylor 2019; Fineburg & Gale, 2005; Kim et al., 2018). Such withdrawal symptoms emulate those which the medication was originally prescribed to reduce, and such symptoms have been found to be prevalent for between two weeks and one year after discontinuation, with some evidence suggesting up to three years of symptoms (Davies et al., 2018). Moreover, the response rate to SSRI medication is significant as it means roughly half of OCD patients do not respond fully, or at all, to the best pharmacological treatment available. This may be because serotonin is not the only neurotransmitter that has been implicated in OCD, as several others (such as glutamate) have been linked to the development of the condition (Koen & Stein, 2011).

It has been proposed that the glutamate system may also be dysfunctional in OCD as research has connected glutamate transporter genes,

such as *SAPAP3* and *SLC1A1*, to the disorder (Abramowitz et al., 2009). Moreover, recent research has demonstrated that compulsive symptoms are related to the balance of glutamate and GABA in the anterior cingulate cortex (ACC) and supplementary motor area (SMA) of the frontal lobes (Biria et al., 2023). This study found that levels of glutamate in participants with OCD were significantly lower than the GABA levels in their ACC and that changes in glutamate levels in the SMA were positively related to compulsive symptoms. Therefore this suggests the balance of these neurochemicals could have a key role in OCD symptoms and thus other pharmacological treatments that target these specific neurotransmitters should be investigated.

In summary, SSRIs appear to be an effective treatment for symptom relief in most OCD patients, however, these negative consequences and response rates should not be overlooked. As a result, alternative therapies may be considered when deciding the treatment.

Neurobiological studies of OCD have determined the involvement of several brain regions in the expression of obsessive-compulsive (OC) behaviours, including the orbito-frontal cortex, anterior cingulate cortex (ACC), caudate nucleus, and the thalamus (Nakao et al., 2014), also regions known to regulate goal-directed behaviour (Kim et al., 2018). Such brain regions have been observed to have abnormally high levels of activity in patients with OCD (Nakao et al., 2014). The presentation of repetitive thoughts and behaviours are presumed to arise from dysfunctions at the subcortical and cortical levels in this neural pathway (Kalra & Swedo, 2009). Such propositions have been expanded upon to suggest that OCD may originate from disruptions within interconnected brain networks, rather than specific brain region malfunctions (Yuste, 2015). The aforementioned serotonergic genes have been linked to the presence of abnormal brain structure and function often observed in brain images from OCD patients (Mercadante et al., 2004; Milad & Raunch, 2012), primarily impacting the region known as the cortico-striatal-thalamic circuit (CSTC) — a neural circuit comprised of the orbito-frontal cortex, the caudate nucleus, and the thalamus (Alexander et al., 1986). This is supported by a review of 37 case reports investigating individuals with OCD, that developed as a result of infarctions (death of tissue) or other brain lesions (damaged area of the brain). This study found that lesions in several brain regions including the CSTC may incite compulsive behaviours (Figee et al., 2013). While brain lesions are not a common cause of OCD, the findings from these case studies provide support for the role of the cortico-striatal circuit in the pathology of OCD, and illustrate how variance within the circuit may result in compulsive symptoms in individuals who were previously healthy.

Additionally, another neural region implicated in the origin of OCD is the OCD-loop model (Saxena et al., 1998), wherein the orbitofrontal cortex projects to the caudate nucleus and the striatum, through the basal ganglia to the thalamus, before returning to the original cortical region of firing. The model has a direct and indirect pathway of activation, the former pathway resulting in an excitatory response, with the latter producing an inhibitory response (Saxena & Rauch, 2022). Studies have proposed that overactivity in the direct pathway could lead to difficulties in the suppression of repetitive behaviours (Ahmari & Dougherty, 2015; Saxena & Rauch, 2022; Ting & Feng, 2011). Additionally, an excessive amount of activity in the orbitofrontal-subcortical pathways has been observed in both people with OCD and also in mouse models that imitated OCD adjacent behaviours (Ting & Feng, 2011). Such excessive activity in these pathways has been shown to result in increased grooming behaviours, which were still maintained after stimulation stopped (Ahmari et al., 2013).

Furthermore, functional imaging literature has consistently found unusually increased activation of the medial and lateral orbitofrontal cortex (OFC; Fitzgerald et al., 2011; Menzies et al., 2008). Consistent with this, fMRI studies have demonstrated a positive correlation between lateral OFC hyperactivation and OCD symptom severity during the performance serial reaction time tasks (Rauch et al., 2007), as well as during symptom provocation (Saxena et al., 2001; Whiteside et al., 2004). Moreover, it is believed that impaired frontal inhibitory processing is associated with OFC dysfunctions, consequently resulting in increased obsessive and compulsive behaviours (Menzies et al., 2008), hence the regulation of the activity in the OFC is the neurological basis for treatment which could alleviate OCD symptoms.

The ACC stands as another key region considered to be linked to the pathology of OCD because of its involvement in error monitoring and detection, and identifying cognitive conflicts (Milad & Rauch, 2012). From cognitive task-based fMRI studies, hyperactivity in the ACC has been attributed to the mediation of flawed error signals which give rise to obsession (Fitzgerald et al., 2005; Maltby et al., 2005; Page et al., 2009). Another theory proposes that heightened activation of the dorsal ACC in OCD could mediate the increased fear and anxiety characteristic of the disorder (Pauls et al., 2014). Therefore, the reduction in ACC activity observed post-treatment indicates the key role of treatment in normalising cognitive functions or alleviating anxiety in situations triggering obsessive and compulsive symptoms.

Finally, more recent research has focused on brain matter volume and how this varies in OCD. A recent meta-analysis compared and found a significant difference between the white matter (WM) and grey matter volume (GMV) of healthy controls and OCD patients (Tao et al., 2023). In addition, the left striatum appeared to have an increase in GMV, while there was a decrease in the right hippocampus, right inferior frontal gyrus, and right superior temporal gyrus; however, it should be noted that Tao et al.'s (2023) findings contradict the results from two other large-scale meta-analyses (Kong et al., 2020; Bruin et al., 2020), which found no difference in brain structure between healthy controls and OCD patients. Nevertheless, other research has linked neurological changes to the mechanism of OCD and have suggested such changes could be key in the onset and development of the condition, as they could impact the functioning of the region. Reess et al. (2018) found significant increases in palladium volumes and decreases in hippocampus volumes in OCD patients compared to control participants. They noted that the pallidum is a core region within the CSTC circuit and that it has been assumed to be key in the mechanisms underlying obsessions and compulsions in OCD. They postulated that the decreased volume of the hippocampus in OCD may be linked to stress-related physiological processes, as is often seen in other stress-related psychiatric disorders such as depression and PTSD, speculating that high-levels of checking behaviour is associated with lower hippocampal volume levels. This is interesting as it suggests that changes at the neural level may not be the cause of OCD, some changes may occur as a result of the condition. These findings have led to the exploration of deep brain stimulation as a potential treatment for OCD.

DEEP BRAIN STIMULATION

Since the 1950s, various forms of ablative neurosurgery have been used to treat TROCD (Goodman & Alterman, 2012); however, over the last 20 years, DBS has become a promising alternative with a similar level of efficacy to ablation and the advantage of being both partially reversible and adjustable (Kohl et al., 2018; Hageman et al., 2021). DBS is an invasive method of treatment for several neuropsychiatric disorders (such as Parkinson's disease, major depressive disorder, and OCD; Malek, 2019; Graat et al., 2017) whereby an electrode is implanted into the brain, enabling the activation of neural circuits in the surrounding areas (Abramowitz, 2009). It has been proposed that the high-frequency stimulation incites "functional ablation" on the target brain structures (Goodman & Alterman, 2012, p. 515). The DBS device has four components: the stimulating lead implanted within the target area of the brain to deliver stimulation; a locking device; a pulse generator (PG), which is stationed under the skin on the chest or abdomen and supplies the current; and an extension cable connecting the PG to the power lead (Goodman & Alterman, 2012).

The majority of DBS literature focuses on white and grey matter volume in striatal areas which are involved in or have an association with the CSTC. For instance, the anterior limb of the internal capsule, subthalamic nucleus, ventral capsule/ventral striatum, nucleus of stria terminalis, and the nucleus accumbens — regions that are speculated to be important in decision-making, reward learning, and regulating mood within the CSTC circuit (Li et al., 2020; Alonso et al., 2015). The connection between such abnormal brain structures may impact the function of each brain region and therefore result in the OC presentations.

Additional evidence has shown that the areas targeted by DBS (striatal regions) are influenced by the CSTC and orbitofrontal networks and impacted pathways through these regions may be detrimental to the symptom improvement (Li et al., 2020; Bijanki et al., 2021).

Literature suggests DBS is a relatively safe and effective treatment for TROCD, with meta-analyses demonstrating an approximate symptom reduction of 50% in severe cases 24 months post-treatment. In addition, when looking at DBS for TROCD and co-occurring depression, it was reported that around half of the patients had a complete response to the treatment, while a further 16% had at least a partial response (Gadot et al., 2022). Although, it should be considered that the patients from Gadot et al.'s (2022) study were patients with co-morbid depression, implying that it cannot be determined whether the presence of another disorder had an influence on the efficacy of treatment. Nonetheless, DBS does appear to be effective in reducing OCD symptoms, with long-lasting effects, and would therefore be a better treatment than SSRIs for patients with TROCD.

Despite the clear evidence of efficacy, DBS has some limitations, some of them being quite dangerous. For instance, studies have found that there is an 8% estimated risk of hardware-related complications within the procedure and between 4.4–5% risk of infection associated with DBS (Kantzanou et al., 2021). There is additional danger as the spread of infection from the surgical site could result in meningitis, cerebritis, or brain abscesses; however, such instances are exceedingly rare and there is a high chance that these rates of infection will reduce if more surgeries are conducted and smaller components are developed (Goodman & Alterman, 2012). Moreover, the surgery for DBS is not a one-time operation as the PG is battery powered and requires replacement between 12 months and 9 years after initial implantation. The time frame for replacement is dependent on whether the PG model is rechargeable or not and the amount of current that is required to produce the optimal effect (Holland et al., 2020; Goodman & Alterman, 2012). That is to say, the patient would undergo multiple open-skull surgeries throughout their life to replace a core component of the DBS device. Such occurrence would further increase the risk of infection and surgical complications. Further, DBS is an expensive procedure which many people may struggle to pay. Based on Holland et al.'s (2020) findings, the average cost for the initial implantation of DBS hardware was $27,035 (± $3,623), while the monthly cost for some participants was $1,878 (± $1,019) until the initial battery replacement for the device. The monthly cost for impulse generator changes for participants with non-rechargeable devices was $1,517 (± $870), while the monthly cost for rechargeable devices was $654 (± $219). They also found that the average replacement of non-rechargeable batteries was every 1.4 years with an average cost of $16,432 (± $9,163). Moreover, a study conducted in the Netherlands found that the cost of DBS for two years, including the cost of the equipment, replacements, and follow-up hospital appointments, is €88,946 (Ooms et al., 2017). This was a significant cost increase as the standard treatment for two years totalled €48,330. Whilst Holland et al. (2020) found rechargeable DBS units to be more cost-effective due to minimised battery replacement cost, the DBS procedure is unlikely to be financially viable for a lot of people in countries without free healthcare, and even in countries with free healthcare services, the treatment would be a large financial strain on such services (i.e., the NHS in the UK).

To summarise, DBS is an effective alternative treatment for OCD patients who have developed treatment-refractory symptoms; however, considering the cost and the risks of DBS, this treatment should only be a last resort option if patients do not respond to standard SSRI treatment or other available treatments.

CONCLUSION

SSRIs are the most common treatment for OCD (Skapinakis et al., 2016) and have demonstrated high rates of efficacy for short-term usage (Pittenger & Bloch, 2014). Despite this, they have limitations such as withdrawal symptoms, emotional blunting, cognitive impairment, bone fractures, and excessive bleeding, and have little to no effect for some patients (Marazziti et al., 2019). Whereas DBS is a more experimental treatment and comes with many long-term surgical risks and hardware complications (Kantzanou et al., 2021), research has shown that it is an effective alternative for treatment refractory individuals with long lasting effects (Gadot et al., 2022). Accordingly, there are several factors that must be considered when attempting to treat each case of OCD: the severity of the patient's symptoms, the cost and availability of the treatments (particularly for individuals where healthcare is not free or subsidised), and the potential risks of the treatment. Therefore, for each OCD patient, an individualistic approach must be taken as the most effective mode of care will be dependent on the specific pathogenesis and presentation of each OCD patient. As research continues to advance, we may see additional treatment options emerge, further expanding the possibilities for managing OCD.

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