Understanding OCD symptoms through Decision Making, Genetics, Metacognition, and Cognitive Control

by

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Statement of Authorship

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ABSTRACT

Understanding OCD symptoms through Decision Making, Genetics, Metacognition, and Cognitive Control

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Obsessive – Compulsive Disorder is a neurocognitive disorder which affects approximately 3% of the general population. Almost 33% of patients with OCD diagnosis remain treatment refractory even after the prescription of pharmacological options we have. Thus, we need more comprehensive understanding of the neurobiological basis of OCD to propose more effective treatment options. One of the remarkable characteristics of OCD is the accompanying insight about the symptoms. The patients with OCD diagnosis acknowledge that there is no need to wash their hands repeatedly in the case of contamination obsession, however they can not abstain from performing this compulsive behavior. In this dissertation, the mechanism behind this discrepancy was tried to be understood. The perceptual decision making characteristics of the patients with OCD diagnosis is scarcely studied area of research. This dissertation focused on perceptual decision making in healthy participants with varying degrees of propensity to OCD. In the first study, the relation between dopamine gene related gene polymorphisms (COMT, DRD2 and DARPP-32) and latent decision making variables in addition to obsessive-compulsive factors. The results of this study suggest that having Met/Met allele of COMT gene is associated with lower decision threshold, higher drift rate and higher obsessive-compulsive factor scores. In the second study, metacognitive assessments of participants, in addition to perceptual decision making task, were collected. This study showed that participants with high propensity to OCD have more efficient metacognitive assessments, however they can not use this metacognitive information to modulate the strategy used in their subsequent action in decision making task. Lastly, current literature about cognitive alterations observed in OCD was reviewed in the framework of Expected Value of Control (EVC) Theory which proposes a computational model and neuronal allocations for the adjustment of cognitive control. Overall, these results suggest that participants with high propensity to OCD struggles in behavioral adaptation and this might be the result of a dysfunction in different parts of EVC.

Keywords: OCD, decision making, COMT gene, metacognition, Expected Value of Control Theory

ÖZETÇE

Karar Verme, Genetik, Üstbiliş ve Bilişsel Kontrol Yoluyla

OKB Belirtilerini Anlamak

Anıl Şafak Kaçar

Doctor of Philosophy in Neuroscience January, 26, 2023

Obsesif – Kompulsif Bozukluk, genel popülasyonun yaklaşık %3'ünü etkileyen nörobilişsel bir bozukluktur. OKB teşhisi konan hastaların yaklaşık %33'ü, elimizdeki farmakolojik seçeneklerin reçete edilmesinden sonra bile tedaviye dirençli kalmaktadır. Bu nedenle, daha etkili tedavi seçenekleri önermek için OKB'nin nörobiyolojik temeli hakkında daha kapsamlı bir anlayışa ihtiyacımız var. OKB'nin dikkat çekici özelliklerinden biri, semptomlara eşlik eden içgörüdür. OKB tanılı hastalar, bulaş takıntısı durumunda ellerini tekrar tekrar yıkamaya gerek olmadığını kabul etseler de bu kompulsif davranışı yapmaktan da geri duramazlar. Bu tezde, bu tutarsızlığın arkasındaki mekanizma anlaşılmaya çalışılmıştır. OKB tanılı hastaların algısal karar verme özellikleri çok az çalışılan bir araştırma alanıdır. Bu tez, değişen derecelerde OKB eğilimi olan sağlıklı katılımcılarda algısal karar vermeye odaklandı. İlk çalışmada obsesif-kompulsif faktörlere ek olarak dopamin genine bağlı gen polimorfizmleri (COMT, DRD2 ve DARPP-32) ile gizil karar verme değişkenleri arasındaki ilişki incelenmiştir. Bu çalışmanın sonuçları, COMT geninin Met/Met aleline sahip olmanın daha düşük karar verme eşiği, daha yüksek sürüklenme hızı ve daha yüksek obsesif-kompulsif faktör puanları ile ilişkili olduğunu düşündürmektedir. İkinci çalışmada algısal karar verme görevine ek olarak katılımcıların üstbilişsel değerlendirmeleri toplanmıştır. Bu çalışma, OKB eğilimi yüksek olan katılımcıların daha verimli üstbilişsel değerlendirmelere sahip olduğunu, ancak bu üstbilişsel bilgileri, karar verme görevindeki sonraki eylemlerinde kullanılan stratejiyi değiştirmek için kullanamadıklarını göstermiştir. Son olarak, OKB'de gözlemlenen bilişsel değişikliklerle ilgili mevcut literatür, bilişsel kontrolün ayarlanması için hesaplamalı bir model ve nöronal tahsisler öneren Kontrolün Beklenen Değeri (KBD) Teorisi çerçevesinde gözden geçirilmiştir. Genel olarak, bu sonuçlar, OKB eğilimi yüksek olan katılımcıların davranışsal uyumda mücadele ettiğini ve bunun KBD'nin farklı bölümlerindeki bir işlev bozukluğunun sonucu olabileceğini düşündürmektedir.

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INTRODUCTION

Obsessive-Compulsive Disorder (OCD) is a neurocognitive disorder which affects 2.5-3% of the general population (Robbins et al., 2019). OCD is characterized by intrusive anxiety-provoking thoughts (e.g., contamination) that typically induce compulsive behaviors (e.g., washing hands) to alleviate the resultant anxiety. In the literature, at least four different symptom dimensions for OCD were defined, namely cleaning (contamination obsessions and cleaning compulsion), symmetry (symmetry obsessions and repeating ordering, and counting compulsion), forbidden or taboo thoughts (for example, sexual, religious, or aggressive obsessions and related compulsions), and harm (for example, fears of harm to oneself or others and checking compulsions) (American Psychiatric Association & Association, 2013; Mataix-Cols et al., 2005). The compulsive behaviors are costly both locally (e.g., in terms of interference with daily tasks as well as time and biomechanical costs) and globally (e.g., in terms of interfering with professional life and personal relations).

A number of biochemical, neuropsychological, and neuroimaging biomarkers have been shown to be significantly associated with OCD, however, none of these biomarkers have reached adequate sensitivity and specificity to become a diagnostic biomarker (Fullana et al., 2020). One of the possible reasons behind the difficulty of detecting an overarching biomarker for OCD is the heterogeneity in the manifestation of the disease itself. As stated earlier, at least four different symptom dimensions were defined for OCD (American Psychiatric Association & Association, 2013; Mataix-Cols et al., 2005). The possible differences in underlying neurobiology of these symptom dimensions might be obscuring the overarching biomarkers for OCD.

The first-line treatment option for OCD is Selective Serotonin Reuptake Inhibitors (SSRIs) or Cognitive Behavioral Therapy (CBT) with Exposure and Response Prevention (ERP) component or both (Hirschtritt et al., 2017). Only 40-60% of patients with OCD

attain partial response to initial treatment (Pallanti & Quercioli, 2006). As an augmentation treatment, antidopaminergic agents, mostly second-generation atypical antipsychotics, are applied to treatment-refractory patients with OCD, however, only about one-third of those patients have a response to antidopaminergic agents (Bloch et al., 2006). Therefore, there is a need for a more comprehensive understanding of the neurobiological basis of OCD in order to propose a novel and more effective treatment options.

One of the aims of this work is to investigate decision-making characteristics of healthy controls with varying degrees of obsessive-compulsive traits. In the first chapter, the decision-making processes of participants will be investigated from the broader perspective of transdiagnostic psychiatry. In addition to the obsessive-compulsive traits, the effect of impulsive and anxious-depressive tendencies on the perceptual decision-making process will also be examined in relation to single nucleotide polymorphisms pertaining to the dopaminergic system. In the second chapter, the decision-making characteristics of healthy controls with varying degrees of obsessive-compulsive traits will be investigated along with their metacognitive performances. Lastly, the pathophysiology of OCD will be discussed within the framework of the Expected Value of Control theory. Before proceeding to those chapters, several aspects of obsessive-compulsive disorder will be summarized in this introductory chapter. The motivation behind those studies will be clarified by the background information provided in this introduction.

Neurobiological Basis of OCD

Twin and family studies provide compelling evidence for the involvement of genetic factors in the expression of OCD (Pauls, 2010). First-degree relatives of people with OCD have a four-fold increased lifetime risk of receiving an OCD diagnosis compared to people without a first-degree relative with the disorder (Nestadt et al., 2000). Twin studies reported that genetic influences are within the range of 45% to 65% in children, and 27% to 47% in adults (Tambs et al., 2009; Van Grootheest et al., 2005). The pathophysiology of OCD does not depend on a single gene mutation, instead, it has a polygenic nature. The most advocated genetic alterations are related with the functions and development of glutamatergic synapses, such as SLC1A1, DLGAP1, and PTPRD polymorphisms.

However, none of these polymorphisms reached genome-wide significance (Arnold et al., 2018).

The standard neuroanatomic model of OCD is based on the disrupted activity of cortico-basal ganglia – thalamic – cortical loops (Dougherty et al., 2018). In principle, the general organizing scheme of these loops is that they project from specific areas in the frontal cortex to corresponding targets within the striatum, and then by direct and indirect pathways through the basal ganglia to the thalamus, and lastly with recurrent projections back to the original frontal area where each loop started (Alexander et al., 1986). Within the basal ganglia, there are two opposing pathways: the direct "excitatory" pathway and the indirect "inhibitory" pathway (Huey et al., 2008). The neurons in the direct pathway express excitatory D1, and neurons in the indirect pathway express inhibitory D2 dopaminergic receptors (Huey et al., 2008). Via these direct and indirect pathways, the CSTC loops have a role in controlling the behavioral and cognitive outputs (Milad & Rauch, 2012). For the understanding of the pathophysiology of OCD, mainly dysregulation of two distinct CSTC loops has been proposed (McGovern & Sheth, 2017). One of those loops involves the OFC and ventromedial caudate nucleus, and this loop has been shown to be hyperactive in patients with OCD diagnosis (McGovern & Sheth, 2017). The other loop, on the other hand, involves the dorsolateral prefrontal cortex and dorsolateral caudate, and this loop has been shown to be hypoactive in patients with OCD diagnosis (McGovern & Sheth, 2017). Thus, this model proposes the OFC hyperactivity as the neural source of obsessions and associated compulsions, and the hypoactive executive network as the limiting factor to switching to a new behavior for patients with OCD diagnosis (McGovern & Sheth, 2017).

The suggestion of the disrupted activity in CSTC loops for the neural mechanism behind OCD is an oversimplification (Dougherty et al., 2018). Later studies have shown that CSTC loops are not multiple, parallel, and segregated circuits as initially conceptualized; instead, those loops have spiral-like structure and cascading connections across circuits (Milad & Rauch, 2012). It is shown that projections from OFC, vmPFC, and dACC converge and overlap in neighboring regions of the striatum (Haber & Knutson, 2010). Although the early CSTC model of OCD placed heavy emphasis on the role of the hyperactive OFC in the pathophysiology of OCD, it is now appreciated that different sub-

regions of the OFC play distinct roles in processing reward, negative affect, fear, and anxiety (Kringelbach & Rolls, 2004; Milad & Rauch, 2007; Milad & Rauch, 2012).

According to a comprehensive meta-analysis of OFC function, the lateral OFC is related to the processing of negative valence, and the medial OFC is associated with processing positive valence (Kringelbach & Rolls, 2004). The lateral OFC appears to be crucial in responding to punishment and escaping danger, and may be involved in ritualized behavioral responses (Elliott et al., 2010; Hollerman et al., 2000; O'Doherty et al., 2003). The medial OFC, on the other hand, seems to be more involved in emotion regulation and reward processing (Milad & Rauch, 2012).

During reversal learning tasks, when behavior change is required, the lateral part of the OFC is found to be hypoactive in OCD (Remijnse et al., 2006). During symptom provocation, on the other hand, the lateral part of the OFC is reported as hyperactive in OCD (Rotge et al., 2008; Rotge et al., 2009; Rotge et al., 2010; Simon et al., 2010). The hyperactivity of lateral OFC with symptom provocation reduces during behavioral therapy for OCD (Morgieve et al., 2014). Contrary to the lateral OFC, the medial OFC has an almost exactly opposite activation pattern in symptom provocation and reversal learning. The medial OFC, as a part of vmPFC, is reported as hypoactive during symptom provocation in patients with OCD (P. Banca et al., 2015). However, the same region has hyperactivity during shock-avoidance and safety learning (Apergis-Schoute et al., 2017; Gillan et al., 2015). These studies exhibit the need for refinement of the hyperactive CSTC loops hypothesis in OCD.

At the molecular level, the dysfunction in the serotonergic system has been considered as the main neurochemical disturbance in OCD because of the established efficacy of serotonin reuptake inhibitors (SSRIs) in the treatment of OCD (Pittenger & Bloch, 2014). Based on neuroimaging studies, decreased serotonin transporter availability in midbrain regions and thalamus, increased 5-HT2A receptor availability in caudate, and decreased 5-HT2A receptor availability in prefrontal regions have been reported in patients with OCD diagnosis (Graat et al., 2017). The reduced serotonin level in CSTC loops has been proposed as one of the reasons for hyperactivity in those circuits in OCD (Dougherty et al., 2018). In addition to alterations in the serotonergic system, alterations related to dopamine and GABA have been also reported in OCD (Dougherty et al., 2018). Based on

positron emission tomography and single-photon emission computed tomography studies, the increased density of dopamine transporter and decreased binding of D2/D3 and D1 receptors in the striatum have been reported (Graat et al., 2017). These findings propose hyperactivity of the dopaminergic system in the striatum (Dougherty et al., 2018). In terms of GABAergic activity, on the other hand, the GABA levels in the medial prefrontal and orbitofrontal cortex have been reported as reduced in patients with OCD diagnosis (Simpson et al., 2012; Zhang et al., 2016). These studies also support the standard model of OCD which relies on the disrupted activity in CSTC loops.

Cognitive Alterations in OCD

Robbins et al. (2019) suggest five plausible cognitive endophenotypes for OCD. The possible disruptions in response inhibition, cognitive flexibility, working memory, error monitoring, and goal-directed action selection were proposed as candidates for core cognitive deficits in OCD. The studies investigating these cognitive faculties in OCD had significant variability and occasional inconsistency, however, these disturbances have been confirmed by meta-analyses (Abramovitch et al., 2013; Mar et al., 2022; Luke J Norman et al., 2019; Shin et al., 2014; Snyder et al., 2015).

Response inhibition refers to the ability to inhibit inappropriate or irrelevant responses. This ability is measured by well-accepted neurocognitive tests such as Go/No-Go and stop-signal inhibition tasks. For the number of commission errors in the Go/No-Go task, the effect of having the diagnosis of OCD has been reported as insignificant, however, studies in this area were significantly heterogeneous (Wright et al., 2014). The mean reaction time of patients with OCD diagnosis was significantly longer than healthy controls, with a small-to-medium effect size (Wright et al., 2014). In another meta-analysis pooling the performance in stop-signal inhibition tasks, the performance of patients with OCD diagnosis has been found to be significantly impaired (Mar et al., 2022). The same meta-analysis also reported a null result for the comparison in mean response time between patients with OCD diagnosis and healthy controls (Mar et al., 2022). There are two other meta-analyses in the literature that pools different neurocognitive tasks (go/no-go, stop-signal, stroop, flanker, multisource interference, continuous performance tasks) measuring response inhibition (Abramovitch et al., 2013; Luke J Norman et al., 2019). Those studies reported a significant deterioration in response

inhibition of the patients with OCD diagnosis. Norman et al. (2019) also reported a longer response time for the patients with OCD diagnosis when compared to healthy controls. Those studies, even some discrepancies, confirm difficulties in response inhibition with complimentary longer response time in OCD.

Cognitive flexibility has been broadly defined as the ability to flexibly adapt behavior to the requirements of a changing environment (Gruner & Pittenger, 2017). This ability is assessed by neurocognitive tests such as the Intradimensional/ Extradimensional (IED) Shift Task, Wisconsin Card Sorting Test (WCST), and Reversal Learning tasks. Two metanalyses on the cognitive functioning of patients with OCD reports overall deficit in accuracy of shifting, and this deficit is more pronounced in intradimensional shifting than extradimensional shifting (Shin et al., 2014; Snyder et al., 2015). The number of perseverative errors in WCST is reported as higher than healthy controls by the same meta-analyses (Shin et al., 2014; Snyder et al., 2015). Studies of reversal learning, on the other hand, have not reported consistent behavioral differences in reversal-related errors in individuals with OCD compared to healthy controls, even if there may be more subtle performance abnormalities (Chamberlain et al., 2008; Remijnse et al., 2006; Valerius et al., 2008). The discrepancy between the behavioral outcomes of WCST and reversal learning tasks might be the result of feedback structure. In WCST, the participants get deterministic feedbacks matching with the cue of the trial; however, in reversal learning task, the feedbacks are mostly probabilistic. Aside from the behavioral outputs of the reversal learning task, the lateral part of the OFC is found to be hypoactive in OCD when a change is necessary during the task (Chamberlain et al., 2008; Remijnse et al., 2006).

On contrary to the cognitive alterations listed above, heightened amplitude of error-related negativity (ERN) is relatively specific to OCD (Robbins et al., 2019). Heightened ERN response among OCD patients has been demonstrated many times (Perera et al., 2019; Riesel, 2019; Weinberg et al., 2015). ERN is an EEG signal with a frontocentral distribution peaking after 50-100 ms committing an error, and the source of ERN is accepted as ACC (Yeung & Summerfield, 2012). The ERN signal is associated with error detection, and there is no difference in amplitude of the ERN signal between aware and unaware errors (Nieuwenhuis et al., 2001). Kaczkurkin et al. (2013) compared ERN responses of participants with varying levels of OC tendencies by using the Flanker task having different difficulty levels. The significant difference between high OC and low OC

groups has been detected only when the task is easy since the ERN response of low OC group increased with the difficulty of the task while the ERN signals of high OC participants have similar amplitude for different levels of difficulty (Kaczkurkin, 2013). Similarly, Riesel et al. (2019) compared ERN responses of OCD patients and healthy controls by using the Flanker task while emphasizing the importance of accuracy or speed of response in the task. While there is no significant difference between ERN responses of OCD patients and healthy controls when the emphasis is on the accuracy, higher ERN amplitude is detected among OCD patients when the emphasis is on the speed (Riesel et al., 2019).

A significant portion of patients with OCD has an insight into their disorder. Those patients who have good insight explicitly know that their compulsive acts are excessive and unnecessary considering the threat associated with the obsessive thoughts. For example, patients with OCD know that there is no further preventative advantage of their checking behavior of hot stove repeatedly against the risk of fire. The insight associated with OCD is not a temporarily stable characteristic of the disorder. OCD patients may have insight about their symptoms at some point in their lives, and then they may lose this insight. Patients with higher insight bother less with the content of their obsessions, feel less anxiety, and their life is less dominated by compulsive acts than patients with lower insight (Penzel, 2017). OCD patients with higher insight may reattribute the discomfort triggered by obsessions as one of the symptoms of their disorder, resultantly, they can refrain from performing the compulsive acts.

Aims of the thesis

As described above, one of the remarkable characteristics of OCD is the accompanying insight into the symptoms. Patients with OCD diagnosis have the information that there is no need to wash their hands repeatedly in the case of contamination obsession, however, they can not stop themselves from performing these compulsive acts. In this dissertation, the aim is to understand the mechanisms behind this discrepancy.

One of the possible mechanisms might be a disruption in perceptual decision making. The perceptual decision making characteristic of the patients with OCD is a relatively less studied area of research. The individual studies were reviewed in the study of Gupta et al.

(2021). In summary, patients with OCD show increased RT (Paula Banca et al., 2015; Erhan & Balcı, 2017; Mandali et al., 2019; Marton et al., 2019), lower drift rate in high signal-to-noise ratio conditions, and higher decision threshold for low signal-to-noise ratio conditions (Paula Banca et al., 2015). The first study will investigate single nucleotide polymorphisms in dopamine related genes on both the parameters of decision making (drift rate and threshold setting) and the propensity to OCD, in addition to the propensity to anxious-depressiveness and impulsivity. The effect of dopamine on DDM parameters was studied before with patients with Parkinson's disease (Huang et al., 2015). By this study, it was shown that drift rates of the patients with Parkinson's disease were significantly lower in the ON medication state than in the OFF dopaminergic medication state. On the other hand, there was no difference between ON medication state and OFF medication state in terms of threshold setting (Huang et al., 2015). However, to our knowledge, there is no study investigating the effect of SNPs in dopamine related genes on DDM parameters and psychiatric dimensions.

Another possible mechanism might be a disruption in metacognitive abilities. Metacognition refers to one's awareness and understanding of his/her thought processes. It also includes the ability to reflect on and regulate one's own thoughts and behaviors, and to monitor and adjust one's thinking strategies as necessary. Impaired metacognition might lead to repetitive enactment of the same behavior regardless of the outcome (Hauser et al., 2017). Similarly, compulsions are repetitive, ritualized behaviors that the person feels driven to perform (Goodman et al., 2014). The second study will focus on the perceptual decision-making parameters and will investigate the metacognitive abilities of healthy participants with varying degrees of propensity to OCD.

Lastly, the pathophysiology of OCD will be discussed within the framework of the Expected Value of Control theory. According to the EVC theory, individuals determine how much cognitive control should be assigned to the targeted task based on the value of possible outcomes, the cost of cognitive control, and the perceived value of their efficacy on the task outcome. Any disruption in this process might be the mechanism behind the discrepancy described above. Patients with OCD diagnosis perform their compulsive behaviors even though they have the knowledge that there is no need to perform those acts. The third study will discuss this issue within the framework of the Expected Value of Control theory.

Chapter 2

THE EFFECTS DOPAMINE RELATED GENES ON DECISION DYNAMICS AND PSYCHIATRIC DIMENSIONS

Abstract

Dopaminergic function is highly implicated in different aspects of cognitive performance and affective states. However, the role of dopamine in decision process is not well known. The current study investigated the association between the dopamine- (DA) function related gene polymorphisms (i.e., COMT, DRD2, DARPP-32) with the latent variables of the decision-process as well as neuropsychiatric states estimated from factor analysis (i.e., obsessive compulsive, anxious depressive, impulsivity). 82 college students were tested in the dot motion direction discrimination task with three different levels of task difficulty and filled out five neuropsychiatric scales. The accuracy and response times gathered from the decision-making task were modeled with a hierarchical Bayesian drift-diffusion model to estimate how the core latent parameters of the decision process changed between different gene polymorphisms. Met/Met allele, which is associated with increased DA in prefrontal cortex (PFC) had less cautious decision making and more efficient evidence integration when compared to Val carriers. Individuals with this polymorphism also had higher obsessive-compulsive and anxious-depressive scores. There were no significant associations with polymorphisms of DRD2 and DARPP-32 genes. Our results suggest a modulatory (through decision threshold) and enhancing (through the rate of sensory evidence integration) role of prefrontal dopamine related gene COMT polymorphism in perceptual decision making. Our results associate Met/Met allele with an increase in obsessive-compulsive and anxious-depressive scores.

INTRODUCTION

Dopamine (DA) is implicated in the control of various functions in the brain (Missale et al., 1998). For example, DA is involved in motor function (Barbeau, 1974), endocrine regulation (Pivonello et al., 2007), reinforcement (Reynolds et al., 2001), emotion (Nieoullon & Coquerel, 2003), cognition (Nieoullon, 2002), motivation (Salamone & Correa, 2012) and reward systems (Wise & Rompre, 1989). The presence of DA in the mammalian forebrain, specifically basal ganglia, is linked with limbic and motor processes (Nieoullon & Coquerel, 2003). Crucially, DA is more readily available in the frontal lobes than posterior cortical regions, which correlates with cognitive abilities of the primates, and is vital for higher-order cognitive processes (e.g., executive functions) of the prefrontal cortex (PFC) (Nieoullon, 2002).

The relation between DA and decision making processes is not fully understood. Perceptual decision making provides an ideal domain to use for the study of the role of DAergic function in choice behavior due to the mechanistic granularity by which the underlying decision process can be characterized. For instance, the choice accuracy and response times gathered from such tasks can be accounted for in a unified fashion by evidence integration to threshold models (Brown & Heathcote, 2008; Ratcliff & McKoon, 2008; Usher & McClelland, 2001). A prominent model that is widely applied to choice behavior is the drift-diffusion model (Ratcliff, 1978; Ratcliff & McKoon, 2008). According to this model, sensory evidence is noisy (drift rate), evidence supporting two different alternatives is integrated over time and when this integrated evidence hits one of the two thresholds, the corresponding decision is made. The latency to threshold first crossing times indexes the decision time.

A number of psychopharmacological studies that used this decision theoretic approach have so far revealed equivocal results regarding the effect of DAergic manipulations on decision making. For instance, Beste et al. (2018) reported increase in the efficiency of evidence integration (i.e., drift rate) and no difference in decision cautiousness (i.e., threshold setting) as a result of methylphenidate administration. On the other hand, Rawji

et al. (2020) reported decrease in both drift rate and threshold as a result of the administration of another DA agonist (i.e., ropinirole). Wagner et al. (2020) reported that the administration of DA antagonist haloperidol did not affect either the drift rate or decision threshold. On the clinical front, patients with Parkinson's disorder had higher drift rate and same threshold setting during ON compared to OFF medication (Huang et al., 2015). These studies suggest that although DA affects the latent processes of decision making, the exact mechanistic nature of this effect needs to be clarified.

These different observations might be due to vast variation in neurotransmitter systems. For instance, there are at least five different subtypes of DAreceptors which are divided into two categories: D1-like and D2-like G-protein coupled DAreceptors (Seamans & Yang, 2004). D1-like DA receptors (D1 and D5) are associated with mostly excitatory but also inhibitory processes (Missale et al., 1998). The action of D2-like DA receptors (D2, D3, and D4) is mostly inhibitory (Missale et al., 1998). D1 receptors are known to be the most abundant-whereas the density of D3, D4, D5 receptors is relatively lower in the brain (Romanelli et al., 2010).

Relatedly, many studies that have demonstrated the effect of DA signaling on cognitive function emphasized the neurobiological aspects and the availability of DA receptors (see (Iversen & Iversen, 2007) for a review). For instance, studies emphasizing how genetic components of DAreceptors affect and alter the function of dopamine in the striatum and frontal cortex have focused on specific DAergic gene polymorphisms (e.g., (Balcı et al., 2013; Frank et al., 2009; Klaus et al., 2017) relating their findings with behavioral outcomes by alluding to DA-dependent cellular and neuronal mechanisms.

The D2 receptor is encoded by the DRD2 gene of 11th chromosome in the human genome (Noble, 1998). Researchers have identified a multitude of polymorphisms associated with structural and functional changes in the D2 receptor (e.g., (Itokawa et al., 1993; Savitz et al., 2013; Zhang et al., 2007). One of the single nucleotide polymorphisms (SNPs) in the DRD2 gene is rs6277, also known as DRD2 C957T. This polymorphism results in one nucleotide change from cytosine (C) to thymine (T), which has been argued to have significant neurobiological effects on the striatum: TT homozygotes have greater D2 receptor density, but lower affinity for DA (Hirvonen et al., 2004). From a cognitive

perspective, CC homozygotes were associated with poorer performance in spatial working memory tasks, indicating their importance for executive function (Klaus et al., 2017), and poorer cognitive abilities in general (Chien et al., 2013). Furthermore, Frank and his colleagues (2007) showed that TT carriers had better and faster performance in avoidance learning.

In addition to the roles of receptor-encoding genes, it is feasible to study the DA receptor signaling through other molecular targets. One of the most studied molecular targets of DA signaling is DARPP-32, an essential protein in striatal medium spiny neurons (Ouimet & Greengard, 1990). Signaling pathways of both D1-like and D2-like DA receptors involve DARPP-32 which is phosphorylated by D1-like receptor signaling (Hemmings Jr et al., 1984). On the other hand, DARPP-32 is dephosphorylated in D2-like receptor signaling (Nishi et al., 1997). A polymorphism of the gene PPP1R1B encoding DARPP-32 is a single nucleotide change to adenine (A) from guanine (G) (rs907094). Individuals with AA genotype have relatively greater amounts of DARPP-32 protein in the striatum (Meyer-Lindenberg et al., 2007). This genotype was formerly associated with better learning from positive outcomes by Frank et al. (2007), greater connectivity between frontal and striatal regions, along with improved cognitive performance (Meyer-Lindenberg et al., 2007).

The role of DAergic activity in the PFC has been most directly implicated in cognitive control (e.g., (Cools, 2008; Cools & D'Esposito, 2011). Catecholamine neurotransmitters (i.e. dopamine, epinephrine, norepinephrine) are catabolized by the Catecholamine-O-methyltransferase (COMT) enzyme in the brain, and its activity becomes significant in PFC where DA receptors are present in comparatively low amounts (Seamans & Yang, 2004). A well-studied polymorphism of the COMT gene is Val158Met (rs4680), resulting in a single G to A nucleotide substitution. Met allele is associated with A nucleotide, and COMT enzymatic activity of Met carriers is reduced by approximately 40% compared to individuals with Val/Val genotype (Chen et al., 2004). Consequently, DA availability of Met carriers is higher in PFC than individuals with Val/Val genotype. Such an effect was associated with an increase in physiological PFC response and responsiveness to reward (Egan et al., 2001; Lancaster et al., 2012) and better adaptation to task when encountered a negative outcome in decision-making (Frank et al., 2007).

The current study investigated the role of aforementioned polymorphisms (rs6277, rs907094, rs4680) in a two-alternative forced-choice (2AFC) decision-making task by comparing genotype groups in terms of RT, accuracy, and the parameters of the diffusion model of decision-making (Ratcliff & McKoon, 2008). These analyses were coupled by the comparison of genotype groups in terms of the neuropsychiatric factors.

METHODS AND MATERIALS

Participants

A total of 82 participants were recruited either from the subject pool or by announcements around the Koç University campus. All participants gave informed consent to participate in the study and to the collection of their saliva samples for genetic analysis, and their participation was compensated by a monetary reward based on their task performance. We removed a total of 10 participants from the analysis (prior to the analysis) since (a) 5 participants completed the behavioral procedure but their saliva samples were not collected, and (b) behavioral data of 5 participants indicated arbitrary response patterns. Therefore, the analyzed sample consisted of 72 participants (40 females) ranging in age from 18 to 24 (M = 19.9, SD = 1.4). Participants were asked to complete a medical screening questionnaire prior to the experiment for medical, psychiatric and neurological information of the participant and their families, as well as drug use and demographic information. All procedures were approved by the Institutional Review Board of Koç University.

Stimuli and apparatus

Each participant was presented with white dots (3 × 3 pixels) moving randomly with a fixed speed. Stimuli were shown in a circular region (3-inch diameter) at the center of the display with a black background. Only a particular portion (0, 8, or 16%) of the dots had a fixed direction either leftward or rightward on each trial, whereas the remaining portion of the white dots were moving randomly. The stimulus was presented to the participants through the Psychophysics Toolbox (40, 41) on a 21.5-inch MAC monitor and generated

in MATLAB (The MathWorks Natick, MA). The participants responded to the stimulus via computer keyboard, and their distance from the monitor was approximately 60 cm.

Procedure

Turkish versions of the following self-report measures were administered to all participants prior to behavioral task: STAI-A-Trait Scale (Öner, 1977; Spielberger et al., 1971), Beck's Depression Inventory (Beck et al., 1961; Hisli, 1989), Barratt Impulsivity Scale (BIS-11) (Güleç et al., 2008; Patton et al., 1995), Behavioral Inhibition-Behavioral Activation Scales (BIS-BAS) (Carver & White, 1994; Sisman, 2012), Padua Inventory (50, 51). The Turkish versions of the questionnaires listed above had sufficient psychometric properties.

The experiment consisted of three sessions. Each session started with a 4-min practice block with 16% motion coherence. Then, participants completed a total of 9 free-response (FR) blocks, each lasted for 4-min. There were 3 blocks for each coherence level (0%, 8%, 16%), and the order of blocks were randomized. In each FR block, participants were expected to indicate the motion direction as accurately and quickly as possible via pressing "M" key for rightward motion with right index finger, and "Z" key for leftward motion with left index finger. In each FR trial, stimulus was presented until a response, and a new trial began after a randomly determined response-to-stimulus time (distributed exponentially in each block, mean = 2 s). Audio feedback was provided for correct responses and participants earned 0.015 TRY for each correct response, while there was no feedback or a penalty for negative responses. Cumulative scores were shown to participants in each 10-trials. Responses given in the first 100 msec after stimulus onset were emitted, as they were premature responses, and signaled by a buzzing sound, followed by 4-sec timeout.

Genotyping

Until the extraction of DNA, the saliva samples collected from participants were stored at -20°C. DNA was extracted from the saliva samples using Macherey-Nagel NucloSpin Tissue Kit and stored at -20°C.

COMT

Tetra-primer PCR procedure was used for the identification of COMT genotypes. Following primers were used: COMT-common-F ‘CCAACCCTGCACAGGCAAGAT’, COMT-common-R ‘CAAGGGTGACCTGGAACAGCG’, COMT-P3-F 'CGGATGGTGGA- TTTCGCTGACG’ and COMT-P4-R ‘TCAGGCATGCACACCTTGTCCTTTAT’ (Ruiz-Sanz et al., 2007). 20 ng DNA was added into each PCR reaction, along with 0.12 mM of COMT-P4-R, 0.20 mM of other three primers, 12.5 ul of Thermo Scientific DreamTaq Green PCR Master Mix (2X) and nuclease-free water up to 25 ul of total volume. Initial denaturation lasted for 4 min at 94°C, then there were 30 cycles of the following steps: denaturation at 94°C for 30 s, annealing at 66°C for 30 s, extension at 72°C for 20 s, followed by 5 min of final extension. PCR products were loaded on 1.5% agarose gel for electrophoresis and then visualized in Biorad Gel Doc XR Imaging System. One of the participant’s DNA was degraded prior to the COMT genotyping therefore it was excluded from the analyses including COMT genotype. Of the remaining 71 samples, 20 of them had no polymorphism (Val/Val), 33 of them had only one polymorphic allele (Val/Met) and 18 of them were homozygous polymorphic (Met/Met). For the analyses, Val/Val and Val/Met genotypes were grouped together to compare with Met/Met genotype (Frank et al., 2009).

DRD2

For the determination of DRD2 genotypes, firstly, PCR product was obtained by using following primer pair: DRD2-F ‘ACCAYGGTCTCCACAGCACTCT’ and DRD2-R ‘ATGGCGAGCATCTGAGTGGCT’ (Mohammadi et al., 2018). For each 20 ul PCR reaction, 2 ul DNA was taken from the original stock (variable concentrations, 35 ng/ul on average) ; 0.2 mM of each primer, 10 ul of Thermo Scientific DreamTaq Green PCR Master Mix (2X) and 7.2 ul of nuclease-free water were added. PCR protocol was started with initial denaturation at 95°C for 5 in, followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 56.9°C for 1 min, extension at 72°C for 1 min, and completed by the final extension step at 72°C for 10 min. Macherey-Nagel NucleoSpin Gel and PCR Clean-up kit was used to obtain PCR products. Afterwards, DRD2 digestion reaction was

prepared with the following ingredients: 200 ng PCR product, 0.5 ul Thermo Scientific TaqI (10U/ul) enzyme, 2 ul Thermo Scientific Buffer TaqI (10X), and nuclease-free water up to 20 ul of total reaction. Digestion procedure took a total of 2.5 hours in the thermocycler at 65°C, no heat activation step was required. 4 ul of Thermo Scientific DNA Loading Dye (6X) was added into each reaction prior to agarose gel (3%) electrophoresis. Digestion products were visualized in Biorad Gel Doc XR Imaging System. Among the 72 samples genotyped, there were 13 CC genotypes (no polymorphism), 35 CT genotypes (heterozygous) and 24 TT genotypes (homozygous polymorphic). For the analyses, CT and TT genotypes were grouped together to compare with CC genotypes.

DARPP-32

The same PCR reactions were prepared as DRD2 by using these particular primers to obtain DARPP-32 PCR products: DARPP-32-F 'GCATTGCTGAGTCTCACCTGCAGTCT' and DARPP-32--R 'ATTGGGAGAGGGACTGAGCCAAGGATGG' (Frank et al., 2009). The PCR protocol was the same as DRD2 for DARPP-32 except the annealing temperature was 63.3°C for the DARPP-32 primer pair. Similarly, PCR products were obtained by using Macherey-Nagel NucleoSpin Gel and PCR Clean-up kit. Then, DARPP-32 digestion reactions were prepared by adding the following: 200 ng PCR product, 0.30 ul BioLabs MseI enzyme (10U/ul), 2 ul BioLabs rCutSmart Buffer (10X), and nuclease-free water up to a total of 20 ul digestion reaction. Digestion protocol was started with 1.5 h of incubation at 37°C, and followed by a heat inactivation step at 65°C for 20 min. After the addition of 4 ul of Thermo Scientific DNA Loading Dye (6X), samples were loaded on 3% agarose gel for electrophoresis. Gels were visualized in Biorad Gel Doc XR Imaging System. Genotyping results revealed that there were two samples with no polymorphism (GG), 41 samples were heterozygous polymorphic (GA) and the remaining 29 samples had two polymorphic alleles (AA). For the analyses, GG and GA genotypes were grouped together to compare with AA genotypes (Frank et al., 2009).

Data Analysis

Factor analysis

We employed factor analysis with all the five questionnaires used in the study. This way, we aimed to reduce the collinearity between the overall results of the individual questionnaires, the number of statistical tests conducted and the associated Type 1 errors. We strictly followed the methodological approach utilized in Gillan et al. (2016) and Rouault et al. (2018) for factor analysis using Maximum Likelihood Estimation (MLE). By using R software, factor analysis was performed by the factanal() function in the Psych package, with an oblique rotation (oblimin). The selection of the number of the factors was determined by Cattell's criterion (Cattell, 1966); wherein a sharp transition from horizontal to vertical ('elbow') indicates that there is no significant benefit in keeping additional factors. The objective implementation of this criterion was employed by the Cattell-Nelson-Gorsuch (CNG) test, which calculates the slopes of all possible sets of three neighboring eigenvalues and determines the point at which there is the largest differences in slope (nFactors package in R) (Gorsuch & Nelson, 1981). The CNG test indicated the existence of a 3-factor latent structure that includes factors we labeled as 'Obsessive – Compulsive', 'Anxious – Depressive' and 'Impulsivity' based on the strongest individual item loadings.

While labeling the factors, we apply 0.25 average loading threshold to the questionnaires as in Gillan et al. (2016). For the 'Obsessive – Compulsive' factor, the only questionnaire that reached the threshold we set is the Padua Inventory (M = 0.42, SD = 0.16). The highest average loadings for the factor 'Anxious – Depressive' came from STAI-A-Trait Scale (M = 0.36, SD = 0.17), followed by the Beck's Depression Inventory (M = 0.29, SD = 0.17). Barratt Impulsivity Scale (M = 0.35, SD = 0.25) is the only questionnaire that reached the threshold for 'Impulsivity' factor. STAI-A-Trait Scale (M = 0.23, SD = 0.16) came very close to the threshold for the 'Impulsivity' factor as in Gillan et al. (2016).

Behavioral Data Analysis

Response times (RTs) and accuracy were obtained from the test sessions and determined as the behavioral units of analysis. There was no exclusion of data based on RT (except for DDM fits for which RTs < 100 ms were excluded and the outlier probability was

defined as 5%). We used the data from the last two sessions (considered as steady state) in the analyses. First, independent samples t-test was used to compare accuracy and RTs of different genotype groups, using Jamovi (Version 1.6.23.0). Then, we fit the data using Hierarchical Bayesian estimation of DDM parameters (Wiecki et al., 2013) in Python to test how the threshold and drift rate differed between each group and difficulty level.

RESULTS

First, we tested whether accuracy and RTs differed across the three difficulty levels (i.e., easy (coherence 16%), medium (coherence 8%) and difficult (coherence 0%)) and determined groups of genotypes (note that accuracy was not tested for difficult condition since it is not possible to label any trial as correct or wrong with 0% coherence). Moreover, we also compared the genotype groups in terms of factor scores calculated from the responses to the questionnaires. Descriptive statistics can be found in Table 1.

The comparison of COMT genotype groups illustrated that subjects with Met/Met genotype ($M = 0.71$, $SD = 0.13$) were faster than Val carriers (Val/Val or Val/Met - $M = 0.83$, $SD = 0.21$) only in easy condition ($t(69) = 2.20$, $p = .031$, $d = 0.60$), but not in medium and difficult conditions (min $p = .353$). There was no significant difference between COMT genotype groups in mean accuracy level in either easy or medium condition (min $p = .242$).

The differences between the genotype groups of DRD2 (CC vs. CT/TT) and DARPP-32 (AA vs. GA/GG) were also investigated in terms of accuracy in easy and medium conditions, RTs for each difficulty conditions, and factor scores. No significant differences were found for any of those comparisons between genotype groups (min $p = 0.24$). Statistics pertaining to the independent samples t-test for aforementioned comparisons can be found in Table 2.

Table 1
Descriptives

	COMT				DRD2				DARPP-32			
	Met/Met		Val/Met & Val/Val		CC		CT & TT		AA		GA & GG	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Mean RT (Easy)	0.714	0.1344	0.831	0.2106	0.821	0.1768	0.801	0.2066	0.835	0.2095	0.735	0.1941
Mean RT (Medium)	0.966	0.2806	1.042	0.3010	1.049	0.2437	1.021	0.3075	1.073	0.2909	0.995	0.2981
Mean RT (Difficult)	1.420	0.8644	1.424	0.7616	1.439	0.4728	1.430	0.8361	1.509	0.6708	1.379	0.8498
Accuracy (Easy)	0.951	0.0711	0.930	0.0739	0.930	0.0634	0.935	0.0755	0.936	0.0716	0.934	0.0749
Accuracy (Medium)	0.855	0.0836	0.820	0.1159	0.822	0.1064	0.830	0.1097	0.829	0.0947	0.829	0.1179
Obsessive - Compulsive	38.49	15.30	28.70	13.45	32.54	14.53	30.89	14.45	28.96	11.55	32.69	15.96

Anxious -Depressive	31.78	8.43	26.18	8.36	30.21	9.08	27.08	8.49	27.48	7.99	27.75	9.10
Impulsivity	55.97	10.95	49.92	13.81	54.18	10.60	49.78	13.52	49.10	10.04	51.60	14.81

Note. RTs are given in sec, and difficulty conditions are given in parentheses. COMT groups were Met/Met vs. Val/Met & Val/Val. DRD2 groups were CC vs. CT & TT, DARPP-32 groups were AA vs. GA & GG.

Table 2

Independent Samples t-test (groups of COMT, DRD2 and DARPP-32 genes)

Variable (Condition)	COMT				DRD2				DARPP-32			
	t	df	p	Cohen's d	t	df	p	Cohen's d	t	df	p	Cohen's d
Mean RT (Easy)	2.2033	69.0	0.031	0.60109	-0.3265	70.0	0.745	-0.1000	1.0383	70.0	0.303	0.24949
Mean RT (Medium)	0.9358	69.0	0.353	0.25529	-0.3091	70.0	0.758	-0.0947	1.0938	70.0	0.278	0.26283
Mean RT (Difficult)	0.0163	69.0	0.987	0.00445	-0.0379	70.0	0.970	-0.0116	0.6900	70.0	0.492	0.16580
Accuracy (Easy)	-1.0572	69.0	0.294	-0.28840	0.2288	70.0	0.820	0.0701	0.1169	70.0	0.907	0.02808
Accuracy (Medium)	-1.1793	69.0	0.242	-0.32173	0.2588	70.0	0.797	0.0793	0.0118	70.0	0.991	0.00285
Obsessive - Compulsive	-2.576	69.0	0.012	- 0.703	-0.372	70.0	0.711	-0.1140	-1.081	70.0	0.284	-0.2597

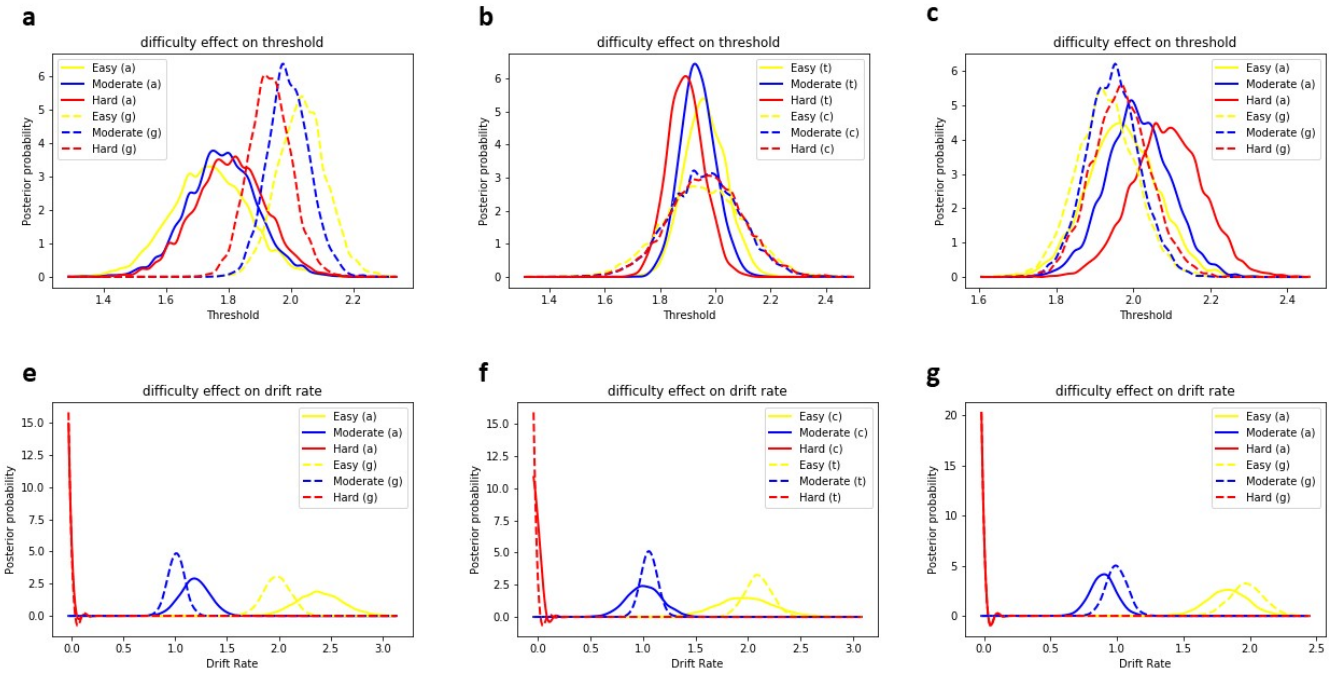
Anxious - Depressive	-2.447	69.0	0.017	-0.668	-1.187	70.0	0.239	-0.3636	-0.129	70.0	0.897	-0.0311
Impulsivity	0.846	69.0	0.400	-0.231	-1.099	70.0	0.275	-0.3369	-0.806	70.0	0.423	-0.1937

Note. Difficulty conditions are given in parentheses. COMT groups were Met/Met vs. Val/Met & Val/Val.

DRD2 groups were CC vs. CT & TT, DARPP-32 groups were AA vs. GA & GG.

Figure 1

Difficulty Effect on Threshold and Drift Rate



Note. Posterior probability distributions for threshold (a) COMT, (b), DRD2, (c) DARPP-32; and for drift rate (d) COMT, (e) DRD2, (f) DARPP-32. For COMT, ‘a’ represents the Met/Met genotype, and ‘g’ represents the Val carriers. For DRD2, ‘c’ indicates the CC genotype, while T carriers are represented by ‘t’. Lastly, for DARPP-32, AA genotype is labeled as ‘aa’, while ‘ga’ includes both GG and GA genotypes.

The scores in ‘obsessive – compulsive’ factor were found to be statistically higher in Met/Met genotype (M = 38.49, SD = 15.3) group than those with Val (M = 28.70, SD = 13.45) genotype (t(69) = -2.58, p = .012, d = -0.70). Similarly, the scores in ‘anxious depressive’ factor were found to be statistically higher in Met/Met genotype (M = 31.78, SD = 8.43) group than Val (M = 26.18, SD = 8.36) carriers (t(69) = -2.45, p = .017, d = -0.69). The comparison of COMT genotype groups with regard to the ‘impulsivity’ scores did not yield any significant difference (p = .40). In terms of DRD2 and DARPP-32 genotype groups, there was no difference in factor scores (min p = .239).

HDDM results revealed that individuals with Met/Met genotype have lower decision thresholds than Val carriers, both in easy (Pa_Met/Met > a_Val = 0.02) and moderate conditions (Pa_Met/Met > a_Val = 0.04). Moreover, the Met/Met genotype had marginally higher drift rates in easy condition (Pv_Met/Met > v_Val = 0.94), while no difference was observed for the medium difficulty condition (Pv_Met/Met > v_Val = 0.86).

There was also no significant difference between determined groups of DRD2 (CC vs. T carriers) and DARPP-32 (AA vs. G carriers) gene polymorphisms in terms of the effect of difficulty on drift rate and threshold parameters of DDM ($0.49 < Pa\_CC > a\_T < 0.70$ and $0.05 < Pv\_CC > v\_T < 0.74$) for DRD2 comparisons; $0.64 < Pa\_AA > a\_G < 0.85$ and $0.21 < Pv\_AA > v\_G < 0.67$ for DARPP-32 groups). Figure 1 illustrates the distribution of posterior probabilities of threshold and drift rate parameters for COMT, DRD2 and DARPP-32 groups.

DISCUSSION

In this study, we investigated the effect of three different polymorphisms associated with the dopaminergic function in the central nervous system on both decision making dynamics and the scores in psychiatric symptom dimensions. Our results suggest that the Met/Met genotype in COMT gene is associated with the decrease in response time and decision threshold, and a tendency for higher drift rate. We could not detect any relation between other investigated polymorphisms and decision making parameters. Similarly, we only detect association between Met/Met genotype in the COMT gene with higher scores

associated with obsessive-compulsive and anxious-depressive traits. The relations between other SNPs in DARPP-32 and DRD2 and the scores in psychiatric symptom dimensions were not statistically significant.

We did not detect any difference between the investigated SNPs in terms of accuracy. Note that the literature also reports equivocal findings on this front. For instance, Malloy-Diniz et al. (2013) reported that individuals having Val/Val genotype showed better performance in a decision-making task. Relatedly, van den Bos et al. (2009) found that participants having Met/Met genotype had the poorer performance in the Iowa Gambling Task, compared to other genotype groups. On the other hand, several studies reported that Met/Met carriers were better in terms of their cognitive performance (Wishart et al., 2011). In terms of DRD2 and DARPP-32, Frank et al. (2007) did not find any significant differences in accuracy levels in the Go/NoGo task.

The only difference in terms of response time observed in our study was associated with Val158Met groups. Our results suggest that the Met/Met group were faster in perceptual decision making task than Val carriers. This finding is in line with the study of Malloy-Diniz et al. (2013) which associates Met/Met group with more impulsive behavior. In another study participants with Met/Met genotype were faster in a cognitive control task (Shehzad et al., 2012). However, because behavioral measures of aforementioned studies did not resemble our experimental paradigm, it is important to further investigate how decision-making behavior differs among Val158Met groups in a two-alternative-forced-choice task. Additionally, future studies should also address the mechanisms that underlie the interaction between task difficulty and genotype (specific effect in easy conditions).

In terms of latent parameters of decision making, we observed that Met/Met group present a tendency to have a higher drift rate. Because individuals with Met/Met genotype have higher levels of DA availability in PFC, which was previously associated with evidence accumulation of the decision-maker (Mulder et al., 2014), prefrontal DA levels might indeed have a role in the efficiency by which sensory evidence is integrated in the decision making context. Moreover, individuals with Met/Met genotype were less cautious in the decision-making process, as they had lower thresholds than Val carriers. Since frontal regions are thought to be significant also for the threshold adjustment

(Mulder et al., 2014), increased levels of DA in PFC may be effective on the decision threshold settings based on fronto-basal ganglia network. Note that this result is also consistent with higher impulsivity in the Met/Met group (Malloy-Diniz et al., 2013).

In addition to the analysis of behavioral performance, we also investigated the association between psychiatric symptom dimensions and aforementioned SNPs. Consistent with earlier studies (Kumar & Rai, 2020; Olsson et al., 2005), we detected associations between Met/Met allele with both obsessive-compulsive and anxious-depressive dimension scores that were in the same direction. Met/Met allele was associated with more anxious-depressive symptoms. Another study showed that patients with OCD diagnosis and Met/Met allele have poorer performance in executive function tasks (Tükel et al., 2013), which is not fully consistent with the behavioral performance of the Met/Met group in the current study. Another meta-analysis reported that Met/Met carriers are more efficient than Val/Val carriers in cognitive processing, but less efficient in emotional processing (Mier et al., 2010). Thus, it is possible that participants with Met/Met allele are associated with better evidence processing and decision making abilities when the task does not require any emotional processing, as in our study.

One of the main limitations of our study is the small sample size for genetic analysis. Thus the results, especially including psychiatric symptom scores, should be interpreted cautiously. The reliability of factor analysis we conducted increases when the sample size is larger. This study must be replicated by a larger group of participants. It is also important to note that our sample only included college students without any diagnosed psychiatric disorders. The generalizability of the result can be improved by admitting participants with a wide variety of age and level of education.

To conclude, this study investigated the single nucleotide polymorphisms associated with dopaminergic function in relation to perceptual decision making and psychiatric symptom dimensions. We found individuals with the Met/Met allele, which is associated with increased DA in PFC had less cautious decision making and a tendency for more efficient evidence integration when compared to Val carriers. Thus, our result suggests an enhancing role of dopamine in perceptual decision making tasks. Consistent with earlier

studies, we also found an association between Met/Met allele and obsessive-compulsive and anxious-depressive scores.

Interim Discussion

In the first study, we investigated the association between obsessive-compulsive scores and latent variables of decision making. We could not find any significant correlation between them. This result is compatible with a number of studies in the literature (Erhan & Balcı, 2017; Mandali et al., 2021). As in our study, two of those studies provided feedback to participants throughout the task, but one of them did not include any information regarding feedback. Thus, these results suggest no disruption in latent variables of decision making of participants with higher obsessive-compulsive scores.

In the subsequent study, we investigated the latent variables of decision making and metacognitive abilities of participants with varying degrees of propensity to OCD. During that study, we did not provide any feedback to participants on contrary to the first study. Thus, participants had to modulate their behavior based on their internal assessment.

As an example of hand washing behavior in case of contamination obsession, there is no definitive feedback provided by the environment. Patients with OCD diagnosis should decide whether their hands are dirty or clean based on their perceptual decision making. When there is an definitive feedback as in the first study, our results suggested that there is no disruption in perceptual decision making. However, the study structure of the second study is more representative of real-life decisions, therefore, it is important to investigate the latent variables of decison making in that context.

Chapter 3

PERCEPTUAL DECISION MAKING AND METACOGNITION IN RELATION WITH OBSESSIVE-COMPULSIVE TRAITS

Abstract

Metacognition is one of the cognitive functions which is shown to be altered in Obsessive Compulsive Disorder (OCD). Studies focusing on metacognitive efficiency have demonstrated a disruption in the precision of confidence estimates in OCD. However, the methodological approaches used in those studies were criticized with the claim that the staircase method is associated with an overestimation of metacognitive efficiency. In this study, we used a two-alternative forced choice task with different difficulty levels within a single block. We collected data from 161 healthy college students with varying degrees of tendencies to OCD symptoms. Our results suggested that the participants with a higher tendency to OCD have higher metacognitive efficiency contrary to the previous literature. Additionally, we utilized the drift-diffusion modeling approach to the first-order decisions of participants, and that analysis showed us that the participants with a higher tendency to OCD have lower drift rates and thresholds. Moreover, we investigated the post-error response time alterations of participants and found that the participants with a higher tendency to OCD have limited adaptation to previous errors and low confidence levels. Overall, our results suggest that having a higher tendency to OCD is associated with sufficient metacognitive capacity, but also with limited utilization of the metacognitive information for behavioral adaptation.

INTRODUCTION

Metacognition describes the ability to think about, reflect, and comment on one's thinking (Hoven et al., 2019; Pouget et al., 2016). This is a key ability since consciously judging one's own performance enables us to calibrate our future behavior (Hoven et al., 2019). Impaired metacognition might lead to continuous enactment of the same behavior regardless of the outcome (Hauser et al., 2017). Similarly, compulsions, one of the main features of Obsessive Compulsive Disorder (OCD), are repetitive, ritualized behaviors that the person feels driven to perform (Goodman et al., 2014).

Confidence judgment is one of the metacognitive operations, and it refers to the subjective feeling of being correct about a choice, decision, or statement (Pouget et al., 2016). Early studies with OCD patients mainly focused on confidence in memory given the high relevance of this domain in the symptomatology of OCD (e.g., re-evaluating whether a person locked the door or not). Patients with OCD diagnosis have comparable memory recollection performance but their confidence level in their memory performance is lower than healthy control. Repeated checking behavior was also shown to be associated with a decrease in the confidence in memory (Boschen & Vuksanovic, 2007; Coles et al., 2006; Van Den Hout & Kindt, 2003).

Metacognitive efficiency is one of the methods used to measure the precision of confidence estimation (Hoven et al., 2019). The precision of confidence estimation refers to how well the confidence judgments of participants match the actual performance (Hoven et al., 2019). Different from the metacognitive sensitivity, which measures how well the participants can differentiate correct and incorrect trials in the signal detection theoretic approach (meta-d'), the metacognitive efficiency (M-ratio) takes into account also the first-order performance (meta-d'/d') (Hoven et al., 2019). This approach is more powerful than the other measures because it eliminates the effects caused by performance differences in the first-order task (Hoven et al., 2019). For an ideal observer, the M-ratio is expected to be 1 as an ideal observer would use all perceptual information that leads to first-order performance (d') during the formation of the metacognitive report (meta-d'). If the M-ratio is less than 1, it means that the observer does not utilize all perceptual

information while generating the metacognitive report; and if the M-ratio is higher than 1, it means that the observer retrieves additional information to form the metacognitive report (Hoven et al., 2019), which could, for instance, result from the continuation of the decision process after the choice is made.

There are two studies in the literature investigating the relationship between metacognitive efficiency and OCD. In the first one, healthy participants with different compulsivity scores were compared with a global dot-motion task with a confidence rating (Hauser et al., 2017). Participants with high compulsivity scores had lower metacognitive efficiency than participants with lower compulsivity scores (Hauser et al., 2017). This implies that high compulsive participants exploited the perceptual signal for their metacognitive judgments less efficiently than low compulsive participants (Hauser et al., 2017). Another study conducted on the general population reported that higher compulsivity scores in self-report scales were associated with overconfidence and reduced metacognitive efficiency (Rouault et al., 2018). Both of these studies utilized the staircase procedure to keep the first-order performance of the participants comparable. However, a more recent study reported that using staircase procedures during perceptual decision-making tasks leads to inflated estimates of metacognitive efficiency (Rahnev & Fleming, 2019). They recommend computing the metacognitive ability for each level of signal strength in the presented stimulus separately (Rahnev & Fleming, 2019). In light of this critique, we designed the current study to investigate the relation between OCD-like features and metacognitive efficiency in different signal strength levels. In addition to the metacognitive efficiency, we investigated the relation between OCD-like features and the first-order decision-making performance of participants and how post-error behavioral adaptations relate to OCD-like features.

METHOD

Participants

161 college students (42 male, mean age = 20.43, standard deviation of age = 1.68) from Koç University participated in this experiment for one extra course credit in return for their participation. The experiment was approved by the local ethics committee at Koç

University. All data collection was conducted online. The data for the behavioral task was collected using the Pavlovia platform (coded in PsychoPy 2020.1.3), and the questionnaire was collected using Qualtrics (Qualtrics, Provo, UT).

Task

We used a two-alternative-forced-choice task, where participants first made a decision and then provided a confidence rating. For the first-order decision, we used a perceptual decision-making task, in which participants observed a 20 x 20 grid containing an unequal number of black and white cells and decided whether the grid was composed of more black or white cells. We used four difficulty levels in terms of the frequency of dominant color (53%, 52%, 51%, and 50.25% for relatively easy to very difficult conditions, respectively). The responses were indicated by pressing the corresponding key on the keyboard (A for white & L for black). The participants were asked to respond as fast and accurately as possible. After participants reported which color that they think is more dominant on the grid, we asked them how confident the participants are about their assessment at three different levels by pressing V (low), B (medium), and N (high) keys. We encouraged the participants to use the entire scale for confidence ratings. Critically and different from our earlier work (Erhan et al., 2017), there was no feedback given for their first order performance. For each difficulty level, we collected data for three blocks of 40 trials each (a total of 120 trials). Before the actual experiment, participants practiced twenty trials with 60% signal without giving any confidence ratings and forty trials with the actual signal levels used in the actual experiment with confidence ratings. During the practice trials, we provided feedback to participants, however during the actual experiment no feedback was given.

Questionnaire

In order to assess OCD-like features of the participants, we applied the Turkish translation of Padua Inventory – Revised (Beşiroğlu et al., 2005; Van Oppen et al., 1995). This questionnaire consists of 41 items with five points Likert scale (0-4). It has five subscales which are impulses, washing, checking, rumination and precision. The Turkish version of

Padua Inventory – Revised was reported to have adequate reliability and validity to apply to the Turkish population (Beşiroğlu et al., 2005).

Analysis

Behavioral Analysis

We excluded the participants (12 out of 161) who performed lower than chance level (determined by binomial test as 54% accuracy in 120 trials) in easy condition from further analysis. Exclusions were made prior to the data analysis. The mean accuracy, the mean response time of first order decision and mean confidence level were compared between different difficulty levels with repeated measures ANOVA. Subsequently, a linear mixed effect model was applied to investigate the effect of OCD-like features on behavioral results.

Metacognitive Efficiency

We estimated metacognitive efficiency by computing M-Ratio (meta-d'/d') where d' is perceptual sensitivity and meta-d' is metacognitive sensitivity. This approach automatically controls for differences in the perceptual decision making performance. If M-Ratio is less (more) than 1, this indicates that the agent uses available information for metacognitive judgement less (more) than for perceptual decision making. To estimate metacognitive efficiency, we used the Matlab code available at http://www.columbia.edu/~bsm2105/type2sdt/ (Maniscalco & Lau, 2012). We estimated metacognitive efficiency scores for each difficulty level separately as recommended by Rahnev & Fleming (2019). Then, we used metacognitive efficiency score estimates in a linear mixed effect model to investigate the relation of OCD-like features with task performance. We complemented these analyses by comparing M-ratios of groups with the low (first quartile) and high (last quartile) PADUA scores by using group-level hierarchical Bayesian estimation.

Perceptual Decision Making

In order to estimate the key parameters of the perceptual decision-making processes of the participants, we treated the data within the drift-diffusion (aka diffusion decision) model (DDM) framework using fast-dm (fast-dm-30) (Voss et al., 2015). For this analysis, we excluded the trials with response time less than 0.1 (anticipatory responses) and more than 5 seconds (task disengagement). According to this rule, we excluded 4.10% of all data points. We used the Maximum Likelihood (ML) method for fitting the model across difficulty levels on a single-subject level. We included drift rate and threshold as free parameters separately for difficulty levels. We let non-decision time and inter-trial variability of non-decision time vary across all conditions. We set the starting point to 0.5, and all other intertrial variability parameters to zero given the low number of trials to reliably estimate the values of these parameters (Voss et al., 2015). Model fit was assessed by following the recommendations of Voss et al. (2015). By using mvtnorm package for R, 1100 parameter sets from a multidimensional normal distribution defined by the covariance matrix of estimated parameter values were drawn. We excluded 100 parameter combinations from this set as they include t0 (non-decision time) and st0 (inter-trial variability of non-decision time) values lower than 0. Additionally, we substituted st0 values as 0 if they are lower than t0. For these parameter sets, data sets were simulated by the construct-sample tool of fast-dm. Subsequently, those simulated data sets were re-fit with the same settings as used for the empirical data. The cut off for exclusion was determined by checking the fit index values of simulated data, and only one of the fit index values of empirical fits were lower than 10% of the fit indices of simulated data. Although the recommended cut-off criteria is 5%, we used a more conservative value as we did some manual changes in parameter sets as described above. Therefore, we excluded only one empirical data from further analysis as described above. The drift rate and threshold estimates of participants were analyzed by using a linear mixed effect model to assess how they relate to OCD-like features.

Effect of Error and Confidence Rating on Response Time of Subsequent Decision

We also examined the effect of error responses and confidence ratings on the response time of subsequent decisions. As explained above, we excluded the trials with response time shorter than 0.1 (anticipatory responses) and longer than 5 seconds (task disengagement). On a trial basis, we calculated response time change with respect to the

previous trial. Then, we analyzed the effect of response type (error or correct) of the previous trial, confidence rating (low, medium, high) on the response time change observed in subsequent trials (RT) by using a linear mixed effect model.

Results

Decision-making Performance:

We tested the effect of Padua score on accuracy level at four different difficulty conditions by using linear mixed effect model with the following formula: Accuracy ~ 1 + Padua Score + Condition + Condition:Padua Score + (1 | Participant). This analysis showed that decision accuracy decreased with both increasing task difficulty ($F(3,447) = 588.53$, $p < .001$) Padua scores ($F(1,149) = 4.62$, $\beta = -0.01$, $SE = 0.01$, $p = 0.033$). As expected, decision accuracy differed between all difficulty conditions (max $p_{bonferroni} < .001$). Interestingly, the effect of Padua score on decision accuracy was dependent on the task difficulty, ($F(3,447) = 3.82$, $p = 0.010$). The effect of Padua Scores on accuracy was statistically significant in only easy and medium difficulty (both $\beta s = -0.02$, $SEs = 0.01$, maximum $p = 0.006$) conditions but not for difficult and very difficult conditions (minimum $p = .301$). The same analysis was repeated with response times (RT); task difficulty had a significant non-monotonic effect on RT ($F(3,447)=4.612$, $p = 0.003$). Response times differed only between easy-medium and easy-very hard comparisons (min $p_{bonferroni} = 0.012$). There was no effect of Padua score ($\beta = -0.06$, $SE=0.05$, $p = 0.241$) on RT or its interaction with task difficulty ($p = 0.900$).

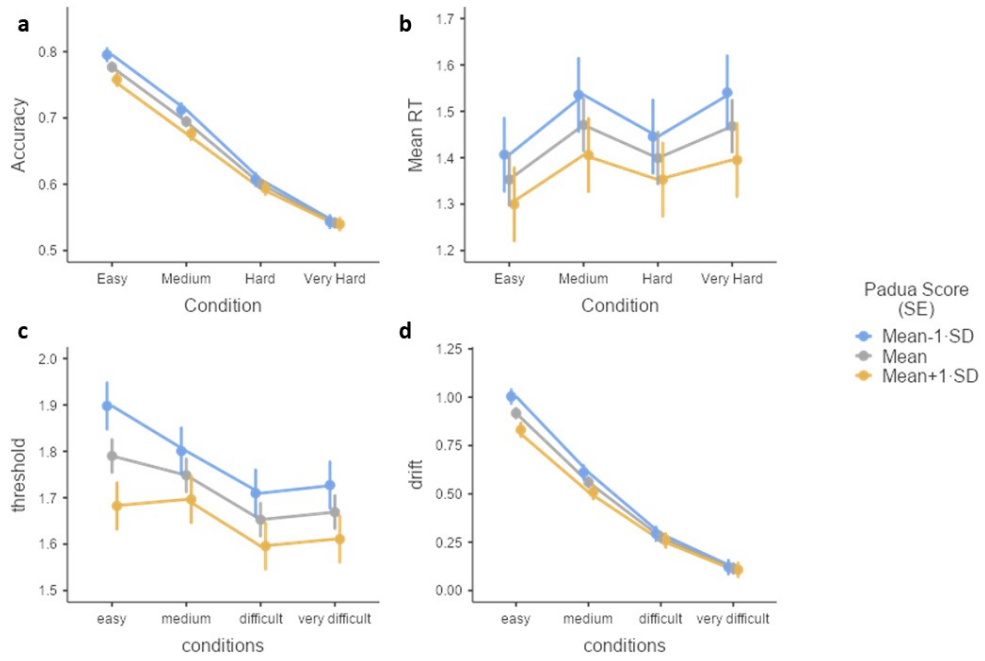


Figure 1. First order decision making parameters with respect to difficulty and Padua scores. Panel (a) shows accuracy , (b) response times, (c) and (d) the output of DDM fits (threshold and drift rate, respectively).

Confidence ratings decreased significantly as a function of increasing task difficulty ($F(3,447) = 53.010$, $p < .001$). There was no effect of Padua score ($\beta = 0.02$, $SE = 0.03$, $p = 0.416$) or its interaction with task difficulty ($F(3, 447) = 0.368$, $p = 0.776$). Similarly, there was an effect of task difficulty on metacognitive efficiency ($F(3, 447) = 4.376$, $p = 0.005$). The post-hoc comparison results showed that this effect was due to the difference between easy and medium conditions (mean difference = 0.15, SE = 0.05, $p_{bonferroni} = 0.007$). The comparison between all other difficulty levels in terms of M-ratio did not yield any significant result (min $p_{bonferroni} = 0.081$). Consistent with the RT and confidence rating results, there was no effect of Padua score ($\beta = 0.02$, $SE = 0.02$, $p = 0.411$); however, its interaction with task difficulty yielded a statistically significant result ($F(3,2.759)$, $p = 0.042$). The simple effect analyses showed that the effect of Padua scores on M-ratio is statistically significant only in medium difficulty condition ($\beta = -0.09$, $SE = 0.04$, $p = 0.009$). Thus, we could not replicate earlier reports of reduced metacognitive efficiency of participants with obsessive-compulsive features (Hauser et al., 2017). On the contrary, our results suggest that participants with obsessive-compulsive features have increased metacognitive efficiency in a fashion that depends on task difficulty.

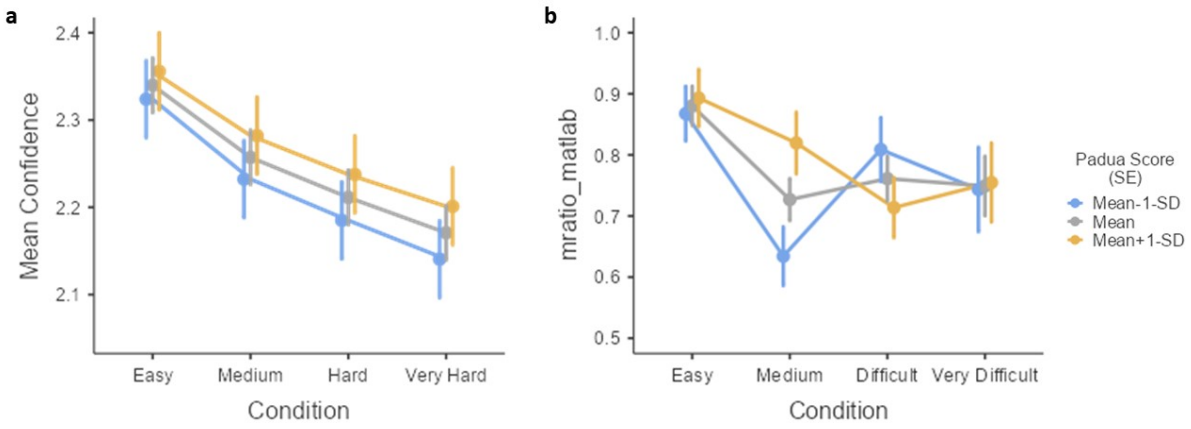


Figure 2. Second order decision making parameters with respect to difficulty and Padua scores. (a) shows raw confidence ratings, (b) shows m-ratio estimates.

The analysis conducted for behavioral outputs reported above is complemented with a similar analysis of DDM outputs gathered from the unified analysis of accuracy and RT. These analyses showed decreasing drift rate with increasing task difficulty ($F(3,334.73)$, $p < .001$) and Padua score ($\beta = -0.04$, $SE = 0.02$, $p = 0.026$). The difference between each pair of difficulty conditions was significant (minimum $p_{bonferroni} < 0.001$). Consistent with our observations with accuracy, the effect of Padua score on drift rate depended on the task difficulty ($F(3,3.47)$, $p = 0.016$). The simple effect analyses showed that the effect of Padua scores on drift rate is statistically significant only in easy ($\beta = -0.09$, $SE=0.02$, $p < .001$) and medium ($\beta = -0.05$, $SE=0.02$, $p = 0.039$) conditions (minimum $p = .486$ in other two conditions). Decision threshold, too decreased with increasing task difficulty ($F(3,14.16)$, $p < .001$) and Padua score ($\beta = -0.07$, $SE=0.03$, $p = 0.031$) without any significant interaction between these two variables ($F(3,2.27)$, $p = 0.079$). Threshold differed between easy-difficult, easy-very difficult, medium-difficult, medium- very difficult conditions (min $p_{bonferroni} = 0.008$) but not between easy-medium and difficult-very difficult conditions (min $p_{bonferroni} = 0.55$). Note that the direction of effect of Padua score was different from our earlier work (Erhan & Balcı, 2017).

Post-error Behavioral Adjustment:

For the investigation of behavioral adaptation to committing an error and having low confidence, we analyzed ΔRT with a linear mixed effect model in which the accuracy and confidence rating in the previous trial, the difficulty level of the trial, and Padua score were used as independent variables. We included, in addition to the main effects of these variables, their interaction with the Padua score with the following formula: with the following formula: RT change ~ 1 + Padua Score + Accuracy_before + Confidence_before + Condition + Accuracy_before:Padua Score + Confidence_before_Padua Score + Condition:Padua Score + (1 | Participant). The accuracy in previous trial ($F(1, 64852) = 90.663$, $\beta = -0.08$, $SE = 0.01$, $p < .001$, with reference to error response), the confidence rating in previous trial ($F(2, 64852) = 277.911$, $p < .001$, the difficulty level ($F(3, 64852) = 5.473$, $p < .001$), and Padua scores ($F(1, 64852) = 6.875$) had statistically significant effect on ΔRT. When compared to decisions following an accurate response, RTs were longer on trials following error response. ΔRT was higher after low compared to medium and high confidence rating, and after medium compared to high confidence rating (maximum $p_{bonferronni} < .001$). This means that when participants are less confident about their first order decision, they slowed down more in subsequent decisions. The effect of difficulty conditions on ΔRT was due to difference between easy – difficult ($p_{bonferroni} = 0.01$) and easy – very difficult ($p_{bonferroni} = 0.002$) comparisons. Other comparisons between difficulty conditions did not yield significant results (minimum $p_{bonferroni} = 0.392$). The modulation of RT was weaker in difficult and very difficult conditions, but it is more profound in easy condition. However, it must be noted that the weaker modulation of RT in difficult and very difficult conditions is confounded with the higher error rate in those conditions (i.e., expected average accuracy in those conditions).

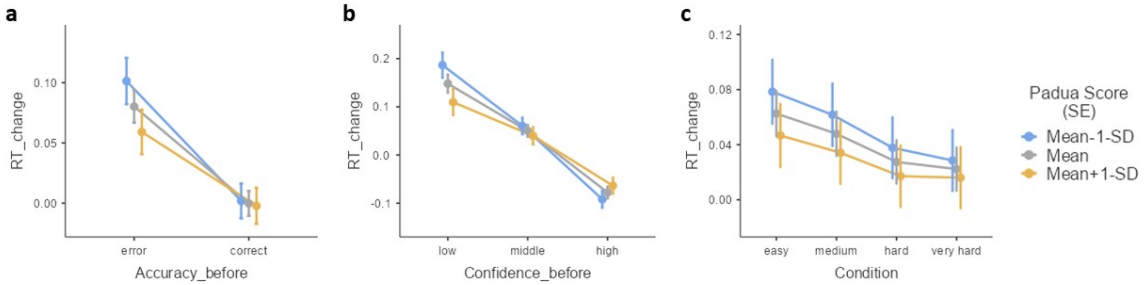


Figure 3. RT changes with respect to features of previous trials and Padua scores. (a) shows post-error and post correct RT changes, (b) shows post-low/medium/high confidence RT changes, (c) shows overall RT changes in different difficulty blocks.

There was a significant interaction between accuracy in previous trials and Padua scores ($F(1, 64852) = 5.204$, $p = .023$). The effect of Padua scores was only significant after error responses ($\beta = -0.02$, $SE = 0.001$, $p = .002$), but not after correct responses ($p = .703$). In other words, an increase in Padua score weakened response time adaptation to erroneous response. The interaction between confidence rating in the previous trial and Padua scores was also significant ($F(2, 64852) = 11603$, $p < .001$). The effect of Padua score was significant when the confidence rating is low ($\beta = -0.04$, $SE = 0.01$, $p < .001$) and when the confidence rating is high ($\beta = 0.01$, $SE = 0.01$, $p = 0.02$), but not when the confidence rating is medium ($p = 0.111$). Specifically, when confidence rating is low, participants with low Padua scores had higher ΔRT than participants with high Padua scores suggesting a difficulty of participants with higher Padua scores in adapting their decision strategy to low confidence level. Similarly, when confidence rating is high, participants with low Padua scores had more negative ΔRT (indicating fastening in the task) than participants with high Padua scores. Thus, the Padua scores affect behavioral adaptation in both conditions. Lastly, the interaction between difficulty condition and Padua score had no significant effect on ΔRT ($p = .839$).

Discussion

In this study, we investigated the effect of OCD-like features on perceptual decision making, metacognition and post-error behavioral adjustments. We showed that there is an inverse relation between accuracy in a perceptual decision-making task and OCD-like features only when the task is easy. This finding is complemented with the lower drift rate in the perceptual decision-making task in participants with more OCD-like features only when the task is not difficult. We did not detect any effect of OCD-like features on the response time of participants. However, different from the literature, we found an inverse relation between the threshold setting and OCD-like features. There was no significant relation between mean confidence rating and OCD-like features; however, the positive effect of Padua scores on M-ratio of participants was observed only when the difficulty of the task was medium. In terms of behavioral adaptation, participants with higher Padua scores had less post-error (and post-low-confidence) slowing and post-correct (and post-high-confidence) fastening. Thus, the participants with higher Padua scores had weaker response time adaptation after both correct (and post-high-confidence) and error (post-low-confidence) responses.

We detected a difference in the accuracy level of participants only in easy and medium conditions. Although the participants with higher Padua scores had comparable accuracy levels in difficult and very difficult conditions, they had lower accuracy in easy and medium conditions when compared to the participants with lower Padua scores. This result suggested that the participants with higher Padua scores could not benefit from higher perceptual evidence in the stimuli (referring to the asymptotic performance). The studies investigating the effect of the difficulty of task on the participants with varying degrees of obsessive-compulsive features on the accuracy mostly presented null results (Paula Banca et al., 2015; Kaczkurkin, 2013; Klawohn et al., 2016; Ma et al., 2021; Riesel et al., 2015). However, different than our study, these studies either provided feedback to the participants (Paula Banca et al., 2015; Ma et al., 2021; Riesel et al., 2015) or applied flanker test instead of perceptual decision-making task (Kaczkurkin, 2013; Klawohn et al., 2016). Moreover, the differences in EEG signals of participants with low and high obsessive-compulsive features were only detected in easy conditions of the tasks

(Kaczkurkin, 2013; Klawohn et al., 2016). Thus, it is possible to suggest that cognitive deteriorations associated with obsessive-compulsive features are more likely to be detected when the applied task is easy.

A similar association between the task difficulty and the Padua scores on the accuracy levels was also observed for the drift rates. We found that the drift rates of participants with higher Padua scores are lower only when the difficulty level of the perceptual decision-making task is easy and medium (corresponding more to the asymptotic efficacy in evidence integration). Similar to our result, Banca et al. (2015) and Marton et al. (2019) showed that participants with OCD diagnosis have slower drift rates only when the coherence level is higher in random dot motion task, but not when the coherence level is low. These results suggest that there might be a ceiling effect in taking advantage of the increase in perceptual evidence for patients with OCD diagnosis. Although the clarity of the perceptual evidence provided by the environment increases, patients with OCD diagnosis might have a certain limit of processing efficacy/speed for that evidence.

On the other hand, the relation between Padua scores and the threshold settings of participants is not compatible with the current literature. The current study found an inverse relation between Padua scores and the decision threshold, which means participants having more OCD-like features set their decision threshold lower than participants having less OCD-like features. However, previous studies reported increased threshold in patients with OCD (Paula Banca et al., 2015; Ma et al., 2021; Mandali et al., 2019) and healthy controls with OC-like features (Erhan & Balcı, 2017; Mandali et al., 2021). There are also studies reporting no difference in threshold setting for patients with OCD (Erhan et al., 2017; Ma et al., 2021; Marton et al., 2019; Rouault et al., 2018) and healthy controls with OC-like features (Mandali et al., 2021). The most critical difference between most of the studies listed above and the current study is the presence of feedback. The studies reporting higher threshold setting in patients with OCD diagnosis and healthy controls with OC-like features provided trial-based feedback to the study participants (Paula Banca et al., 2015; Erhan & Balcı, 2017; Mandali et al., 2021; Mandali et al., 2019)Thus, the reason behind the decreased threshold setting in the current study might be that we did not provide any feedback throughout the task to the participants. In support if this rationale, previous literature has indeed shown that OCD is related to abnormal

feedback processing (Becker et al., 2014). These studies reported a clear differentiation of neural responses to negative, positive, and ambiguous feedback in the ventromedial prefrontal cortex among healthy controls; however, this differentiation was absent in patients with OCD diagnosis. Thus, it is harder for patients with OCD diagnoses to utilize the information gathered from the feedback. Consequently, the provided feedback might function as a distractor for patients with OCD diagnosis and the feedback might cause an increase in the threshold settings. Thus, feedback processing might influence the decision threshold settings and this important relation should be investigated in future research.

We reported an increased M-ratio for the participants with higher Padua scores. In contrast to the current study, both Hauser et al (2017) and Rouault et al (2018) reported an inverse relation between OC-like features and M-ratio. Hauser et al. (2017) utilized the global motion detection task and applied a staircase approach to keep the performance of the participants constant. Rouault et al (2018) asked participants to choose which of the two boxes contained more dots. Similar to Hauser et al (2017), Rouault et al (2018) also used a calibration procedure to maintain a stable performance. However, using staircase procedures during perceptual decision-making tasks led to inflated estimates of metacognitive efficiency in a more recent study (Rahnev & Fleming, 2019). After following Rahnev & Fleming (2019)'s suggestions to investigate different difficulty levels separately, we found a positive relation between OC-like features and M-ratios. Higher metacognitive efficiency could be expected in OCD as their insight is almost always intact. But note that this was only presented in the medium task difficulty level and the reasons that underlie such specificity should be addressed in future work.

For the behavioral adaptation, the participants with higher Padua scores showed lower adaptation both for post-correct and post-error decisions. Specifically, the magnitude of post-error slowing and post-correct fastening is reduced among the participants with higher Padua scores. Our results suggest that the cognitive alteration in participants with OC symptoms could be observed in behavioral adaptation instead of metacognitive efficiency. The cognitive control-related brain areas were reported as hyporesponsive in OCD patients (Luke J Norman et al., 2019). Thus, although patients with OCD diagnosis could track the errors they've made, they could not take action not to repeat the same mistake or be more cautious after committing an error.

As stated before, the effect of accuracy on the RT change is more prominent when the task is not difficult. This finding could be explained by lower prediction error in difficult conditions when the response is incorrect (e.g., average accuracy - zero (for errors)) while committing an error is less expected, thus the negative prediction error is high when the task is easy. Thus, the behavioral adaptation following prediction error is more pronounced when the difficulty of a task is easy.

Conclusion

In this study, we investigated the metacognitive efficiency of healthy college students with varying degrees of a tendency of OCD symptoms. Our results suggested that having a higher tendency for OCD is associated with an increase in metacognitive efficiency but a decrease in behavioral adaptation, measured in terms of adaptive change in response time. These results provide preliminary evidence for the decrease in the utilization of metacognitive knowledge for behavioral adaptation in OCD; this requires further elaboration.

Interim Discussion

In studies 1 and 2, we investigated the perceptual decision making characteristics of participants with varying degrees of propensity to OCD. In study 1, we provided feedback to participants; however, in study 2 we did not provide any feedback and asked for their confidence in their performance. The results of these studies were not compatible with each other. We could not find any correlation between latent variables of decision making process and obsessive-compulsive factor scores, but, there was a decrease in threshold and drift rate with an increase in obsessive-compulsive symptoms.

Additionally, in study 2, our results suggested that participants with higher scores on the OCD scale had higher metacognitive efficiency than participants with lower scores on the same scale. However, our results also suggested that they could not use this metacognitive advantage to adapt their decision making processes, as they could not change their response times based on the features of previous trials (e.g. error, low confidence). This result is compatible with the recurring example of OCD used in this thesis. Patients with OCD diagnosis wash their hands repeatedly even though they know there is no need to act like this.

In study 3, we will propose a theory within the framework of the Expected Value of Control Theory in order to clarify the incompatible results in the literature about latent variables of decision making characteristics and the dissociation between confidence and performance. The Expected Value of Control Theory briefly suggests a model in which agents decide how much cognitive control to assign to the given task and which task should be attained higher cognitive control. The pathophysiology and cognitive alterations observed in OCD will be discussed within the framework of the Expected Value of Control Theory in the subsequent chapter.

Chapter 4

UNDERSTANDING OBSESSIVE-COMPULSIVE DISORDER USING THE EXPECTED VALUE OF CONTROL THEORY

Abstract

In the current study, we use the Shenhav, Cohen, & Botvinick (2013)'s Expected Value of Control (EVC) theory to conceptualize the information processing bases of OCD. We show how different components of the EVC theory correspond to and can explain obsessions and compulsions in OCD. Specifically, we here argue that patients with OCD have high intensity of EVC, which can explain compulsive behavior. In opposition to the intuitive positive relationship between the high intensity EVC and goal-directed responding, we argue that the high intensity of EVC signal in OCD favors habitual responding over goal-directed responding. We further, ground the EVC on different neural systems that are impacted in OCD such as orbitofrontal cortex, dorsal anterior cingulate cortex, dorsolateral prefrontal cortex, and basal ganglia referring to different components of EVC. We discuss the implications of the application of EVC to OCD for treatment efforts.

Introduction

When our hands are dirty, we often feel the urge to wash them, and we can adjust how long/well we will wash our hands by considering how and the extent to which they were soiled and the subsequent manual activity. For instance, a longer and more deliberate handwashing episode would be expected if the next task is preparing food compared to taking the garbage out. Flexibly responding to the changing requirements of the environment is indeed one of the fundamental adaptive roles of a functional cognitive control system. To this end, the Expected Value of Control (EVC) theory proposes a framework for understanding how the optimum amount of cognitive control is estimated (Shenhav et al., 2013). According to this theory, the intensity of EVC is optimized based on the estimates of the expected payoff and cost of the task. The EVC represents the net value difference between the reward and its cost, which implies how much cognitive control should be invested in the corresponding task. For instance, handwashing is associated with more significant outcomes in relation to cooking (due to risk of contamination and food poisoning) compared to taking the garbage out, and thus despite the higher resultant cost more time and attention should be paid to hand washing before cooking. Therefore, the intensity of EVC signal must be calculated as high in that scenario, indicating higher cognitive control.

Obsessive-Compulsive Disorder (OCD) is characterized by obsessions (intrusive thoughts) and compulsions (behavioral and mental acts that aim to alleviate the anxiety provoked by obsessions) (American Psychiatric Association & Association, 2013). Incidental to the handwashing example, one of the most common symptom dimensions of OCD consists of obsessive thoughts related to contamination and washing/cleaning compulsion (Rosario-Campos et al., 2006). Patients suffering from these symptoms spend excessive time and energy in related avoidance responses. The current paper aims to provide a psychomechanistic understanding of the cognitive profile and symptoms of OCD within the framework of the EVC theory. Specifically, we will exercise how OCD symptoms can result from disruptions in different stages of the cognitive control allocation process. In particular, the over/undervaluing in the estimation of the expected payoff, the associated cost, and/or the net value difference (EVC) between them; and/or the disruption in the implementation of the estimated EVC can cause disproportionate allocation of effort

to unnecessary tasks. Importantly, in this paper, we will use the EVC theory/framework to understand the symptoms of OCD.

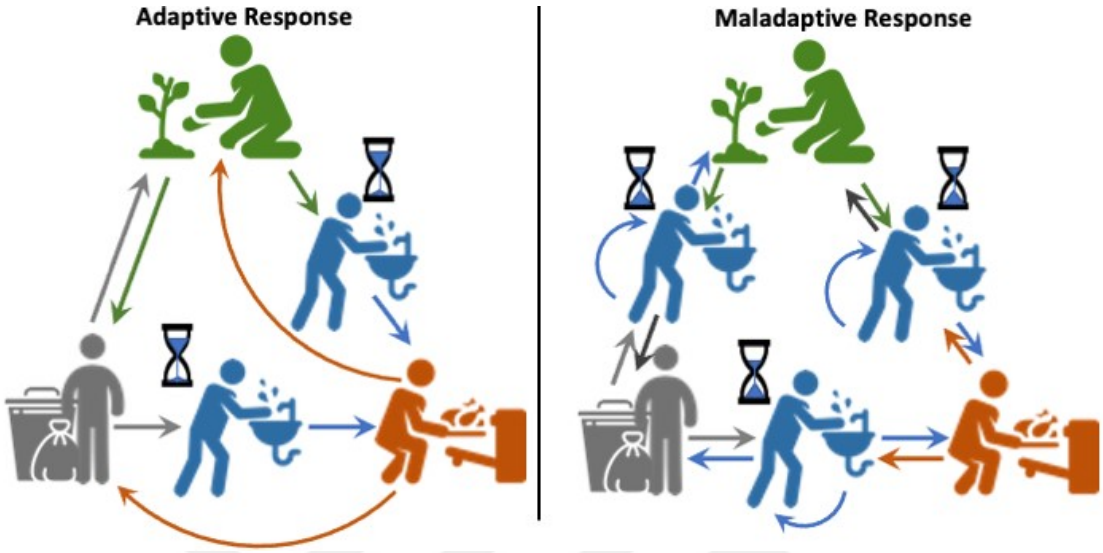


Figure 1. Illustration of adaptive and maladaptive handwashing based on the examples outlined in the main text. This illustration has been designed using images from Flaticon.com

Previously, McGovern et al. (2017) aimed to discuss the symptoms of OCD within the framework of EVC theory. They suggested that OCD symptoms emerge from mis-specified and persistent EVC signal activity in the dorsal anterior cingulate cortex (dACC). In this paper, we aimed to extend the scope and breadth of their proposal to other components of EVC theory and to discuss computational implementation of the mis-specified EVC signal intensity and identity.

The EVC theory postulates three stages for estimation and implementation: *valuation*, *specification*, *regulation* (Fig 2). In the *valuation* stage, the expected payoff, associated cost, and the controllability of outcome are estimated based on signals such as feedback, conflict, and reward rate, and thus its disruption would result in the miscalculation of the expected payoff and associated cost of the task. For instance, not washing hands could be associated with excessive negative subjective outcomes for OCD patients. The disruption in *valuation* might also emerge in cost estimation, which would for instance result in the

underestimation of the objective (including their opportunity cost) cost of avoidance responses adopted excessively by OCD patients. In both cases, the error in *valuation* would cause patients to wash their hands more deliberately with more cognitive effort even if it is not an objective requirement of the environment.

In the *specification* stage, the EVC signal is estimated based on the expected payoff and associated cost. Thus, even though the appropriate input signal might be provided by the *valuation* stage, the disruption in the *specification* step can still result in the misestimation of the intensity and identity of EVC signal. This can emerge because of giving more weight to expected payoff than associated cost and/or having a constant value in the calculation of the net difference between expected payoff and associated cost. Accordingly, although the disrupted *specification* might result in the same set of behaviors as the disrupted *valuation*, the former mostly is applicable to those patients who explicitly know their behaviors are excessive and unnecessary for the requirements of the environment (insightfulness). Critically, although these patients have good insight into the excessiveness of their behaviors, they can't abstain from the corresponding compulsive acts. This implies possible disruptions in the *regulation* stage in which implementation of pre-specified EVC signal occurs.

In addition to the heightened intensity feature of EVC (i.e., amount of cognitive effort to be allocated to the task commensurate to the net difference between the expected value and associated cost), the disruption associated with OCD could also be expected in the *identity* feature of EVC. The *identity* feature implies to which task or set of rules the cognitive effort should be allocated. This feature can be exemplified with a classical Stroop task, where participants make judgments about stimuli with conflicting features. Participants are required to respond to one of the features (e.g., the color of the word) of the presented stimulus while inhibiting to respond to the other feature (e.g., the word itself which implies another color) of the stimulus. The difference between automatic and controlled actions can be determined based on their differential speed, flexibility, and susceptibility to interference from other ongoing processes (Botvinick & Cohen, 2014). As reading the word is a more automatic response than attending to its color, responding to the color requires much more cognitive effort. According to the EVC theory, the feature of the word (e.g. the color of the word), which is worthwhile for the cognitive effort to be allocated, is decided by comparing EVC signal intensity and identity associated with that

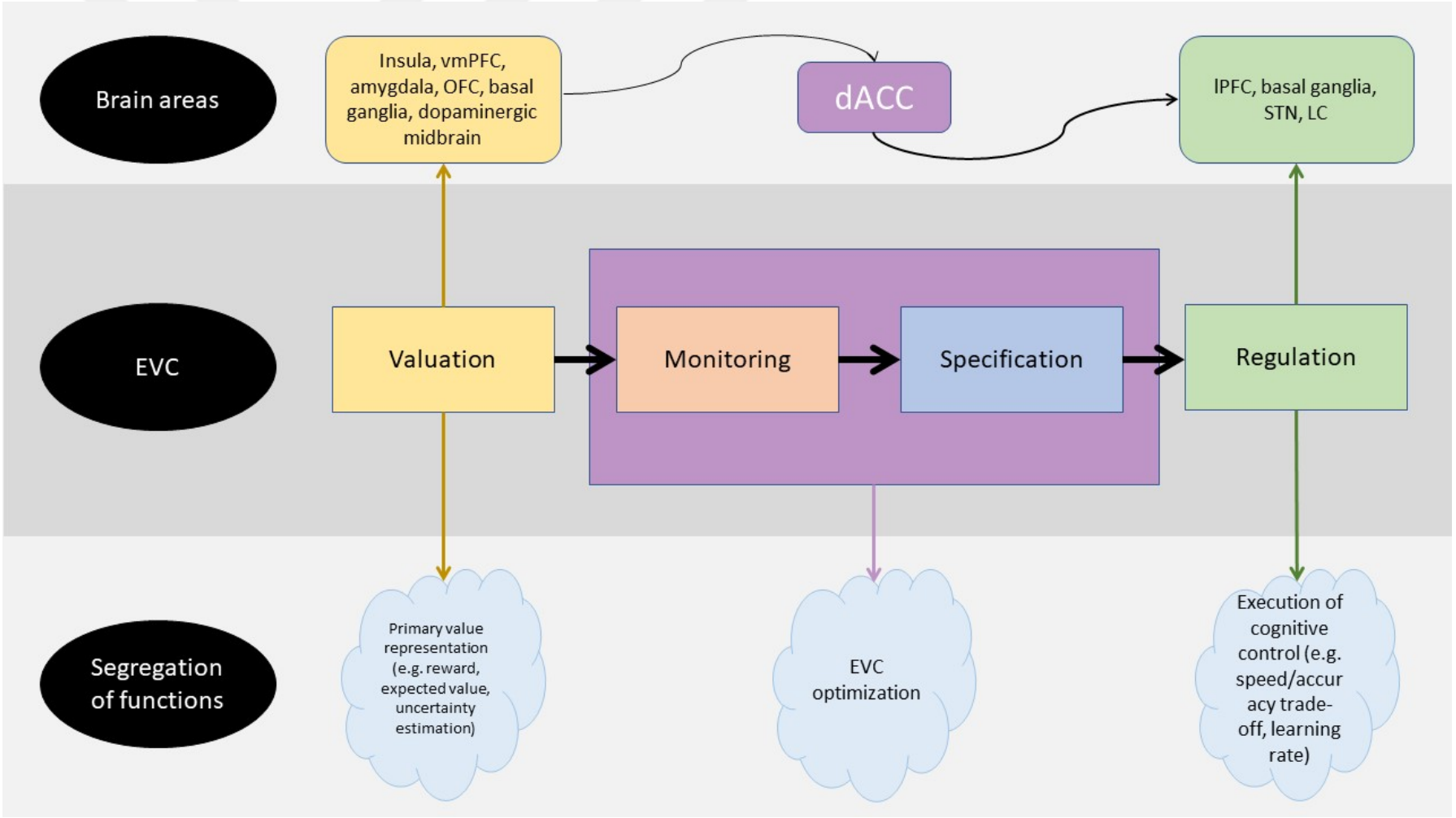


Figure 2 Expected Value of Control (EVC) Theory, the segregation of functions in allocation and specification of cognitive control and associated brain areas. vmPFC: ventromedial prefrontal cortex, OFC: orbitofrontal cortex, dACC: dorsal anterior cingulate cortex, lPFC: inferior prefrontal cortex, STN: subthalamic nucleus, LC: locus coeruleus.

feature to other features of the word (e.g., semantics). If there is a disruption in the *identity* selection of EVC, this results in the misallocation of control to the tasks/set of rules.

We will formulate the implementation of EVC model within the framework of the Stroop task as follows. In this task, EVC assumes that the rate of evidence accumulation toward one of two responses (word vs. color) in the task is regulated by a controlled and an automatic component.

$$drift = drift_{control} + drift_{automatic}$$

The automatic component represents automatic processing to the color feature and word feature of the stimulus, which is not affected by control,

$$drift_{automatic} = a_{color} + a_{word}$$

a_{color} and a_{word} refers to the absolute magnitude of the color-response and word-response association, respectively. These terms depend on the strength of the association of each stimulus feature with a given response (left button or right button). For congruent trials, a_{color} and a_{word} have the same sign, but, for incongruent trials their signs are opposite. As reading the word is a more automatic response than attending to its color, the absolute magnitude of a_{word} is expected to be higher than a_{color}.

The controlled component of the drift rate is the sum of the two stimulus values with matching intensity of control signal:

$$drift_{control} = u_{color} \cdot a_{color} + u_{word} \cdot a_{word}$$

Therefore, each control signal biases decision processing towards one of the two stimulus dimensions. As a result, higher control signal intensity for processing the color dimension improves performance in Stroop task. According to EVC theory, the optimal set of control signals $U = \{u_{color}, u_{word}\}$ is specified by weighting the expected reward for an outcome against the cost associated with the chosen control signal combination based on the internal model of the next trial $S= \{\hat{a}_{color},\hat{a}_{word}\}$:

$$EVC(U, S) = P(correct|U, S)V(R) - Cost(U)$$

P(correct|U, S) represents the probability of reaching the decision threshold for the correct response and V(R) represents the subjective value of responding correctly (Musslick et al., 2015).

The disrupted *identity* feature of EVC could also be responsible for the OCD symptoms. According to the EVC theory, both the intensity and identity features of EVC are specified jointly. However, this does not mean that if the intensity of EVC is high, then, the cognitive effort will be allocated to a less automatic (requiring more cognitive effort) pathway. It is possible to have alternative EVC signal identity-intensity pairings. As in the example of Stroop task explained above, the optimal set of control signal $U = \{u_{color}, u_{word}\}$ is specified by the EVC model. By increasing the magnitude of u_{color}, the performance during the task improves, whereas increasing the magnitude of u_{word} deteriorates the performance. In both cases, the intensity of EVC signal is high, but the identity of EVC signal is misattributed for the later one. The EVC model chooses the task rule to engage by taking into account both the reward probability and difficulty of the task (Musslick et al., 2015). By increasing the reward, it is possible to make the model choose the more difficult task. However, when the difficulty of the preferred task increases, the model first tries to increase the intensity of the EVC signal in order to improve performance, but as the difficulty of the task increases further, the model eventually chooses to switch to the other task. The EVC model also suggests that the intensity and identity features of EVC signal do not necessarily inform each other. As explained in the computational model of EVC signal optimization, the intensity and identity features of the EVC signal are defined separately. Thus, the computational model allows the agent to have "high" intensity EVC signal but engage with "automatic control", rather than "goal-directed" control on the contrary to the intuition. In the *regulation* stage, the estimated EVC is implemented to allocate cognitive control accordingly, and thus disrupted regulation might lead to the dissociation of the allocation of cognitive control from the EVC signal. In this case, even though the agent might have an appropriate EVC estimation, the cognitive control allocation would not follow the estimated EVC.

By considering the repeatedly reported cognitive alterations of OCD, we suggest that patients with OCD are more likely to have an EVC signal that dictates both high intensity and high automaticity. As stated repeatedly in the literature, patients with OCD diagnosis tend to rely more on habitual control (default) instead of goal-directed (cognitively costly)

control (Gillan et al., 2011; Simmler & Ozawa, 2019). The first is the habitual (model-free) system, which leads to action selection merely based on stimulus-response associations, whereas the second one is the goal-directed (model-based) system, which encodes actions that are performed to achieve specific outcomes. Importantly, these two systems also differ in terms of the costs associated with engaging them; the goal-directed system is more labor-intensive than the habitual system as the former requires continuous monitoring of both the environment and outcomes with the benefit of being more flexible in adapting to changes in the state of the environment and/or the agent. On the other hand, the habitual system is more efficient at the expense of flexibility. Patients with OCD have a tendency to have habitual control rather than goal-directed control. The tendency for habitual control rather than goal-directed control implies that the identity feature of the EVC signal of the patients with OCD diagnosis dictates high automaticity in responding. Similarly, patients with OCD have higher inhibitory control errors in inhibition tasks such as inhibiting responses in no-go trials in the go/no-go task, or inhibiting interference of irrelevant feature of stimulus as in stroop, flanker, simon, multisource interference task (Luke J. Norman et al., 2019). However, the reaction times of OCD patients during inhibitory control are also longer than those of healthy controls (Luke J. Norman et al., 2019). Thus, these results also suggest that OCD patients cannot take the advantage of their tendency for habitual responding in terms of faster reaction time. An agent with a low-intensity EVC signal dictating habitual responding is expected to respond quickly with a high error rate. Patients with OCD, on the other hand, respond with both higher error rates and with longer response times. Therefore, as suggested before, OCD patients might have high intensity in their EVC signal, and this high intensity does not let them respond rapidly even if their response strategy is habitual. For the symptoms of OCD, the EVC with high intensity and high automaticity is also explanatory. For example, for a patient with cleaning obsession and washing compulsion, the feeling of dirty evokes a washing compulsion immediately. OCD patients can't delay the urge or flexibly accommodate the requirements of the environment; thus this is a default response for them. However, they have very meticulous rituals for washing compulsions which are compatible with the high intensity of the EVC signal.

In light of these claims, this paper suggests that the cognitive profile and symptoms of OCD are associated with the disruption in the stages of cognitive control allocation within

the framework of EVC theory. The following sections of this paper will investigate the different stages of EVC and how they relate to OCD in more detail.

Valuation

To calculate EVC, the agent needs information regarding the value, efficacy, and cost of possible outcomes (Grahek et al., 2019). The value refers to the perceived payoff assigned to possible outcomes in terms of reward and punishment. It is expected that EVC intensity will increase as the value of outcome increases. The intensity of EVC signal is also expected to increase with the efficacy of the agent, which is a perceived estimate of the ability to control the outcomes. Lastly, the cost refers to how much cognitive effort will be spent to reach the desired outcome, and thus as the EVC signal intensity increases, the associated cost also increases. Based on these three factors, the optimum EVC for a given task is estimated at the *specification* stage which will be covered in the next section.

Both external feedback and internal motivation of performing well can serve as the source of the estimation of the value of the possible outcomes. To investigate how these estimations occur and affect the allocated cognitive control, many manipulations such as changing the reward rate, adding penalty, and changing the task instructions can be utilized. In the literature, there are only a few studies that directly investigated the effect of these factors on the behavioral outcomes of patients with OCD diagnosis in comparison to healthy controls. In one of those studies, Stern et al. (2011) tested three conditions (gain, loss, and null trials) in the flanker task; in gain trials correct responses led to monetary incentive, in loss trials errors led to monetary loss, and in null trials were associated no monetary gain or loss. Stern et al. did not find a difference in error rates between patients with OCD diagnosis and healthy controls with varying motivational contexts. However, the response time of OCD patients was longer than healthy controls in gain and loss trials. This result suggests that healthy controls can, but OCD patients cannot speed up their response times when the motivational significance of trials increases. Additionally, OCD patients reported higher rates of frustration after error response when compared to healthy controls. In another study, Kaufmann et al. (2013) applied a monetary incentive delay task in which participants are required to press a button as soon as possible when the stimulus appeared on the screen in different reward and punishment conditions (Kaufmann et al., 2013). Responding to stimulus before an individually tailored deadline resulted in monetary gain in reward trials. In loss-avoidance trials, participants

avoided losing money when they responded to stimulus in a timely manner. Lastly, in null trials, they did not gain or lose any monetary incentive. The results of this study showed that patients with OCD diagnosis have fewer delayed (>deadline) responses in loss-avoidance trials than in reward trials whereas healthy controls had fewer delayed responses on reward trials than loss-avoidance trials. This result suggests that participants with OCD diagnosis performed better in conditions that contained penalty than reward. Results of these studies suggest that the performance (mainly the response time) of patients with OCD diagnosis is affected by punishment when compared to reward.

Studies investigating the neural response to reward and punishment of the patients with OCD diagnosis report equivocal outcomes. During the monetary incentive delay task, the attenuated reward anticipation activity at bilateral nucleus accumbens and left insula of OCD patients was reported with no difference between the groups after receiving the reward (Figee et al., 2011). Using the same task, Kaufmann et al. (2013) reported that there is no alteration in striatal activity between patients with OCD diagnosis and healthy controls; but instead, the patients with OCD diagnosis had higher activity in the medial frontal cortex region (SMA and pre-SMA) while waiting for punishment. The same region showed lower activity during reward anticipation in patients with OCD diagnosis when compared to healthy controls. Another study did not find any difference in ventral striatal activity during reward anticipation between the patients with OCD diagnosis and healthy controls; however, during punishment anticipation, the patients with OCD diagnosis showed less activation in lateral prefrontal and inferior parietal cortices (Jung et al., 2011). During reward expectation, reduced activity in the ventral putamen and amygdala of OCD patient was also reported (Marsh et al., 2015). In general, these findings suggest that patients with OCD diagnosis have lower neural response to reward expectation but higher neural response to punishment expectation when compared to healthy controls. Thus, for patients with OCD diagnosis, the information provided in *valuation* step to dACC could be weighted in favor of the avoiding punishment rather than seeking reward. This might be the one of the possible explanations behind selecting meticulous handwashing in order to avoid infections despite the associated waste of time.

The orbitofrontal cortex (OFC) is another brain region which takes a role in the valuation step of the estimation of the EVC signal. Early studies investigating the role of OFC in OCD pathophysiology reported disrupted activity without making explicit distinction

between medial and lateral OFC (Saxena & Rauch, 2000). Later studies showed that OCD is associated with hyperactivity in lateral OFC and hypoactivity in medial OFC (Milad & Rauch, 2012). The lateral part of the OFC is shown to be involved in responding to punishment and escape from danger, on the other hand, the medial part of OFC appears to have a role in emotion regulation and reward processing (Elliott et al., 2010). Thus, the hyperactivity in lateral OFC and hypoactivity in medial OFC in OCD also supports the punishment sensitivity in OCD. Thus, patients with OCD diagnosis might indeed assign more weight to the possible punishment than possible reward while calculating the value of the task at hand. This difference in the calculation of the value of the task might lead to improper optimization of EVC signal.

Another parameter used to calculate the EVC is the efficacy which refers to having control over the possible outcomes, namely the belief that our actions lead to what we desire. According to the EVC theory, having such a belief will increase the expected value of control, which can be tested by manipulating action-outcome contingencies. To this end, Vaghi et al. (2019) asked participants to press space bar whenever they want. There are three different blocks in this task: the first one has a positive contingency between pressing the spacebar and getting a reward, the second one has degraded contingency between response and outcome, and the last type of block has negative contingency which means that the chance of getting a reward was higher when they do not press the spacebar. Vaghi et al. reported that patients with OCD diagnosis responded more than healthy controls when the contingency between action and outcome is low, although the patients with OCD diagnosis reported low action-outcome contingency explicitly. Thus, they pressed the button even though they thought that the action-outcome contingency is low; which suggests that their actions were dissociated from their sense of efficacy. Another study compared the patients with OCD diagnosis with healthy controls in a shock avoidance task (Gillan et al., 2014). In this task, participants learned the association between conditioned stimuli (colored rectangles) and which wrist they will get an electrical shock, and pressed foot pedals to avoid the corresponding shock. Participants with OCD diagnosis pressed the pedals more than healthy controls during the devaluation test after extended training. Even though the participants pressed the pedals more than healthy controls in this stage, the shock expectancy of the participants with OCD diagnosis was not higher than healthy controls. According to the results of these two studies, it is possible that the efficacy of patients with OCD diagnosis has a lower weight

on the estimation of EVC when compared to healthy controls. Even in the situations that the patients with OCD diagnosis know their efficacy is low, this knowledge does not inhibit their responding.

The last parameter which is needed to estimate EVC is the cost of cognitive effort. If the patients with OCD diagnosis underestimate the cost of repeatedly and excessively performing their compulsive acts, this might lead to the continuation of the compulsive actions/symptoms. The compulsive behavior and intrusive thought were associated with less avoidance from mental effort (Patzelt et al., 2019). Patzelt et al. (2019) applied the demand selection task to a large sample of participants (n = 811). In the demand selection task, participants were required to choose one of two cues that are associated with the high or low demand version of a trial. The high demand condition included more frequent task-switching than the low demand condition. Overall, participants chose low demand cue more than high demand cue which means that participants showed avoidance of mental effort. However, this avoidance behavior was observed less as the score of participants in compulsive behavior – obsessive thought factor increased. This study does not directly suggest that the patients with OCD diagnosis underestimate the cost of the task at hand, but, they possibly are not as sensitive to the cost of the task while calculating the EVC.

To summarize, the patients with OCD diagnosis are more sensitive to punishment than reward, and less likely to consider their efficacy and the cost of the cognitive effort. On the premise of this interpretation, it is possible that the patients with OCD diagnosis give more weight to punishments than rewards while calculating the value of possible outcomes and give less weight on their efficacy and the cost of cognitive effort than healthy controls while estimating EVC. All of these alterations are expected to lead to high intensity EVC signals.

Specification

EVC theory postulates that the expected value of control is estimated by an optimization process that relies on the difference between the expected value of outcomes and the cost associated with the cognitive effort (Shenhav et al., 2013). The dorsal anterior cingulate cortex (dACC) is suggested to be the neural locus of this estimation. Formerly, dACC has been associated with several cognitive processes such as error monitoring, conflict monitoring, decision-making, and the EVC theory offers a unifying function for the dACC

(Shenhav et al., 2013). According to this theory, valuation signals (responsible for the regulation of cognitive control) that are source localized at the orbitofrontal cortex, ventromedial prefrontal cortex, insula, amygdala, basal ganglia, and midbrain dopamine pathways converge on the dACC. Dorsal ACC, in turn, integrates these signals and serves as an executive entity in monitoring the discrepancy between the goal states or ongoing behaviors (e.g., performance monitoring; conflict monitoring) or both, judging the need for engaging cognitive control in addition to deciding how much cognitive effort should be allocated to the task at hand. This integrative executive role of dACC requires it to evaluate the expected value of cognitive control by taking into account the outcomes against the costs of cognitive control (Shenhav et al., 2013). This way dACC chooses the identity of the control signal (which signal) as well as its intensity (how much signal). Based on these features of the control signal, cognitive control is exerted by the lateral prefrontal cortex and basal ganglia in the *regulation* stage of EVC, which will be investigated in the next section (Shenhav et al., 2013).

As suggested above, OCD patients might have a disruption in the optimization of the EVC signal, and this disruption might be the primary cause of their symptoms and cognitive alterations. Giving high weight to expected gain, especially when it is avoidance from punishment and low weight to cognitive cost or both are expected to lead to having a high-intensity EVC signal. However, the computational process of the EVC optimization is not directly observable, and we are not aware of any empirical study investigating the disruption in the EVC optimization process in OCD. Thus, in this section, we will mainly summarize the studies focusing on dACC function in OCD.

Arguably, the most consistent finding in the literature regarding OCD is the increased error-related negativity (ERN) amplitude in the patients with OCD diagnosis compared to healthy controls (Perera et al., 2019). ERN is an ERP component with frontocentral distribution peaking after 50-100 ms committing an error, and the source of ERN is accepted as dACC (Yeung & Summerfield, 2012). The studies investigating the ERN signal in OCD mainly focused on error monitoring, conflict, response inhibition, task switching, or symptom provocation (McGovern & Sheth, 2017). A recent meta-analysis reported a robust increase of ERN amplitude in patients with OCD diagnosis in response conflict tasks (Riesel, 2019).

In addition to the increase in amplitude of the ERN signal in OCD, there are studies in literature suggesting the invariability of the ERN signal. Kaczkurkin et al. (2013) compared ERN responses of participants with varying levels of OC tendencies by using the Flanker task having different difficulty levels. The significant difference between high OC and low OC groups has been detected only when the task is easy since the amplitude of ERN signal of low OC group increased with the difficulty of the task while the ERN signals of high OC participants have similar amplitude for different levels of difficulty (Kaczkurkin, 2013). Another study applied the flanker test in two conditions: one was the neutral/standard condition and the other one included punishment (Endrass et al., 2010). By comparing the patients with OCD diagnosis and healthy controls, Endrass et al. (2010) reported that increased amplitude of ERN was observed only in the neutral condition because healthy controls upregulated the dACC activity in punishment condition however the dACC activity of the patients with OCD diagnosis did not differ between conditions. Similarly, Riesel et al. (2019) compared ERN responses of OCD patients and healthy controls by using the flanker task while emphasizing the importance of accuracy or speed of response in the task. While the amplitude of ERN signals was modulated by speed vs. accuracy instructions in healthy participants, the ERN amplitude in OCD patients was not sensitive to these task relevant instructions (Riesel et al., 2019). Another study, by using n-back task, showed that dACC activity of the patients with OCD diagnosis was not linearly increasing with the working memory load of the task as opposed to the healthy controls whose dACC activity increased with the task difficulty (Koch et al., 2012). These studies suggest that dACC activity of healthy controls is modulated by the requirements of the environment, however increased activity of dACC was observed in the patients with OCD diagnosis is invariable.

In summary, the dACC activity which is suggested as the neural source of the EVC optimization process is high in OCD. The high activity of dACC in OCD is affected more weakly by the requirement of the environment than healthy controls. In terms of the EVC optimization process, it is possible that there could be a constant added to the EVC signal in OCD. The response of regulatory brain regions to the EVC signal will be reviewed in the next section.

Regulation

According to the EVC theory, the regulation is the last stage of the allocation of cognitive control. After the EVC signal is generated with its intensity and identity, the related brain regions, mainly lateral prefrontal cortex and subcortical structures, implement the requirements of this signal (Shenhav et al., 2013). In this stage, the speed-accuracy tradeoff is adjusted, the attentional focus is directed to important parts of stimuli, or the learning rate is controlled based on the EVC signal (Shenhav et al., 2016). The change between habitual and goal-directed action selection strategies is implemented if necessary. This part of the paper will summarize the findings in OCD regarding these parameters and will evaluate whether the disruption in regulatory brain regions could be suggested as the reason for the OCD symptoms.

Banca et al. (2015) investigated the decision making processes of the patients OCD diagnosis by random dot motion task with varying difficulty levels. In this task, the participants were required to decide the dominant direction of randomly moving dots. As the coherence of randomly moving dots increases, the dominant direction is more easily decided. Patients with OCD had higher thresholds (required more information before making a decision) than healthy controls when the coherence of the dots was lower (difficult condition). The same study also reported that the drift rate of the patients with OCD are lower than the healthy controls, and this difference did not disappear when there was a cost of late responses (Paula Banca et al., 2015). By using a similar uncertainty level in dot motion, the higher threshold setting in decision making is also reported for pediatric patients with OCD diagnosis and healthy participants with obsessive-compulsive traits (Erhan & Balcı, 2017; Erhan et al., 2017). Thus, this finding suggests that patients with OCD delayed their response to collect more data from the environment even when not much information was provided by the stimulus. This effect was reversed when there was a cost of late responding. In this condition, the decision threshold of the patients with OCD was lower than healthy controls when the signal-to-noise ratios were higher. Another study applied a sequential learning task that includes stimuli associated with varying degrees of conflict (the degree of similarity between reward probability of each pair) and uncertainty (variance of reward probability distribution) (Mandali et al., 2019). During trials in which both conflict and uncertainty is high, the patients with OCD diagnosis have higher thresholds than healthy controls (Mandali et al., 2019). These studies suggested that healthy controls have the ability to reduce their investment in the task when the return rate is low or uncertain; however, the patients with OCD have

difficulty in adaptively adjusting the decision-making characteristics according to the requirements of the environment. Similarly, another study utilized the stop signal reaction time task and reported that the patients with OCD diagnosis had longer mean reaction time even after successfully inhibited stop trials than healthy controls (Berlin & Lee, 2018). Thus, the inhibitory effect of stop trials did not wane for the patients with OCD diagnosis. By considering these studies, it is possible that the patients with OCD diagnosis have a high intensity EVC signal even if the environment does not require such signal. Moreover, it is possible that the regulatory brain regions of the patients with OCD diagnosis respond to this high intensity EVC signal.

On contrary to this suggestion, Agam et al. (2014) reported that the patients with OCD diagnosis showed increased default mode network activation in post-error trials in the anti-saccade task. Compared to the patients with OCD diagnosis, healthy controls showed reduced activation in the default mode network. This study suggested that the patients with OCD diagnosis have difficulty in disengaging from evaluative processes after error, and this interferes with redirecting attention to the task (Agam et al., 2014). This claim predicts differential post-error behavioral adjustments in OCD patients but a similar magnitude of post-error slowing was reported for both patients with OCD diagnosis and healthy controls by Agam et al (2014). Although there is a limited number of studies reporting aberrant post-error slowing in patients with OCD diagnosis (Fitzgerald et al., 2005; Liu et al., 2012), the null finding in terms of the difference between patients with OCD diagnosis and healthy controls was more common in literature (Paula Banca et al., 2015; Carrasco et al., 2013; Endrass et al., 2008; Endrass et al., 2010; Gründler et al., 2009; Riesel et al., 2014; Rueppel et al., 2022). Erhan et al. (2017) also did not find a behavioral difference between OCD patients and healthy controls in terms of post-error slowing but they found higher decision-threshold setting in trials that followed errors; any differences in terms of distraction would have been manifested as lower drift-rate.

A recent meta-analysis reported that the patients with OCD diagnosis have hypoactivation in rostral and ventral ACC, bilateral thalamus, caudate nucleus, medial orbitofrontal cortex, right anterior insula/frontal operculum, and supramarginal gyrus during inhibitory control (Luke J. Norman et al., 2019). The same meta-analysis also reported hyperactivation in dACC, SMA, pre-SMA, right anterior insula/frontal operculum, and anterior lateral prefrontal cortex during error processing for the patients with OCD

diagnosis (Luke J. Norman et al., 2019). These results suggested that hyperactivity in the error monitoring system of the patients with OCD diagnosis emerges as a compensatory mechanism to the hypoactive regulatory system.

In addition to the discussion of how high-intensity EVC signals are controlled by the regulatory system, the identity feature of the EVC signal should also be considered. The accumulating evidence in the literature supports the over-reliance on the habitual system among patients with OCD (P. Banca et al., 2015; Gillan et al., 2011). For instance, Vaghi et al. (2017) investigated the learning characteristics of the patients with OCD. During the predictive inference task, the researchers asked participants to make predictions about where the ball which is thrown from the center of a circle will land on that circle. In order to perform this task, participants must infer the most possible location for ball landing based on previous trials. The location for ball landing was a normally distributed random variable, and time-to-time the mean of that distribution was changed. Thus, participants needed to detect those changes, and update their predictions accordingly. Additionally, participants were asked to report their confidence level about their predictions on every trial. This study has shown that there is no difference in confidence levels of OCD patients and healthy controls, but the learning rates of OCD patients are higher than healthy controls (Vaghi et al., 2017). According to the results of this study, OCD patients seem to change their behavior excessively with respect to external feedback, thus they performed relying only on the feedback they received without considering the overall structure of the task.

In summary, there is some evidence that regulatory brain regions are not responsive to the dACC activity during inhibitory control. Similarly, patients with OCD rely more on a habitual action selection system than the goal-directed one. The difficulties in inhibiting the default response might be the result of unresponsive regulatory brain regions or impairments in identity specification of EVC signal, or both. It is hard to differentiate whether identity feature of EVC signal dictates the habitual action selection, or there is no other choice than responding habitually as regulatory brain regions are not responsive to EVC signal in OCD. Remarkably, patients with OCD have cautious decision-making strategies even when there is no task requirement for that. This inference supports the suggestion of high intensity EVC signal in OCD.

Table 1. Summary of studies that correspond to different components of EVC.

	Condition	Results	Meaning in terms of EVC	Reference
VALUATION	The increase in motivational significance of trials	Insufficient increase in response time	Valuation: no differentiation for motivational significance; Specification: having a constant high intensity EVC signal	(Stern et al., 2011)
	Punishment vs reward	Fewer delayed response when there is possibility of punishment	Valuation: higher weight for punishment; Regulation: higher response in sensorimotor network, lower response in associative network during punishment expectation	(Kaufmann et al., 2013)
		Higher activity in the medial frontal cortex region (SMA and pre-SMA) while waiting for punishment, but lower activity in the same region during reward anticipation		(Kaufmann et al., 2013)
		Attenuated reward anticipation activity in nucleus accumbens and left insula		(Figee et al., 2011)
		Less activation in lateral prefrontal and inferior parietal cortices during punishment anticipation		(Jung et al., 2011)
		Reduced activity in the ventral putamen and amygdala during reward anticipation		(Marsh et al., 2015)
		Hyperactivity in lateral OFC and hypoactivity in medial OFC		(Milad & Rauch, 2012)
	Efficacy	Dissociation between sense of efficacy and actions	Valuation: having a lower weight for efficacy in EVC estimation	(Gillan & Robbins, 2014; Vaghi et al., 2019)
	Cost of Cognitive Effort	Avoidance from mental effort	Valuation: having a lower weight for cost of cognitive effort in EVC estimation	(Patzelt et al., 2019)
I	dACC function	Increased error-related negativity (ERN) amplitude	Specification: a constant added to the EVC	(Perera et al.,

	in OCD		signal in OCD	2019)
		Invariable ERN signal regardless of difficulty levels		(Endrass et al., 2010; Kaczkurkin, 2013; Riesel et al., 2019)
REGULATION	Hypoactive regulatory system	Hyperactivity of dACC as a compensation for hypoactive regulatory brain regions during inhibitory control	Regulation: unresponsive regulatory brain regions	(Luke J. Norman et al., 2019)
	Habitual action selection	Difficulties in contingency degradation	Specification: mis-specified identity feature of EVC; Regulation: unresponsive goal-directed action selection system	for a review, see; (Robbins et al., 2019)

Conclusion

This paper proposes that the cognitive profile and symptoms of OCD can be explained with the disruption in the stages of cognitive control allocation within the framework of EVC theory. The EVC theory postulates three stages for estimation and implementation: *valuation*, *specification*, *regulation*. In the *valuation* stage, the agent takes into account the value, efficacy and the cost of possible outcomes. The cognitive performance and the neural response of patients with OCD diagnosis has shown to be affected by punishment more than reward. Thus, for patients with OCD diagnosis, the value of the task at hand is more pronounced when the possibility of punishment is high. In terms of efficacy, the patients with OCD diagnosis are more prone to take actions even though they know their actions may not have an effect on the outcomes. Lastly, the patients with OCD diagnosis consider the cognitive cost of the task less than healthy controls. All of these alterations in valuation step are expected to lead to an increased intensity of EVC signals. The second step of EVC optimization is suggested to be underlain by dACC activity. The neural activity of dACC in OCD is reported as high regardless of the requirements of the task at hand. The enhanced neural activity in dACC in OCD suggests that the patients with OCD diagnosis could have a constant in calculation of EVC signal in addition to the net difference between cost and reward information supplied by valuation step (akin to the intercept effect in regression). In addition to having an EVC signal with high intensity, the patients with OCD diagnosis are shown to be more prone to habitual action selection rather than the goal-directed one. Thus, the determination of the identity of EVC signals is also disrupted in the patients with OCD diagnosis. During the regulation step of EVC, the regulatory brain regions of patients with OCD diagnosis have shown to be hypoactive. The hypoactivity of regulatory brain regions in OCD are associated with the disruption of inhibitory control. The disruption in inhibition of default response implies aforementioned disturbance in the identity specification of EVC signal. On the other hand, the patients with OCD diagnosis have more cautious decision-making strategies when compared to healthy controls. The more cautious decision making could be the result of EVC signals with high intensity. In conclusion, the intense EVC signal favoring default response could be the underlying mechanism of the cognitive profile and symptoms of OCD.

The EVC theory provides a unifying framework for the understanding of the symptoms and cognitive profile of the patients with OCD diagnosis. The prevailing neurobiological

model of OCD suggests its symptoms are caused by the disruption in the activity of cortico-striato-thalamo-cortical (CSTC) loop pathways (Alexander et al., 1986). The hyperactivity in the loop involving OFC and ventromedial caudate and the hypoactivity in the loop involving dlPFC and dorsal caudate have been implicated in OCD. The CSTC loop pathways have been later shown to have a spiral-like structure rather than being parallel and segregated as previously proposed (Haber & Knutson, 2010). Thus, it is important to consider these loops in a more unifying framework. In EVC theory, OFC takes a role in valuation step and the hyperactivity of OFC is associated with punishment sensitivity in OCD. dlPFC, on the other hand, takes a role in regulation step, and the hypoactivity of dlPFC is associated with reduced responsiveness of regulatory brain regions in OCD.

The EVC theory assigns a central role to dACC which is shown to be hyperactive in OCD. High dACC activity is arguably the most consistent finding in OCD literature. The higher activity of dACC suggests the increased intensity of EVC signal. Behavioral studies suggest that the patients with OCD diagnosis tend to select action habitually. These findings could be implemented in the computational model of EVC optimization in two different ways. The first one is assigning a high value to signal response association for the default response (a_{word} in the Stroop task). This high value corresponds to an association between obsession (e.g. having a thought that one's hands are dirty) and compulsion (e.g. action of hand-washing). When the external requirement of the environment is not suitable for hand-washing action, the EVC signal intensity for goal-directed action (u_{color} in the formula) is increased to select another action instead of handwashing. However, if the magnitude of a_{word} term is very high, then, it might not be possible to override this default response even with an EVC signal with high intensity. This implementation predicts a reduction in reaction time in the case of habitual responding as the association between signal and response is high. However, this is not a finding reported for patients with OCD diagnosis. Instead, the patients with OCD diagnosis tends to have increased response time when compared to healthy controls. Thus, this implementation does not fit the symptoms and cognitive profile of the patients with OCD diagnosis. The very quick response when there is a provocative stimulus could be the mechanism behind the tic disorders, however, it is outside the scope of this review. Another implementation that could explain the symptoms and cognitive profile of OCD is having higher EVC signal intensity for habitual action selection (u_{word} in the formula) than

goal-directed action selection (u_{color} in the formula). In this case, it is, again, possible to have high-intensity EVC signal dictating habitual action selection. However, the response is not expected to be associated with quick response time.

This paper summarized how EVC can be used as a conceptual framework to account for the cognitive and behavioral symptoms associated with OCD. Our results provide an EVC-based theoretical framework and guideline for future behavioral, neuroimaging, and neuromodulation studies that aim to elucidate the neurocognitive bases of OCD in specific and other disorders of behavioral rigidity. For instance, our application of EVC to OCD can be used to generate theory-driven predictions regarding how specific brain circuits can map onto the cognitive profile of these disorders.

GENERAL DISCUSSION

Obsessive-Compulsive Disorder (OCD) is a neurocognitive disorder characterized by intrusive anxiety-provoking thoughts which commonly induce compulsive behaviors to decrease the subsequent anxiety. There is a gap in the literature in terms of the perceptual decision making characteristic of the patients with OCD. It is important to understand the characteristics of decision making processes of patients with OCD, as they stuck in the repetitive acts even though they have the information that these acts deteriorates their functionality. Thus, in this study we focused on the decision making characteristics of participants with different levels of tendency to OCD in relation to dopamine function related gene polymorphisms and their metacognitive functions. Finally, we reviewed the current literature pertaining to cognitive alterations in OCD in the framework of Expected Value of Control (EVC) Theory.

In the first study, we examined the association between dopamine function related polymorphisms with the latent variables of the decision process. Our results showed that COMT polymorphism (Met/Met allele) had both modulatory and enhancing role in perceptual decision making as well as was associated with an increase in obsessive-compulsive and anxious depressive scores. On the other hand, we did not find any effect of DRD2 and DARPP-32 polymorphisms on both decision making parameters and neuropsychiatric scales.

In the second study, we investigated the metacognitive functions of participants with different levels of tendency to OCD in addition to decision making characteristics. Our results suggested that the participants with a higher tendency to OCD have higher metacognitive efficiency and lower drift rates and thresholds. Our results also showed that the participants with a higher tendency to OCD have limited adaptation to previous errors and low confidence levels. Thus, according to our results, having a higher tendency to OCD is related with sufficient metacognitive capacity, but also infers the utilization of the metacognitive information in behavioral adaptation.

In the third study, we reviewed the literature about cognitive alterations in OCD within the framework of Expected Value of Control theory (Shenhav et al., 2013). This theory

suggests a computational model for how an agent allocates cognitive control to different tasks. With this review, we propose that patients with OCD have high intensity of EVC signal, which can explain compulsive behavior. We also suggest that the high intensity of EVC signal in OCD favors habitual responding over goal-directed responding, even though there is an intuitive positive association between the high intensity EVC signal and goal-directed responding. This framework could also be used to understand the alterations of latent decision making processes in OCD, which indicates higher threshold and lower drift rate.

In the first study, we investigated the effects of SNPs related to dopamine function and the latent variables of decision making. Our results suggested that higher prefrontal dopamine level is associated with a lower threshold and drift rate. This result is compatible with the possible prediction of the Expected Value of Control theory. The role of dopamine in the implementation of the EVC signal is complex and multidimensional. It has been demonstrated that dopamine modulates the neural representation of expected outcomes. Moreover, dopamine has been shown to influence the motivational aspects of decision making, affecting the salience of outcomes and the preference for specific choices. Thus, a decrease in drift rate and the threshold is expected as an increase in the prefrontal dopamine level.

The literature is complex about the status of the decision threshold of patients with OCD diagnosis when compared to healthy controls. In the literature, there are studies suggesting a decrease in the decision threshold of participants with varying levels of OCD symptoms, as well as studies suggesting an increase in the decision threshold. Considering the symptomatology of patients with OCD diagnosis, both alterations could be possible depending on the context. It seems that patients with OCD diagnosis can easily (lower threshold) decide that their hands are dirty in case of contamination obsession; however, they can not easily decide (higher threshold) that their hands are clean even after repeatedly washing their hands. In study 3, we suggested that the patients with OCD diagnosis have high-intensity EVC signal, however, this signal dictates habitual decision making rather than goal-directed one. Thus, for the decisions which include strong stimulus-response associations based on their obsessions, they have a lower threshold to

initiate compulsions. However, it is not easy to stop compulsive acts as the threshold for "stopping" is high.

In study 2, we detected better metacognitive efficiency in participants with a higher propensity to OCD. In that study, we did not use a stair-case method contrary to previous studies in the literature, because it is shown that using the staircase method results in inflation in metacognitive efficiency estimates. However, studies using the staircase method reported that participants with a higher propensity to OCD had lower metacognitive efficiency. Based on these results, it is possible to suggest that participants with a higher propensity to OCD could not take advantage of the changes in the environment. As healthy participants could generate additional metacognitive information based on the changes in the environment, the metacognitive abilities of the participants with higher levels of OCD symptoms deteriorate with those changes. This might be a result of the disruption in dopamine levels of patients with OCD diagnosis. According to the literature, as well as study 1, OCD is associated with Met/Met allele in the COMT gene. With that allele, there is an increase in tonic dopamine level in the prefrontal cortex but a decrease in phasic dopamine level. This alteration could give an advantage in steady stable tasks, however, it deteriorates cognitive flexibility.

Future Directions

Our results suggest mixed results in terms of latent variables of decision making processes of participants with different levels of tendency to OCD. This discrepancy should be investigated in future studies. One of the reasons for this discrepancy in our study might be providing or not providing feedback during perceptual decision making task. Patients with OCD has low level of confidence to external feedback, thus, having feedback during perceptual decision making task might have a deteriorative effect on decision making abilities of participants with high tendency to OCD contrary to what is expected for a participant without OCD. This possibility should be examined in further studies.

Our findings demonstrated that, without external feedback, participants with high tendency to OCD had the greater ability to generate accurate metacognitive information about their first-order task performance. However, they could not take advantage of that

information to lead their subsequent actions. This might be the result of having a high intensity EVC signal constantly. This suggestion might be tested by using Transcranial Magnetic Stimulation (TMS). By stimulating dorsal anterior cingulate cortex with TMS, it is theoretically possible to obtain high intensity EVC signal throughout a perceptual decision making task. This might help to demonstrate the possible relation between constant high intensity EVC signal and behavioral rigidity in OCD despite of the accurate metacognitive reports. Additionally, inhibiting the function of dorsal anterior cingulate cortex by TMS in a clinical OCD sample might also present useful evidence. This option could also be considered as a treatment modality for treatment-refractory patients with OCD. The decrease in constant high activity in the dorsal anterior cingulate cortex might have a beneficial effect in the reduction of OCD symptoms.

We reported some differences in the decision making processes of the participants with high and low levels of OCD tendency. It is important to note that, the difference appeared only when the perceptual decision making task was easy. As the difficulty level of the task increased, the performances of both groups declined. On the other hand, when the task was relatively easy, the participants with low tendency to OCD benefited more than the other group. In order to avoid ceiling effect, other researchers might focus on relatively easy tasks while designing their studies.

The interaction between single nucleotide polymorphism related to dopamine and compulsivity has not been well understood yet. Similarly, the effect of those SNPs on the performance of cognitive tasks has not provided a clear picture. One of the main reasons behind this complexity might be the alterations in dopamine receptor families. There are two main families of dopamine receptors in the brain: D1-like receptors (D1 and D5) and D2-like receptors (D2, D3, and D4). These receptors are responsible from different aspects of brain function, including mood regulation, motivation, reinforcement, and compulsive behavior. Abnormalities in dopamine receptor expression or function have been implicated in the pathophysiology of OCD. In OCD, dysregulation of D2-like receptors in the basal ganglia has been linked to the development of compulsive behaviors. Thus, the relation between the dopamine receptor families and compulsivity is complex, and further research is needed to better understand the underlying mechanisms.

Lastly, the results presented in this work could also be used in psychoeducation sessions with patients with OCD. Informing them about what is metacognition, how it helps to guide our future behavior, how we attribute cognitive control to different tasks, and how we can choose which task to engage in might help to gain more sense of control over their symptoms. Therefore, our results might provide useful implications for the clinicians who work with patients with OCD diagnosis.

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