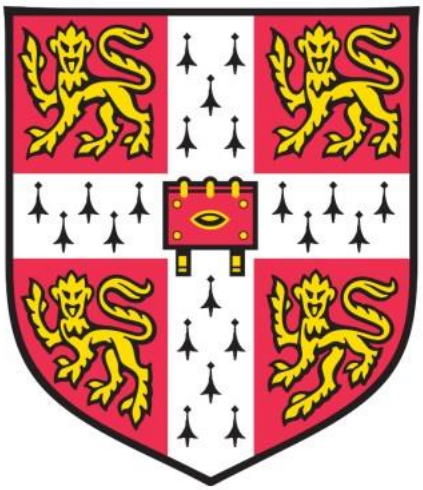
Electroencephalographic and Cognitive Underpinnings of Inhibitory Control in Obsessive-Compulsive Disorder: From Actions to Thoughts



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To the path.

Be great in act, as you have been in thought

King John, Act V, Scene 1

William Shakespeare

DECLARATION

I hereby declare that this thesis is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the preface and specified in the text, and that it is not substantially the same as any work that has already been submitted before for any degree or other qualification except as declared in the preface and specified in the text. This dissertation does not exceed the prescribed word limit for the Degree Committee for the Faculty of Biology.

ACKNOWLEDGEMENTS

I can no other answer make but thanks

And thanks; and ever thanks; (…)

Twelfth Night, or What You Will, Act III, Scene 3

William Shakespeare

I have received so much advice regarding how to write the thesis, many of them suggesting that I should start with the 'low-hanging fruit', the easier parts. This would give me a sense of progress and minimise procrastination, they said. Well, I can say that the advice worked for tasks like designing the cover or writing the declaration, but certainly not for acknowledgements. Now, at the verge of submitting the thesis, I am faced with the impossible task of thanking all those that contributed along the path.

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ABSTRACT

This thesis aimed to investigate cognitive and neural underpinnings of cognitive control in obsessive-compulsive disorder (OCD), focusing on suppression of thoughts and actions, cognitive flexibility, and habitual behaviour. Four experiments addressed hypotheses that, in comparison with appropriate control groups: (i) Patients with OCD are impaired in their ability to control actions as measured by the Stop-Signal/Go No-Go task; (ii) They also present deficits in attentional set-shifting in an extra-dimensional set-shifting task; (iii) OCD is marked by difficulties in the ability to control thoughts, as demonstrated by a Retrieval-Induced Forgetting (RIF) paradigm; (iv) Deficits in inhibitory control correlate with electroencephalographic markers, especially error monitoring and action tendencies; (v) Habitual and ritualistic actions in OCD are driven by both motor deficits and intolerance of uncertainty; (vi) Learning and practising a finger tapping sequence on a smartphone application (app) can have clinical benefits as a 'habit-reversal' treatment; and (vii) Metacognitive functions such as memory confidence and vividness are impaired in OCD, prompting the need to repeat actions. The thesis is structured in seven chapters, with experiments presented in chapters 3, 4, 5 and 6.

Chapter 3 reports inhibitory deficits in a large group of OCD patients, showing impairments in action cancellation in this sample. These results are discussed alongside neural EEG markers and self-report measures, highlighting roles of error monitoring and enhanced action tendencies in the maintenance of OCD symptoms.

Chapter 4 presents the results of a clinical trial conducted in collaboration with the NHS Highly Specialised OCD Clinic in Hertfordshire, where patients were randomised to either Treatment as Usual (TAU), a combination of Cognitive-Behaviour Therapy (CBT) and Exposure-Response Prevention (ERP), or Habit-Reversal Treatment (HRT). The latter consisted of a mobile phone application, and participants were asked to practise sequences of finger tapping movements. Participants were assessed at 3 timepoints (Baseline, Midterm and Endpoint). Results showed that HRT was equivalent to TAU in reducing symptoms, and indeed superior at enhancing quality of life in OCD. These results are discussed alongside neural markers and cognitive deficits in inhibitory control and extra-dimensional set-shifting.

Chapter 5 presents data on a second group of patients with OCD and a matched control group, aiming to further clarify neural and cognitive dynamics of inhibitory control, error monitoring, and motor learning in OCD. For that end, both patient and control group were further separated into app and no-app training, enabling assessment of how the mobile application affects healthy participants, and whether the changes in OCD symptomatology seen

in **Chapter 4** were related to app training or to the passage of time. Electroencephalographic and behavioural data were collected at two different timepoints, separated by a month, to parallel the previous study and allow for comparisons.

Chapter 6 further investigates inhibitory control deficits in OCD in an online study with yet another group of patients and control participants. The comparison between ability to control actions, as measured by the Stop-Signal Task, and thoughts, as per the RIF paradigm, showed significant RIF effects on controls, but not on patients, suggesting impaired thought inhibition in OCD. These results are discussed alongside a metacognitive memory test, which reveals the role of memory confidence as a possible cause of repetitive actions in OCD.

A final Discussion **(Chapter 7)** brings together the findings of this thesis and considers their implications for the neuropsychological basis of OCD and its future treatment.

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CHAPTER 1 – INTRODUCTION

To be, or not to be: that is the question:
Whether 'tis nobler in the mind to suffer
The slings and arrows of outrageous fortune,
Or to take arms against a sea of troubles,
And by opposing end them?(…)

Hamlet, Act III, Scene 1

William Shakespeare

1. Background

Once described as the *folie du doute* (from the French, 'the madness of doubt') (Bourgeois, 1975; Saulle, 1875), Obsessive-Compulsive Disorder (OCD) is a highly debilitating mental disorder, characterized by persistent, intrusive and distressing obsessions and/or compulsions, affecting individual's social, occupational and other areas of functioning lives and causing considerable distress (American Psychiatric Association, 2013). It is estimated to affect between 1-3% of the population around the world (Fawcett et al., 2020; Ruscio et al., 2010) and can frequently present a chronic course when not treated (Riesel et al., 2015)

The main characteristics of OCD are the presence of obsessions or compulsions, the first being defined as "recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress" and the latter consisting of "repetitive behaviours (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly" (American Psychiatric Association, 2013). The level of insight the individuals present regarding their compulsions can vary from high to absent (Gillan, Fineberg, & Robbins, 2017), and, although in many cases the subjects are aware of the poor connection between the compulsion and the obsession (i.e. checking if the oven is turned off several times to avoid harm to a beloved relative), they yet feel an urge to perform the compulsion, characterising OCD as an ego-dystonic disorder (Jacob et al., 2014; Vaghi et al., 2017).

The neurobiology of OCD is not yet consistently established, however, extensive research indicates a dysfunction in the cortico-striato-thalamo-cortical (CSTC) circuits of the brain in the aetiology of this disease (Ahmari & Rauch, 2022; Rauch et al., 1994; Robbins et al., 2019). More specifically, an overactivation of the orbitofrontal (OFC) and anterior cingulate (ACC) cortices, as well as the caudate, insula and amygdala, and an hypoactivation of the dorsolateral prefrontal cortex (DLPFC) appear to be present in individuals with OCD (Apergis-Schoute et al., 2018; Baxter et al., 1988; Robbins, Vaghi, & Banca, 2019; Milad & Rauch, 2012). However, some evidence also indicates the influence of the Supplementary Motor Area (SMA) and of the Pre-Supplementary Motor Area (pre-SMA) in the inhibitory control dysfunction perceived in OCD patients, which could potentially be related to their lack of control over the performance of compulsions (Bonini et al., 2014; de Wit et al., 2012; Grützmann et al., 2016, 2022; Lee et al., 2017). OCD has been, therefore, conceptualized as a disorder of self-control and behavioural inhibition, and patients tend to perform their compulsions despite negative consequences (Banca, Voon, et al., 2015). A possible candidate neural centre for the deficient inhibitory control of actions (compulsions) and thoughts (obsessions) in OCD is located in the basal ganglia. A recent meta-analysis has suggested that this brain region, extensively studied for its role in motor inhibitory control, might also be involved in higher-order cognitive processes, for instance, memory retrieval and thought inhibition (Guo et al., 2018).

Another of the recent theories advanced to explain the acquisition and maintenance of compulsions in OCD is the imbalance between goal-directed and habit learning systems (Banca et al., 2015; Dayan, Berger, & Anholt, 2017; Gillan & Robbins, 2014; Gillan et al., 2011, 2016, 2017; Vaghi et al., 2017; Voon et al., 2015). This approach postulates that patients with OCD tend to rely on habits rather than on goal-directed behaviours, despite appearing aware of more appropriate actions (Vaghi et al., 2017), and that the basal ganglia, SMA, pre-SMA and ACC are involved in this process by affecting inhibitory control and goal-directed behaviour and thereby facilitating the acquisition of compulsive habits (Gillan & Sahakian, 2015; Grützmann et al., 2016; Lee et al., 2017; Riesel et al., 2015). It is possible, thus, to infer that these mechanisms are connected to what are called “slips of action”, a commonly seen feature of OCD in laboratory studies. Those behaviours occur in situations when subjects are performing tasks and suddenly commit errors due to the lack of ability to suppress a response that was previously reinforced, hypothetically indicating a reliability on habits (Gillan & Robbins, 2014; Gillan & Sahakian, 2015). Whilst the ACC is responsible for inhibitory control, the SMA and pre-SMA are important for ‘readiness to act’, which could explain increased performance of “slips of action” if these mechanisms are impaired in OCD. It is important to emphasise,

though, that the extent to which compulsive responding in OCD is instrumental remains the subject of current investigation (Gillan, 2021).

Indeed, it has been proposed that compulsions, rather than obsessions, drive OCD symptoms, with the latter commonly being expressed *a posteriori* (Gillan, Robbins, et al., 2016; Gillan & Sahakian, 2015), as a result of reverse inference (Gillan, Morein-Zamir, Urcelay, et al., 2014). In addition, the incipient studies on the neurobiology of obsessions make it rather difficult to draw robust conclusions about this phenomenon, which so far has been linked to fear conditioning models (Milad et al., 2013).

Threat avoidance is, undeniably, a core component of OCD, with compulsions being performed to alleviate anxiety and prevent a possible harmful event (American Psychiatric Association, 2013, Salkovskis, 1999). Nevertheless, it is well known that, rather than decreasing anxiety levels, compulsions tend to, paradoxically, increase them by making individuals feel 'stuck' in a loop of incompleteness (Fradkin et al., 2020; Summerfeldt, 2004). If this is the case, then why would patients continue to engage in compulsive behaviour?

A plausible explanation derives from the sensorimotor theory of OCD, which postulates that individuals with the disorder present a weakened sense of agency (Gentsch et al., 2012; Giuliani et al., 2021; Morand-Beaulieu et al., 2021; Szalai, 2019). This can be seen in two important features of the disorder: repetitive actions (accompanied by the "just right" feeling), and overreliance on sensory and external feedback (Cougle et al., 2013; Fradkin et al., 2020; Reuven-Magril et al., 2008; Seow & Gillan, 2020; Szalai, 2019). The former represents a phenomenon in which actions must be repeated a certain number of times, until the patient feels that they have been done properly and achieved their goal (Fornés-Romero & Belloch, 2017). The neurocognitive mechanisms driving this sense of completeness are not properly established, but seem to be rooted in motor deficiencies and in an inability to register that an action has already been performed, despite conscious awareness of it (Gentsch et al., 2012; Summerfeldt, 2004). As for the latter, it seems that this faulty internal feedback regarding action completeness contributes to the feelings of uncertainty, which thus lead to reliance on external and/or sensory feedback (Fradkin et al., 2020). Indeed, a study has attempted to explain OCD symptomatology through the Bayesian Brain Framework (Fradkin et al., 2020; Knill & Pouget, 2004). This framework proposes that the brain makes probabilistic inferences regarding states through sensory feedback, predictions and beliefs weighted according to their perceived uncertainty. For example, someone with checking symptoms of OCD might put more weight on sensory feedback (the action of checking and seeing that the stove is turned off) than on the 'uncertain' belief that they have already turned off the stove. According to Fradkin et al

(2020), the core symptom of OCD is excessive uncertainty regarding state transitions, which could be described as the ability to understand and predict changes (or the lack of them) from one state to the next. The authors propose that this "transition uncertainty" could explain the impairment in planning, excessive checking and overreliance on sensory feedback seen in this condition.

Corroborating the defective feedback system hypothesis of OCD, a plethora of studies have shown hyperactivation of the Anterior Cingulate Cortex (ACC) in this disorder, a brain region responsible for conflict monitoring, threat detection, and cognitive control (Botvinick et al., 2001, 2004; Marzuki et al., 2020; Robbins et al., 2019; Shenhav et al., 2013; Weinberg, Kotov, et al., 2015; Weinberg, Dieterich, et al., 2015). This region (particularly its dorsal portion) generates an extremely robust marker of OCD termed the Error-Related Negativity (Gehring et al., 1993; Riesel et al., 2015; Weinberg, Dieterich, et al., 2015; Weinberg et al., 2016), which operates as an 'alarm' signalling the detection of threat. However, an overactive alarm is likely to turn on more times than necessary, generating fear response, anxiety, and attempts to minimise threat by controlling the environment and reducing uncertainty (Hajcak et al., 2003a; Ladouceur, 2016).

Although patients are aware of the poor connection between their obsessions and compulsions, it is plausible to hypothesise that compulsions arise from the need to control an uncertain environment. For instance, one could aim to protect a beloved relative by turning the light switches on and off, behaviour characterised as magical thinking (Einstein & Menzies, 2004; West & Willner, 2011). One of the most commonly known strategies for dealing with uncertainty and the consequential anxiety derived from it is the creation of, and engagement in rituals (Graybiel, 2008; Hobson et al., 2018). From children's pre-bed routines to the habits of athletes prior to competitions, rituals have served the purpose of controlling an uncertain environment by providing order to an unpredictable world (Tonna, Marchesi, & Parmigiani, 2019). An enhanced need for control might therefore explain many symptoms in OCD, for instance, checking (to avoid making a mistake), hoarding (to avoid the loss of something that may be useful in the future), mental rituals (to avoid harm), and many others, behaviours that describe what is termed "illusion of control" (Reuven-Magril, Dar, & Liberman, 2008).

Rituals are described as predefined sequences of symbolic actions that are performed in a strict and repetitive way and lack instrumental purpose (Brooks et al., 2016; Hobson et al., 2017). This definition, similar to the meaning of compulsion, differs in one key aspect of the latter: rituals are symbolically meaningful. If compulsions are derived from an imbalance between goal-directed and habitual behaviours, with the preponderance of the latter, one could

argue that they have served a purpose formerly. Indeed, evolutionary studies propose that the acquisition of habits serves an important role in automatising and expediting instrumental actions which could potentially lead to higher survival rates (Eilam et al., 2006). For instance, routinisation would allow for less attention required to perform habitual tasks, fewer errors due to training (Banca et al., 2020), and more resources available for monitoring potential threats (Fentress, 1976) and detecting conflict.

It is possible that in OCD the anxiety reported when compulsions are not performed is a misrepresentation of an overactive striatum and enhanced action tendencies rather than an actual fear response. The relationship between anxiety and motor behaviour does seem to present some clues regarding the aetiology of OCD symptomatology. Two recent studies have attempted to manipulate anxiety and electrophysiological amplitudes of error-monitoring through the introduction of rituals in healthy volunteers (Brooks et al., 2016; Hobson et al., 2017). Participants were asked to perform novel random ritualistic motor behaviours prior to an anxiety-inducing task. Electroencephalographic recordings were measured at baseline and following the execution of the ritual, showing decreased amplitudes. The authors propose that the execution of rituals acts as a buffer against anxiety and by increasing confidence in performance, which in turn diminishes the sensitivity to self-generated errors (Hobson et al., 2017). This study is particularly important for differentiating compulsions from rituals, introducing a completely novel set of ritualised behaviours. Despite the lack of research in OCD patients, this could shed light on the reason why rituals are perceived by patients as anxiety-reducing.

This is further supported by Habit Reversal Therapy (HRT), which operates based on the assumption that habits can be replaced by competitive actions (Azrin & Nunn, 1973). HRT has been successfully employed to treat tic disorders and trichotillomania (Chamberlain et al., 2009; Woods et al., 2006), with incipient evidence supporting its use for OCD (Lee et al., 2019). Indeed, the use of competitive stimuli has been employed for a myriad of disorders and mechanisms, from Post-Traumatic Stress Disorder (PTSD) (Holmes et al., 2009; James et al., 2015) to memory retrieval (Anderson et al., 1994; Demeter et al., 2014).

For instance, Holmes and colleagues (2009) conducted an experiment employing the computer game ‘Tetris’ within 30 minutes of participants viewing a traumatic video, a crucial period for memory consolidation (Walker et al., 2003), in an attempt to reduce the occurrence of flashbacks, a core feature of the disorder (American Psychiatric Association, 2013). Given the nature of flashbacks as sensory-perceptual images with visuo-spatial components (Brewin & Holmes, 2003) and the limited capacity of brain resources (Holmes et al., 2009; James et al.,

2015), the authors predicted that a competitive visuo-spatial cognitive task could deplete those, which was later proven true (Holmes et al., 2009).

An analogous phenomenon seems to occur with memory retrieval (Anderson, 2003; Anderson et al., 1994; Anderson & Green, 2001), typically demonstrated by the *retrieval practice paradigm* (Anderson et al., 1994; Demeter et al., 2014). In this task, participants are asked to study a list of category-exemplar pairs, for instance 'precious stone – quartz'; 'precious stone – emerald'; 'toy – doll'; 'toy – kite'. Half of the exemplars from half of the categories will then be displayed to the individuals for retrieval (i.e. only precious stone – emerald from the example above), with the category and the first letter of the exemplar as a cue (precious stone – e------). A distracting task is then introduced, promoting a delay between the study and practice phase and the final recall test, when all categories studied are presented for retrieval of the associated exemplars. Typical results demonstrate what is called a Retrieval-Induced Forgetting (RIF) effect, with non-practised words from the practised categories (i.e. quartz, since precious stone was a studied category) being less accessible than the words 'doll' and 'kite', given that toy exemplars were not practised (Anderson et al., 1994; Demeter et al., 2014).

Albeit still undergoing scrutiny, with opposing theories advocating for inhibitory mechanisms versus interference of retrieved memories as the cause of RIF, neuroimaging and electrophysiological studies have proposed that this retrieval process over competitive stimuli is actually a product of inhibitory control (Hellerstedt & Johansson, 2014; Wimber et al., 2015). Interestingly, deficits in the Stop-Signal (SST) (Lappin & Eriksen, 1966; Logan & Cowan, 1984; Vince, 1948) and Go/No-Go (GNG) tasks (Gordon & Caramazza, 1982) seem to correlate with memory inhibition/suppression difficulties (Guo et al., 2018), indicating the existence of a domain-general inhibitory control over actions and thoughts (Apšvalka et al., 2022). Deficits in the SST and GNG task are well known in OCD (Mar et al., 2022), however, perhaps not surprisingly, Demeter and colleagues (2014) have found no RIF effect in their participants with OCD (Demeter et al., 2014), adding further evidence to the inhibitory control impairments seen in the disorder (Chamberlain et al., 2005; Demeter et al., 2014; Marzuki et al., 2020; Robbins et al., 2019).

Brain areas implicated in inhibitory control include the dorsolateral and ventrolateral prefrontal cortices (Apšvalka et al., 2022), the inferior frontal cortex (Aron et al., 2014), and the basal ganglia (Guo et al., 2018), all associated with deficits in OCD (Robbins et al., 2019). Particularly, the Anterior Cingulate Cortex (ACC) seems to play a major role as the recruiter

of cognitive control (García et al., 2022), and will be explored in more detail later in this chapter.

To address those deficits and markers of OCD, this thesis will focus on cognitive and behavioural paradigms, associated with electroencephalographic (EEG) measures. The next sections will, therefore, introduce how an EEG approach can further advance knowledge of OCD.

2. Electroencephalography

Since German Psychiatrist Hans Berger's (1873-1941) first recordings of brain electrical activity in 1924 (Luck & Kappenman, 2012), electroencephalographic measures have been increasingly applied in research in the fields of psychiatry, neurology and neurosciences. Described as "a technique for recording electrical activity of the human brain from the surface of the head" (Millet, 2002), electroencephalography (EEG) has achieved status and followers due to its relative low-cost, high tolerability and non-invasive characteristics (Kappenman & Luck, 2016). It is imperative, though, to understand this technique and the processes underlying the generation of the EEG signal, in order to fully comprehend its results, contributions and limitations.

2.1. What can an electroencephalographic approach provide to the understanding of OCD?

The technique of measuring neuronal signalling is called Electroencephalography (EEG) and has been widely used in research for diagnostic purposes and uncovering cognitive processes (Kappenman & Luck, 2016). It provides a rapid method for measuring brain activity, which has considerable temporal resolution that can help dissect cognitive processes prior to behavioural manifestation. This velocity is particularly relevant since cognitive processes may happen in fractions of seconds and offers a remarkable advantage in comparison with other gold standards of neuroimaging such as functional Magnetic Resonance Imaging (fMRI). Whilst fMRI data provide excellent spatial resolution, the Blood Oxygen Level Dependant (BOLD) response on which they rely typically requires a few seconds to be completed (Glover, 2011), proving its unsuitability for measuring rapid cognitive processes (Luck & Kappenman, 2012).

Although electroencephalographic recordings provide excellent temporal resolution, the method is not without its pitfalls. The signal recorded by the electrodes placed on the scalp is a result of the summation of the activity of populations of neurons that have fired in response

to a stimulus or spontaneously and have crossed several layers of brain tissue and especially a very resistant skull (Burle et al., 2015). Due to the fact that it has been originated several centimetres below the scalp, where it is recorded, the signal originated from the EEG carries activity from underlying brain sources and does not necessarily correspond to the area underneath the channel where it is maximal (Cacioppo, Tassinary, & Berntson, 2017). This diffusion results in a signal that is potentially generated in a different location from the one in which it is captured, perhaps similar to sensing an electric shock when touching a power plug, which could lead to the conclusion that the current had originated there (instead of from the power outlet). EEG recordings, therefore, are not ideal for deriving conclusions concerning their spatial source (Luck & Kappenman, 2012), although powerful methods of mathematical transformations can be applied to the EEG signal, minimising this limitation (Michel & Brunet, 2019).

Another disadvantage associated with this technique is the low signal-to-noise ratio. To validate robust conclusions, a high number of trials and a long duration of the recordings are necessary. EEG experiments, therefore, require careful design and laborious data analysis (Keil et al., 2014). Nevertheless, EEG recordings can provide important information about the brain and specific cognitive processes, for instance, how humans adapt to errors, detect conflict and receive feedback.

2.2. Event-Related Potentials

The electrical signal captured in the scalp resulting from a specific sensory, motor or cognitive event or stimulus is called an Event-Related Potential (ERP). The first studies of ERP date from 1935, when Pauline and Hallowell Davis recorded data from awake humans (Luck, 2005). It was only later, in 1964, that the first ERP waveform was discovered, namely the Contingent Negative Variation (CNV), by Walter and colleagues (Walter et al., 1964).

ERP research is now one of the most widely used methods for mapping cognitive processes. By creating time windows (epochs) that are "locked" to specific events (e.g. a button press) it is possible to average electrical activity in the brain across multiple trials, uncovering a resulting waveform (Luck, 2005). It was through this process that many cognitive phenomena have been elucidated, including attention, memory, conflict detection, and error monitoring (Luck & Kappenman, 2012). Given the particular advantages of temporal resolution and high-tolerability, ERP research has long been used as a tool for diagnostic purposes of both neurological (e.g. sleep disorders and epilepsy) and psychiatric disorders (e.g. schizophrenia,

attention deficit hyperactivity disorder, obsessive-compulsive disorder, among others) (Kappenman & Luck, 2016).

3. Obsessive-Compulsive Disorder and Electrophysiology

In an attempt to clarify the underlying mechanisms depicted in section 1 (i.e. inhibitory control, "slips of action", habitual behaviour), electroencephalography has been widely used in patients with OCD, with techniques ranging from: (i) Quantitative EEG (QEEG) (also referred to as "brain mapping"). This is an analytical technique that describes EEG parameters related to band power, synchronisation and activation patterns in the brain during electroencephalographic recordings, resulting in a map of the brain (Tong & Thakor, 2009); (ii) intracerebral electroencephalography (iEEG). This technique involves placing electrodes directly onto the exposed surface of the brain in order to monitor activity from the cortex, providing excellent anatomical precision (Parvizi & Kastner, 2018); and (iii) ERP (Bonini et al., 2014; Perera et al., 2019; Riesel et al., 2015).

A recent review of the electrophysiological literature of OCD has suggested frontal asymmetries in alpha and theta band power in these patients (Perera et al., 2019). Asymmetries are defined as the difference between right and left activity over frontal regions of the brain (Davidson et al., 1990). The band power suggests which of the areas (left or right) is more strongly active. Band types have been extensively studied in psychiatric disorders and present some clues regarding cognitive functions (Perera et al., 2019). Whilst alpha band asymmetries have been linked to avoidance motivation in OCD (Ischebeck et al., 2014), theta band asymmetries are thought to suggest impairments in active inhibition during cognitive tasks, a previously reported robust cognitive marker of OCD deficits (Menzies et al., 2007; Min et al., 2011; Riesel et al., 2015). Perhaps not surprisingly, research evidence proposes that this theta activity is mainly generated in the ACC, a widely recognised area for mediating inhibitory impairments in OCD (Wang et al., 2005). On the other hand, task related alpha asymmetries have also been associated with difficulties in suppressing distractors or task-irrelevant details. Taken together, these results might elucidate the strains experienced by patients with OCD in suppressing obsessive thoughts (Crawford et al., 1995; Perera et al., 2019).

In addition, several ERP components have been studied in order to investigate the cognitive processes associated with the disorder (Figure 1). Examples include the Readiness Potential (RP) (Dayan, Berger, & Anholt, 2017), the N_2 (Dayan-Riva, Berger, & Anholt., 2020; Dieterich Endrass, & Kathmann, 2017; Riesel et al., 2017), the error Positivity (Pe) (Klawohn et al.,

2014), the feedback Error-Related Negativity (fERN) (Hajcak et al., 2006; Holroyd, Hajcak, & Larsen, 2006) and perhaps the most widely recognised, the Error-Related Negativity (ERN) (Grützmann et al., 2016; Klawohn et al., 2014; Moser et al., 2013; Olvet & Hajcak, 2008; Riesel, 2019; Weinberg, Dieterich, & Riesel, 2015).

Figure 1. *OCD-related ERP components and the brain regions generating the signals, associated cognitive processes, and experimental paradigms.*

ERP	**Main Generators**	**Cognitive Process**	**Paradigms**	**Timeframes**	**OCD findings**
Readiness Potential (RP)	-Pre-SMA -SMA -ACC -Basal Ganglia	Motor preparation	Motor tasks (Reaction-time tasks)	Up to 1.5s prior to movement	Enhanced amplitudes
N_2	ACC	Conflict detection	-Mismatch detection -Cognitive control (inhibitory tasks)	~ 200-350ms post stimuli	Mixed results with studies describing enhanced and diminished amplitudes
Error-Related Negativity (ERN)	-ACC -SMA	Error monitoring	Inhibitory control	~50-100ms post erroneous response	Enhanced amplitudes
Feedback Error-Related Negativity (fERN)	ACC	Error detection	Inhibitory control tasks with feedback	~250-300ms after feedback	Diminished amplitudes.

3.1. Mismatch detection and the N_2

The discrepancy between an expected and an actual outcome generates an ERP termed N_2. As the name suggests, this negative deflection peaks around 200ms after a conflict is detected by the brain and is usually measured experimentally through inhibitory control, mismatch detection and probabilistic learning tasks (Azizian et al., 2006; Dieterich, Endrass, & Kathmann, 2017; Folstein & Van Petten, 2008; Riesel et al., 2017).

In OCD, studies seem to report both enhanced (Ciesielski et al., 2011; Riesel et al., 2017; Ruchsow et al., 2007) and diminished (Dayan-Riva, Berger, & Anholt., 2020; Dieterich, Endrass, & Kathmann, 2017) amplitudes of N_2. However, it is important to note that different paradigms may actually be capturing diverse cognitive processes. Research that suggests diminished N_2 is often based on paradigms that require response inhibition, a mechanism well-known to be impaired in OCD (Chamberlain et al., 2005), whereas enhanced N_2 amplitudes are seen in response to conflict processing paradigms, such as the Flanker Task (Riesel et al., 2017). Despite the contradictory results, research seems to be unanimous regarding the role of the N_2 as a marker of inhibitory control and mismatch detection. It appears that the N_2 is part of a monitoring network, which detects conflict and signals the need for cognitive control, even in situations where monitoring would not be as necessary or beneficial (Riesel et al., 2017). A perceived increased need for control might also explain the reason why conflict is highly monitored in OCD (Riesel et al., 2019) and reflects another key feature of the disorder: intolerance of uncertainty.

3.1.1. Uncertainty as a generator of the N_2 and OCD symptoms

Uncertainty appears to play an important role in the generation of the N_2 and is also a marker of OCD (Dieterich, Endrass, & Kathmann, 2017; Scholl & Rushworth, 2017) as well as other anxiety-related disorders. Patients with OCD have been shown to present difficulties when making decisions, especially in uncertain contexts (Holaway et al., 2006; Marzuki et al., 2020, 2021; Morein-Zamir et al., 2020). In fact, unpredictability seems to be evaluated negatively, is not well tolerated by patients with OCD, and increases demand for attentional control, anxiety levels and neural markers of conflict detection (i.e. N_2) (Dieterich, Endrass, & Kathmann, 2017). In addition, stress is thought to reduce Reward Positivity, an ERP that measures sensitivity to reward (Burani et al., 2020), which could explain non-optimal decision-making in unpredictable – and consequently stressful - tasks by OCD patients. Confidence levels, on the other hand, are not necessarily predictive of most advantageous choices and patients with

OCD seem to discard acquired knowledge and instead explore the tasks further. In a predictive inference learning task in which uncertainty was a major element determining performance, Vaghi and colleagues (2017) reported a dissociation between action and confidence, with OCD patients demonstrating similar confidence rates to healthy volunteers but not acting in accordance to the optimal choices. The same pattern has been shown in children with OCD undertaking the Information Sampling Task (Clark et al., 2006). Patients seem to discount subjective costs of time spent performing the task, such as fatigue and impatience in order to turn more cards before making a decision (Hauser et al., 2017).

Intolerance of uncertainty might also be one of the underlying mechanisms driving checking behaviour in OCD. Since patients with this disorder present enhanced amplitudes of N_2 in response to conflict processing paradigms implicating overactive conflict/mismatch detection mechanisms (Riesel et al., 2017), it is possible to infer that checking compulsions may be generated to serve a protective role in avoiding a heightened sense of error commission. The features of behavioural rigidity and perfectionism, also key markers of OC symptoms (American Psychiatric Association, 2013), might be added to this model as a means of controlling the environment and alleviating anxiety facing uncertainty (Moser et al., 2013).

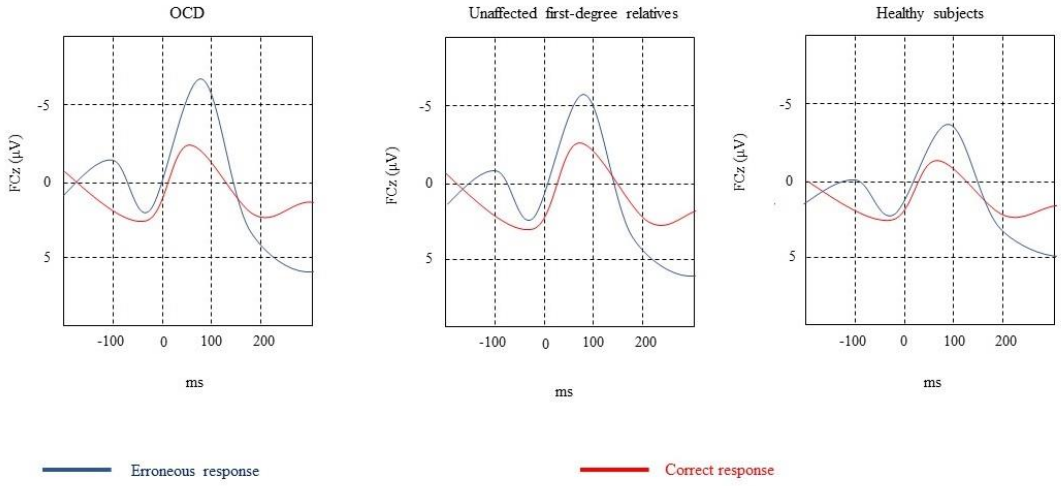
3.2. Error-Related Negativity as an endophenotype of OCD

After the 1990's and the 'decade of the brain' (Bush, 1990), much biological research entered the "age of the endophenotypes". An endophenotype constitutes a heritable trait that is associated with an augmented genetic risk for a disorder (Chamberlain & Menzies, 2009). Traits classified as endophenotypes mediate the relationship between genes and a behavioural phenotype (Olvet & Hajcak, 2008), are state independent and occur in unaffected relatives at a higher rate than in the general population (Gottesman & Gould, 2003). Additionally, endophenotypes are thought to be impervious to treatment, despite the improvement of symptoms (Hajcak et al., 2008; Riesel et al., 2011, 2015). For a more comprehensive view of endophenotypes, see Box 1.

The Error-Related Negativity (ERN) is a component of the ERP that reaches a maximum amplitude between 50 and 100ms after the commission of an error in forced-choice inhibitory control tasks (e.g. Stroop Colour and Word Task (SCWT, Stroop, 1935); Flanker Task (Eriksen & Eriksen, 1974); and the Go/No-Go Task) (Luck & Kappenman, 2012; Olvet & Hajcak, 2008; Weinberg, Dieterich, & Riesel, 2015). It was independently discovered by two research groups in the early 1990s. In Germany, Falkenstein and colleagues (1991)

reported what they called the Error Negativity (Ne), whereas in the United States, Gehring and his team (1993) described the Error-Related Negativity (ERN) (Falkenstein et al., 1991; Gehring et al., 1993; Weinberg, Dieterich, & Riesel, 2015; Wessel, 2012). Within less than three decades of its discovery, the ERN has become the most widely investigated index of error processing (Wessel, 2012) and is implicated in multiple forms of psychopathology (Riesel et al., 2017). Figure 2 depicts an example of the ERN component, created for illustrative purposes.

Figure 2. *Example of the ERN component in OCD, unaffected first-degree relatives of OCD patients and healthy subjects*.



The validity of the ERN as an endophenotype for psychiatric disorders has been extensively investigated and remains unrefuted, having been proven in different conditions (Gillan et al., 2017; Moser et al., 2013; Olvet & Hajcak, 2008; Perera et al., 2019; Riesel et al., 2011, 2017; Weinberg, Dieterich, & Riesel, 2015). Several studies have attempted to contrast ERN amplitudes in disorders such as attention deficit hyperactivity disorder (ADHD) (Marquardt et al., 2018), psychosis (Foti et al., 2012), substance abuse and addictions (Franken et al., 2007; Riesel et al., 2019), depression (Holmes & Pizzagalli, 2008), generalised anxiety disorder (GAD) (Hajcak, McDonald, & Simons, 2003a; Moser et al., 2013), among many others (Olvet & Hajcak, 2008). Conditions such as ADHD, psychosis, substance abuse, addictions and other disorders characterised by impulsivity seem to be marked by reduced amplitudes of ERN when compared to healthy volunteers, whereas disorders in the spectrum of anxiety and OCD show larger amplitudes (Olvet & Hajcak, 2008). Depression appears as a

contradictory case, with studies showing both enhanced (Holmes & Pizzagalli, 2008) and diminished (Weinberg, Kotov, & Proudfit, 2015; Weinberg et al., 2016) ERN amplitudes. It seems, then, that ERN amplitudes are less related to diagnostic conditions than to individual differences on the evaluation of mistakes (Hajcak et al., 2005), fitting well within the trans-diagnostic RDoC framework (Weinberg, Dieterich, & Riesel, 2015) (see Box 1).

Amongst different psychiatric disorders, OCD is the disorder in which the ERN has been most extensively studied. The findings of enhanced amplitudes of the ERN in unaffected family members of OCD patients and its imperviousness to the effects of treatment indicate that the ERN represents an endophenotype of the disorder (Olvet & Hajcak, 2008; Riesel, 2019). Indeed, a recent systematic review of the literature has investigated whether the six proposed endophenotypes for OCD (impairments in Decision-Making, Action Monitoring, Inhibition, Memory (working, verbal and nonverbal), Reversal-Learning (either behavioural or associated with Orbitofrontal Cortex (OFC) dysfunction) and Cognitive Flexibility (Menzies et al., 2007)) would also apply in adolescents with the disorder (Marzuki et al., 2020). The most robust findings suggested increased action monitoring as a shared trait between paediatric and adult OCD, potentially indicating this as a deficit with an onset that precedes that of the others. Indeed, research has evidenced that an abnormally enhanced action monitoring tendency, as measured through EEG in unaffected children as young as six years old re-tested at the age of nine, could predict the later development of anxiety disorders (Meyer et al., 2015).

In order to fully comprehend the ERN's role as an endophenotype, though, it is important to clarify its functional significance and biological basis. Many theories have been developed to elucidate this question, with the three major accepted ones described below.

Box 1. *ERN and the RDoC*

Albeit not new, the interest for endophenotypes is likely to have risen as a consequence of the proposition of the Research Domain Criteria (RDoC) framework (Cuthbert & Insel, 2013; Insel et al., 2010; Insel, 2014; Sanislow et al., 2010). Launched in 2008 by the National Institute of Mental Health (NIMH), the RDoC aims at combatting the categorical classification that has dominated psychiatric diagnosis for the past 150 years and incorporating neuroscience findings to the formulation of a clinical hypothesis (de Souza, Nonohay, & Gauer, 2018). Within the RDoC framework, researchers are encouraged to investigate disorders such as OCD dimensionally and trans-diagnostically (Gillan, Fineberg, & Robbins, 2017), providing insights into mechanisms underlying mental disorders (Cuthbert & Insel, 2013; Insel et al., 2010; Insel, 2014; Krueger et al., 2018; Sanislow et al., 2010).

The RDoC matrix currently comprises five domains (negative valence systems, positive valence systems, cognitive systems, social processes and arousal and regulatory systems) and eight units of analysis (i.e. genes, molecules, cells, circuits, physiology, behaviour, self-report and paradigms), thought to encompass all processes responsible for impacting behaviour and cognition, though more domains could be added (Cuthbert & Insel, 2013; Etkin & Cuthbert, 2014; Insel et al., 2010; Sanislow et al., 2010). Due to its involvement in different processes, the ERN is a physiological unit of analysis of three RDoC domains: i) **Performance Monitoring** in the Cognitive domain; ii) **Sustained Threat** in the Negative Valence Systems domain and; iii) **Reward Learning** in the Positive Valence Systems domain (de Souza, Nonohay, & Gauer, 2018). Thus, the ERN is thought to be implicated in the recognition of threat, learning from feedback and performance monitoring, which are thought to be impaired in OCD (Apergis-Schoute et al., 2017; Riesel, 2019; Vaghi et al., 2017).

3.2.1. Error Detection/Comparator Theory

Detecting mistakes and adapting behaviours efficiently is essential in a changing environment (Riesel, 2019; Weinberg, Dieterich, & Riesel, 2015; Weinberg et al., 2016). The ability to detect and respond to the mismatch between a motor response and the expected outcome gave rise to the "Comparator Theory" as developed in the first studies of ERN (Falkenstein et al., 1991; Gehring et al., 1993). Essentially, the ERN was thought to reflect the comparison between the correct response and that of the individual, and to be generated when

the two were not the same (i.e. when a perceived error had occurred) (Coles, Scheffers, & Holroyd, 2001). This theory indicates that the error processing system represented by the ERN might even be triggered by correct responses, if they are interpreted as incorrect by the subject, i.e. not necessarily indicating mistakes objectively, but the individual's subjective evaluation of them (Coles, Scheffers, & Holroyd, 2001; Hajcak et al., 2005; Vidal et al., 2003). This could also explain why some disorders are marked by enhanced ERN amplitudes (e.g. anxiety, OCD) and others by blunted (e.g. addiction, ADHD), despite individuals with these disorders being unimpaired in detecting errors. The ERN may thus reflect the 'motivational salience' of errors rather than a literal representation of them (Olvet & Hajcak, 2008).

Researchers have further proposed that the ERN represents an affective response to errors, processed by the limbic system for action regulation (Luu et al., 2003). Indeed, a plethora of studies has been conducted in an attempt to manipulate the subjective value of committing errors, ranging from monetary rewards (Hajcak et al., 2005), to punishment (Endrass et al., 2010) and social evaluation (Moser et al., 2013), among others. The detection of errors, conflict and the loss of reward could provoke an emotional response (Luu & Pederson, 2004), which is particularly aversive in the case of perfectionism (a trait commonly seen in obsessive compulsive and related disorders), for instance (Perrone-McGovern et al., 2017). Motivational state is especially relevant for interpreting the ERN, as disengagement from the task is predictive of a smaller ERN, as seen in the case of depression (Weinberg, Kotov, & Proudfit, 2015). Therefore, the ERN has also been conceptualised as a putative marker of negative affect (Hajcak, McDonald, & Simons, 2004).

It is important to emphasize, though, that the ERN is a task dependent measure, being elicited in speeded reaction-time experiments (Riesel, 2019; Riesel et al., 2013). Thus, it is possible that most of the errors committed in the classic ERN-generating tasks (e.g. SCWT, Flanker Task and the Go/No-Go Task) are caused by a premature response of the subject, before stimulus evaluation is complete (Coles, Scheffers, & Holroyd, 2001).

3.2.2. Conflict-Monitoring Theory

The Conflict Monitoring Theory is derived from the view that the Error-Detection Comparator Theory was implausible, since the brain would have to possess the information of what the intended (correct) response was and be able to compare this with the actual response. If this was the case and the brain had access to this information, then why would the error be committed? (Carter, 1998; Luck & Kappenman, 2012). It suggests that conflicts are generated

from the activation of multiple competing responses, which alerts the brain to the ongoing dispute. Therefore, it does not postulate that the brain possesses all the information to respond, but rather signals the need for increased control in high-conflict trials. Following those, performance will be improved through feedback and learning, and less control will be required (Luck & Kappenman, 2012). The locus of this conflict-monitoring is the main generator of the ERN, the Anterior Cingulate Cortex (ACC), specifically its dorsal portion (dACC) (Falkenstein et al., 1991; Gehring et al., 1993; Riesel, 2019; Weinberg, Dieterich, & Riesel, 2015).

The functional role of the ACC has sparked an effervescent debate, with some authors proposing that it monitors conflicts in information processing (Botvinick, 2007; Botvinick, Cohen, & Carter, 2004; Shenhav, Botvinick, & Cohen, 2013) and others that it informs optimal decision-making and guides voluntary actions (Behrens et al., 2007; Kennerley et al., 2006). Given the fact that an enhanced ERN is a convincing endophenotype of OCD (Olvet & Hajcak, 2008; Riesel, 2019; Riesel et al., 2011; Weinberg, Dieterich, & Riesel, 2015) and that several neuroimaging studies have suggested an overactivation of the ACC in OCD patients (Apergis-Schoute et al., 2017; Gillan et al., 2017; Robbins, Vaghi, & Banca, 2019), it is imperative that this region is studied in more detail.

OCD deficits of goal-directed behaviour have been extensively reported in the literature (Banca et al., 2015; Gillan et al., 2011, 2017; Gillan & Robbins, 2014). In fact, a predisposition for the formation of habits and preference for model-free over goal-directed model-based learning seems a potential candidate endophenotype of the disorder (Gillan et al., 2011, 2016; Gillan & Robbins, 2014; Gillan & Sahakian, 2015; Vaghi et al., 2017; Voon et al., 2015) . If that is the case, it is possible to infer that the overactive dACC is not informing goal-directed behaviours, but rather monitoring them through the ERN.

One possible explanation for the dissociation between knowledge and action in OCD can be derived from the neurobiological evidence relating to habitual behaviour. Neuroimaging studies show that the basal ganglia are overactive in OCD and regions responsible for the formation of habits such as the striatum (comprising caudate and putamen) are particularly affected (Banca et al., 2015; Fineberg et al., 2018; Gillan et al., 2015). The striatum seems exceptionally important in this context, given that its neurons are thought to fire at the beginning and end of a behavioural routine. Thus striatal overactivity could explain the exaggerated urge to perform compulsions and why such sequences must be performed until completion (Graybiel & Grafton, 2015; Guo et al., 2018). It is thus also possible to hypothesize that an over-functioning striatum contributes to increased habit formation in OCD by failing to interrupt motor sequences regardless of the dACC signalling that they are erroneous. It is

conceivable, therefore, that the ACC is trying to engage cognitive control and inform optimal decision-making (Behrens et al., 2007; Kennerley et al., 2006) as is the case with the generation of the N_2, however, in patients with OCD, this activity is being overridden by striatally-driven habitual behaviour (Gillan et al., 2011, 2015).

A further possible explanation concerns the function of the ERN. The fact that it signals the need for employment of cognitive control does not necessarily result in this being achieved. In fact, the ERN may be an early warning signal of conflict generated by the ACC, which is then followed by a cascade of events, including activation of defensive systems and of the dorsolateral prefrontal cortex (DLPFC), a region responsible for the employment of planning and cognitive flexibility that is also found to be impaired in OCD (Robbins, Vaghi, & Banca, 2019; Weinberg et al., 2016). In the case of the ERN, conflict monitoring responses are observed in patients following the commission of errors (Hajcak, McDonald, & Simons, 2003b), representing their evaluation, but the compensatory behaviours that follow depend on intermediary processes (Weinberg et al., 2016).

3.2.3. Reinforcement Learning Theory

Proposed by Holroyd and Coles (2002), the Reinforcement Learning Theory (RL-ERN) suggests that a monitoring system in the basal ganglia produces an error signal when adverse events occur that are worse than expected (Hajcak et al., 2006; Holroyd, Hajcak, & Larsen, 2006; Luck & Kappenman, 2012). The system is modulated by the midbrain dopamine system that sends the signal to the ACC, where it is hypothetically used to improve performance by adapting motor behaviour (Haber, 2014; Holroyd & Coles, 2002; Luck & Kappenman, 2012). Perhaps not surprisingly, this system relies heavily on feedback and predictions. Dopamine neurons are thought to demonstrate increased rates of firing resulting from unexpected or better than expected results, events termed positive prediction errors. On the contrary, firing rates diminish following the omission of expected rewards, generating negative prediction errors as measured by the BOLD response during fMRI. These cingulate negative prediction errors appear to be enhanced in OCD (Murray et al., 2019) and can be modulated by dopaminergic drugs, including the dopamine receptor antagonist amisulpride, which was found to ameliorate the excessive negative prediction error in OCD (Murray et al., 2019). Albeit not considered first-line treatments for OCD, dopamine receptor blocking agents can be used for refractory cases with positive results, as shown by meta-analysis (Veale et al., 2014). It is therefore possible that one of the therapeutic effects of dopamine antagonists in OCD involves the

suppression of exaggerated cingulate negative prediction errors, which could be tested electrophysiologically in future studies using the ERN.

3.3. Feedback Error-Related Negativity (fERN) and evaluation of errors

Another ERP component generated by the ACC and closely related to prediction errors, with a later time course than the ERN, is the feedback Error-Related Negativity (fERN). This potential reaches maximum amplitude following negative feedback from tasks when the subject does not know the correct answer and has his predictions unexpectedly violated, therefore differentiating it from the ERN (Potts et al., 2011). Many researchers propose that the fERN is in fact the same component as the ERN, simply occurring at a later stage (Nieuwenhuis, 2004; Nieuwenhuis et al., 2004, 2005). The ERN would reflect a mistake committed when the correct response is known (i.e. simple reaction-time paradigms), whereas the fERN indicates a prediction error that has solely come to awareness through later feedback. As the subject progresses with a task and learns the rules, the ERN starts being elicited and feedback is no longer necessary (Potts et al., 2011). The fERN is particularly relevant in tasks with high difficulty levels or probabilistic tasks, when feedback is essential and participants are unable to be confident in the accuracy of their judgement (Luck & Kappenman, 2012). The RL-ERN suggests that the ERN/fERN reflect the arrival of a negative reward prediction error signal to the ACC and the subsequent employment of the dopamine systems and motor areas to adapt behaviour (Holroyd & Coles, 2002).

Concerning OCD patients, however, this relationship presents some complexities. Although it has been established that individuals with OCD are oversensitive to errors and to punishment, with subjects expressing a tendency to switch more after negative feedback on probabilistic reversal learning tasks (Kanen et al., 2019), it is still unclear why patients perform the tasks sub-optimally. A recent study has shown that fERN amplitudes are actually blunted in OCD patients, regardless of the enhanced ERN (Endrass et al., 2013). As proposed by Hajcak (2005), the ERN seems to be sensitive to the subjective significance of errors, rather than to their external evaluation, and has been thought to reflect the degree to which errors are considered threatening (Weinberg et al., 2016). Thus the ERN is signalling more endogenous (self-perceived) than exogenous (externally signalled) errors (Weinberg et al., 2016). This could potentially contribute to perseveration deficits as well as the impairment of overt goal-directed behaviour in OCD.

Several studies have aimed to manipulate the magnitude of gains and losses in electroencephalographic tasks with OCD participants, as well as to correlate the ERN with symptom severity (Hajcak et al., 2005; Nieuwenhuis et al., 2005; Riesel et al., 2017, 2019; Weinberg, Dieterich, & Riesel, 2015). Perhaps not surprisingly, the ERN does not seem to be affected by external variables, such as reward and punishment, but rather expresses the internal evaluation of errors (Weinberg et al., 2016). Not even highly efficacious drug treatments like the Selective Serotonin Reuptake Inhibitors (SSRIs), the first-line treatment for OCD, are able to attenuate ERN amplitudes (Endrass et al., 2010; Stern et al., 2010).

Interestingly, a recent study has attempted to manipulate the magnitude of the ERN through a computerised cognitive-behavioural treatment targeting error-sensitivity. Two groups of participants were tested at baseline and after a computerised intervention consisting of information and quizzes about either general health (control group) or error-sensitivity (experimental group). Results suggested that the experimental group showed diminished amplitudes of ERN (Meyer et al., 2020). For this reason, amongst the units of analyses of the RDoC, many researchers have suggested its suitability as a marker of sustained threat (Ladouceur, 2016).

Moreover, it is disputed whereas the functional role of ERN is as a signal of cognitive control (Azizian et al., 2006; Scholl & Rushworth, 2017) or reward learning (Holroyd & Coles, 2002; Nieuwenhuis et al., 2004). Nevertheless, these processes are probably both relevant to OCD. A clear deficit concerning the execution of optimal actions can be seen in this disorder. One possible explanation for this is the motor inhibition deficit seen in this population resulting in rigidity that hinders patients' ability to flexibly adapt behaviour and marks out OCD and other obsessive-compulsive related disorders (American Psychiatric Association, 2013) (Chamberlain et al., 2021). In any case, motor systems, as represented by the employment of compensatory behaviour following errors and by perseveration, seem to play a role in the aetiology of OCD symptoms (Grützmann et al., 2016).

3.4. The Readiness Potential

Another ERP poorly studied in OCD, although undoubtedly important in this disorder, is the *Bereitschaftspotential* or the Readiness Potential (RP). First reported in 1965 as a marker of initiated voluntary action (Kornhuber & Deecke, 2016), this brain component is initiated around 1.5ms before the onset of motor responses and represents motor preparation or the decision to initiate movement.

The Supplementary Motor Area (SMA) has been indicated as the main generator of the RP (Cunnington et al., 2003; Deecke & Kornhuber, 1978) and many studies have been conducted to address the individual's degree of control over movements (Libet, 1985). In a famous experiment, Libet and colleagues examined conscious intention of movement while brain activity was being recorded. Their findings suggested that motor preparation preceded the subjective intention to move by an average of 800ms, casting doubt and debate about humans' sense of agency and free will. If that is the case, it may be possible to argue that compulsions generated in OCD might be involuntary, just as tics in Tourette's Syndrome or tremor in Parkinson's Disorder. Indeed, recent studies have investigated the RP in OCD patients, finding enhanced amplitudes of the RP in this population and proposing that OCD patients have increased action tendencies (Dayan et al., 2014, 2017; Dayan-Riva et al., 2021; Kalanthroff et al., 2017; Morand-Beaulieu et al., 2021). It is possible that the RP and the ERN interact in patients with OCD, producing their deficits in goal-directed behaviour and the dissociation between knowledge and action.

A few studies have also suggested that the ERN might be generated in the SMA and pre-SMA (Bonini et al., 2014; Grützmann et al., 2016; Luck & Kappenman, 2012). Both the ACC and the motor areas of the brain are considered part of a motor preparation network (Nguyen, Breakspear, & Cunnington, 2014), which could explain the increased action tendencies in OCD (Dayan, Berger, & Anholt, 2017). Given the evidence for impaired goal-directed behaviour and habitual learning in OCD (Gillan, 2021) and the fast and somewhat involuntary character of the RP (Libet et al., 1983; Libet, 1985), it is possible to infer that enhanced action tendencies might be the cause of excessive reliance on habitual behaviour in OCD (Dayan, Berger, & Anholt, 2014, 2017). The automatic character of habits (Hardwick et al., 2019; Robbins & Costa, 2017) might explain perseveration in patients and the consequent commission of errors once task parameters change, leading to enhanced ERN and N_2 amplitudes (Riesel et al., 2017).

Abnormal SMA function has been proposed as another endophenotype of OCD (van den Heuvel et al., 2016). The authors propose that the pre-SMA is a key region for the inhibition network, from which the stop signal is conveyed to the motor cortex through CSTC projections, finally arriving at the DLPFC (van Velzen et al., 2014). A dysfunction in this region leads to altered recruitment of the dorsal cognitive control system, which then contributes to maladaptive behaviours, including habits (van den Heuvel et al., 2016). However, the relationship between the ERN, the RP and OCD remains unclear.

A few clues, nevertheless, are provided by Transcranial Magnetic (TMS) and Deep Brain Stimulation (DBS) studies, with target sites in the SMA and subthalamic nucleus promoting

good results (Lee et al., 2017; Mantovani et al., 2013; Tremblay et al., 2015; Tyagi et al., 2019). Motor areas seem, therefore, a crucial feature in the OCD aetiology (Haber, 2016), which await further investigation.

4. The current studies

The ability to inhibit prepotent actions and thoughts in favour of goal-directed behaviour is essential (Chambers et al., 2009; Lopez-Sosa et al., 2021; MacLeod, 2007), and it is strikingly evident that inhibitory control deficits are at the very core of obsessive-compulsive symptomatology, leading to both obsessions and compulsions (van Velzen et al., 2014). Indeed, actions and thoughts seem to be regulated by overlapping brain networks (Apšvalka et al., 2022; Guo et al., 2018), with results from DBS studies showing that stimulation of the subthalamic nucleus (STN), a link between the DLPFC and the dACC, leads to interruption of the compulsive actions and thoughts repetitive cycle (Tyagi et al., 2019). Nevertheless, the relationship between motor and cognitive inhibition is yet to be explained (Bari & Robbins, 2013).

This thesis, thus, aimed at investigating inhibitory mechanisms of actions and thoughts in OCD patients through behavioural paradigms and electroencephalographic recordings. For this purpose, four experiments were designed, focusing on three main ERPs, namely: i) the Error-Related Negativity; ii) the Error Positivity; and iii) the Readiness Potential. Those components were specifically selected due to the extensive research suggesting their role in inhibitory mechanisms (see Section 3 of the introduction), their generators (dACC and SMA), and their capability of elucidating the relationship between cognitive and motor abnormalities in OCD. They will, therefore, be presented in all experimental chapters, shedding light on neural activity across different study manipulations and participants' groups.

The first study (Chapter 3) assesses a large sample of participants with OCD and matched healthy volunteers, aiming to consolidate basal differences in both groups regarding cognitive flexibility (as measured by the Intra/Extra Dimensional Set Shifting task (IED) – described in Chapter 2), behavioural inhibition (assessed through the Stop Signal Go/No-Go task (SSGNG), see Chapter 2), error monitoring, mismatch detection and action tendencies, as measured by event-related potentials (ERN, Pe, and RP, respectively). It was hypothesised that: (i) individuals with OCD would present impairments in cognitive flexibility, committing a higher number of Extra Dimensional (ED) errors, as previously shown by Chamberlain and colleagues (Chamberlain et al., 2021); (ii) patients would show impairments in response

inhibition as measured by the probability of responding to stop signals and by longer stop-signal reaction times (SSRT), as hitherto demonstrated in the literature (Mar et al., 2022); (iii) participants in the OCD group would present higher amplitudes of ERN, Pe, and RP, corroborating former studies (Dayan et al., 2017; Riesel, 2019; Riesel, et al., 2017); and (iv) enhanced ERN and RP amplitudes would correlate to severity of OCD symptoms and higher reliance on habitual control and impairment in cognitive flexibility, in alignment with the theory of an imbalance between goal-directed and habitual responding in OCD (Gillan et al., 2011).

Study 2 (Chapter 4) is part of a feasibility trial conducted in the National Health Service (NHS), aiming to investigate the effects of Habit Reversal Therapy (HRT) through a mobile application as a component of Treatment as Usual (TAU), versus TAU only in OCD. Behavioural (IED and SSGNG), clinical and electroencephalographic measures (the same as above) were collected from both groups of OCD participants, and it was hypothesised that the HRT group would present higher symptom improvement, lower anxiety levels, higher quality of life reports and lower amplitudes of RP, given the competitive nature of HRT (Chamberlain et al., 2009; Holmes et al., 2009; Lee et al., 2019), and ERN, as heretofore shown by soothing effects of rituals (Hobson et al., 2017).

The third study (Chapter 5) was designed to conclude on the effects of training motor habits by studying participants with and without OCD, sub-divided in ‘app’ and ‘no-app’ (as per the mobile application used to train the motor sequences) groups. This was done to allow for comparisons between the effects of the app training versus TAU and versus an OCD group not submitted to any interventions, plus a healthy control group either practising the motor habits or not. Electroencephalographic measures were once again recorded alongside the original behaviour measures, clinical questionnaires, and self-report questionnaires. It was hypothesised that the OCD group practising the app would show improvements in behavioural inhibition and diminished amplitudes of ERN and RP when compared to the no-app group, which was expected to not show any symptoms/deficits alterations.

Finally, the fourth study (Chapter 6) consisted of an online experiment assessing patients with OCD and healthy volunteers in their abilities to inhibit memories and actions. Participants completed the Stop-Signal Task, the RIF paradigm and the Stovetop Checking Task (van den Hout & Kindt, 2003), in addition to clinical and self-report questionnaires. It was hypothesised that: (i) patients would perform worse than healthy volunteers in the SST; (ii) participants with OCD would not show a RIF effect, as previously demonstrated by Demeter and colleagues (Demeter et al., 2014), and (iii) the OCD group would show lower

levels of memory confidence and accuracy in the stovetop task (Burns et al., 2020). A summary of all chapters' goals and hypotheses in presented in Figure 3.

The next chapter will introduce the methods for data acquisition and analyses and the main paradigms utilised in this task, being followed by specific and detailed chapters for each study.

Figure 3. *Summary of chapters' aims and hypotheses*

CHAPTER	AIMS	HYPOTHESES
1 – Introduction	Present literature review and overarching hypotheses.	Overarching hypotheses: patients with OCD present a general-domain deficit of inhibitory control, encompassing thoughts and actions, and affecting clinical, behavioural, and neurocognitive markers.
2 – Methods	Describe studies' methods	Not applicable
3 – Baseline OCD vs HV	Present clinical, behavioural, and neurocognitive profile of OCD and matched control participants.	- Individuals with OCD would commit a higher number of Extra Dimensional (ED) errors, present higher SSRT, and higher probability of responding to Stop Signals; - The OCD group would present larger amplitudes of ERN, Pe, and RP, which would correlate to symptom severity.
4 – NHS trial in OCD	Assess the feasibility, tolerability, and augmenting effects of habit-reversal treatment + TAU in OCD in comparison to a TAU group.	- The HRT group would present higher symptom improvement, lower anxiety levels, higher quality of life reports and lower amplitudes of RP.
5 – App training in OCD vs HV	Compare the effects of introducing a novel ritualised behaviour in OCD and control participants on clinical, behavioural, and neurocognitive measures.	- The OCD-APP group would show improvements in behavioural inhibition and diminished amplitudes of ERN and RP when compared to the no-app group, which was expected to not show any symptoms/deficits alterations.
6 – RIF in OCD vs HV	Evaluate memory and motor suppression in OCD and control participants, further elucidating the general domain hypotheses of inhibitory control.	- Patients would perform worse than HV in the SST; - Participants with OCD would not show a RIF effect; - The OCD group would show lower levels of memory confidence and accuracy in the stovetop task.
7 - Discussion	Integrate studies' findings and limitations	Not applicable

CHAPTER 2 – METHODS

Though this be madness, yet there is method in it.

Hamlet, Act II, Scene 2

William Shakespeare

This chapter describes the methods for data acquisition and analyses of the electroencephalographic (EEG) recordings, behavioural paradigms, and self-report and clinical questionnaires employed in the thesis. Procedures were kept consistent throughout the face-to-face studies in order to allow for comparisons between different groups of participants and conditions. Detailed study-specific procedures will be described in each experimental chapter.

1. General overview of studies

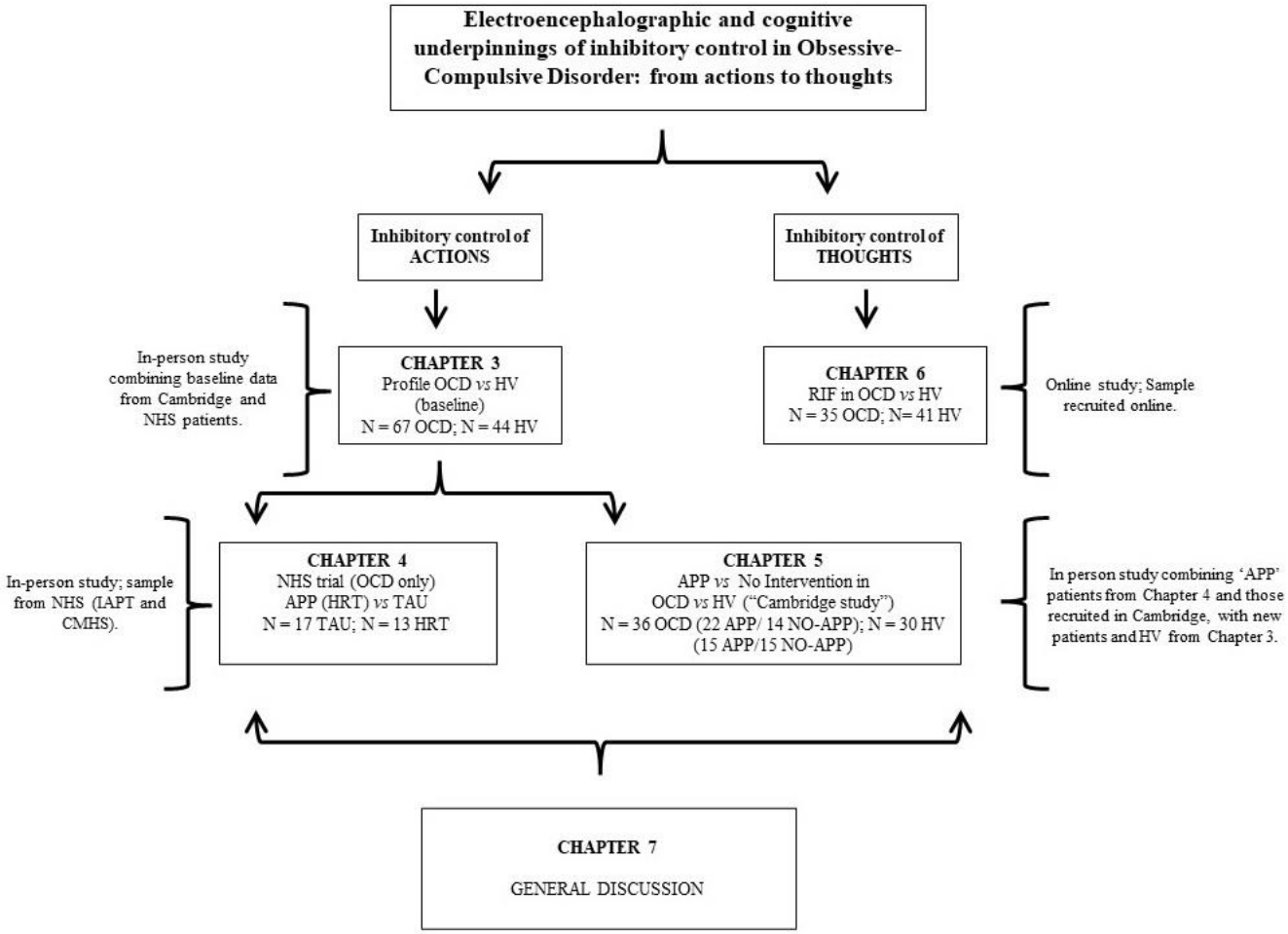
First and foremost, it is important briefly to describe the electroencephalographic (EEG) studies, given that, albeit conducted separately, are complementary parts of this thesis. Two extensive EEG studies were designed, aiming at comparing patients with OCD and age/gender matched control participants to address the hypothesis that introducing a new motor habit could benefit the treatment of OCD.

The first study, which shall be described in more detail in chapter 4, was conducted at a clinical facility in Hertfordshire, where the Highly Specialised OCD Clinic is based, as part of an NHS feasibility trial designed to assess the acceptability and tolerability of inducing a non-maladaptive habit as an interventional component of habit-reversal therapy (HRT) in the treatment of obsessive-compulsive disorder. Given the fact that it was a clinical trial, only patient groups were assessed as part of this study, randomly divided into those receiving HRT in combination with treatment as usual (TAU), and those following TAU protocol solely. Patients were evaluated at three time-points, namely: (i) baseline (prior to any intervention); (ii) midterm (after six weeks of TAU or after six weeks of HRT training); and (iii) endpoint (following completion of interventions). Forty patients were expected to complete the trial, 20 in each group. This study is currently ongoing, with 17 patients having completed baseline and midpoint assessments following treatment as usual, and 13 completing both timepoints following habit-reversal therapy. This trial was approved by the Hertfordshire Partnership

Foundation Trust (HPFT) through the Integrated Research Application System (IRAS), with the identification 233606.

Albeit informative, this trial was unable to conclusively address the impact of HRT in OCD, given the lack of a patient group receiving no intervention. In addition, the absence of a control group hindered the possibility of drawing robust conclusions about the effects of a new habit on brain activity. Therefore, a second EEG study was designed, comprising a patient and a matched control group either learning the motor habit (the exact same intervention given to the HRT group) or not receiving any intervention. This experiment consisted of two sessions, separated by a month, mimicking the previous study. Thirty-six patients have completed the study, 14 comprising the 'no-habit' group and 22 forming the 'habit' one. In the control group, 30 participants completed the study, equally divided between 'habit' and 'no-habit' groups. Data collection for this experiment was conducted in Cambridge, with the same EEG system as the one used in the NHS study. Ethics approval was obtained by the Department of Psychology of the University of Cambridge (REC 16/EE/0465) and by the Cambridge and Peterborough NHS Foundation Trust (CPFT) with the identification IRAS 208351. Chapter 5 describes this study in detail. Figure 1 depicts a flowchart of the studies' design.

Figure 1. *Flowchart of the studies presented in this thesis*



1.1.Participants

The participants' sample was composed of individuals diagnosed with obsessive-compulsive disorder and by healthy volunteers, all matched in age, gender, and IQ. The latter was assessed through the National Adult Reading Test (NART) (Nelson & Willison, 1991).

Patients with OCD were recruited through two main sources: for the NHS clinical trial, patients were referred by their local (Hertfordshire) mental health teams (Community Mental Health Services (CMHS) or Improving Access to Psychological Therapies (IAPT)); whereas patients that took part in the 'Cambridge study' were recruited through social media (online posts and OCD charities advertisement). Conversely, participants in the healthy control group (Cambridge study only) were recruited through social media and flyers placed around the town.

Inclusion criteria for both studies established that participants should: (i) be 18-65 years old; (ii) have no history of neurological disorder or brain trauma; (iii) have no current or

previous history of alcohol and drug abuse; (iv) not be taking anticonvulsant drugs; (v) have normal or corrected-to-normal hearing and vision; (vi) have no motor disabilities. Group-specific criteria established that patients had to score 16 or higher on Y-BOCS (described in more detail later in the chapter) and have OCD as their primary diagnosis (comorbidities are invariably present (Mathes et al., 2019)). Psychiatric conditions such as autism spectrum disorder (ASD) and psychosis were excluded. On the other hand, the healthy control group should not present any history of psychiatric disorders and could not be taking psychiatric medication. In addition, scores higher than 42 on the obsessive-compulsive inventory (OCI – described later) or scores indicating depression as measured by the MADRS were exclusion criteria for the control sample.

Screening was conducted by a trained clinician in the NHS trial, and by trained researchers in the Cambridge study. For the latter, a collaborator psychiatrist was available to clarify doubts about diagnoses through a telephone assessment with the patient. All participants completed the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) or the Modified Mini Screen (OASAS, 2002), the MADRS, and the OCI (exclusive for participants of the Cambridge study). Demographic data such as scholarity, ethnicity, working circumstance, among others, were also collected. Participant data from each study will be described in detail in the relevant chapters.

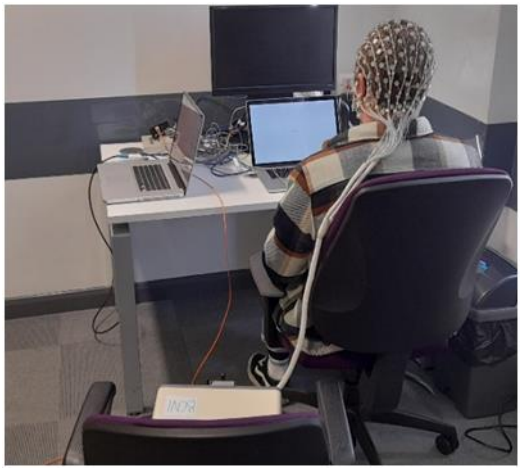
2. Electroencephalographic recordings

All participants followed the same protocol prior to electroencephalographic recordings, in order to enhance the quality of the EEG data. Subjects received an e-mail message with instructions the day before the testing session, asking them to refrain from alcohol for a minimum of 12h, and from caffeine for at least the 4h preceding the experiment, given the known effects of these substances on cognitive functioning and brain activity (Chen et al., 2020; Dager & Friedman, 2000; Dimpfel et al., 1993; Fairbairn et al., 2021; Jung et al., 2014). It was also requested that participants washed their hair before the experiment, and that they did not apply gels or conditioners to it, as these substances could interfere with the electrodes' recordings. Moisturisers and make-up were not allowed also, as some electrodes were placed on the forehead and cheeks. Finally, a restful night of sleep the night before the recordings was recommended, and the researcher kept a record of all these information during the session.

EEG data was acquired with a Net Amps 300 (Electrical Geodesic Inc. (EGI)) amplifier connected to a high density 128-electrode geodesic sensor net (EGI). Data was referenced to vertex (electrode Cz), and impedances were kept below 100 kΩ, to maximise signal-to-noise ratio (SNR). Recordings were measured in microvolts (μV) and the sampling rate was kept at 500Hz.

Data acquisition was performed at two main sites: the Herchel Smith Building for Brain and Mind Sciences, part of the biomedical campus of the University of Cambridge, in a room specially designed for EEG testing, and the NHS highly specialised OCD service at Rosanne House, in Welwyn Garden City, Hertfordshire. For the latter, clinical rooms were used, given the absence of specialised facilities, and the researcher aimed at minimising potential noise to the data. Figure 1 depicts a typical acquisition setting at Rosanne House.

Figure 2. *EEG data acquisition setup in a clinical facility.*



2.1. Pre-processing

EEG data were pre-processed with customised scripts from MATLAB (The MathWorks Inc., 2021) EEGLAB (Delorme & Makeig, 2004) version 14.1.1.b and ERPLAB (Lopez-Calderon & Luck, 2014) version 8.30 plugins. A detailed description of the pre-processing pipeline can be found below.

2.1.1. Importing data

Event lists based on triggers from the Stop-Signal Go/No-Go Task were extracted from the EEG raw data through a customised ERPLAB script. Events were then manually converted into numbers, which enabled the creation of bin-based epochs.

2.1.2. Resampling and filtering

Continuous EEG data were resampled to 250Hz, a common step to preserve memory and disc storage on the computer. Afterwards, a high-pass filter of 0.1Hz and a low-pass filter of 30Hz were applied. This excludes from the dataset any signal below 0.1Hz and above 30Hz, which are not likely to result from the brain functions of interest for the study. Due to edge artifacts caused by filtering, 1.5 seconds of data were then removed from the boundaries of the dataset.

2.1.3. Channel selection

Electrodes located on the neck, forehead, and cheeks were excluded, since the signal in their location tends to insert noise to the overall dataset. Thirty electrodes were removed as part of this step (E1, E8, E14, E17, E21, E25, E32, E38, E43, E44, E48, E49, E56, E57, E63, E64, E68, E69, E73, E74, E81, E82, E88, E89, E94, E95, E99, E100, E107, E113, E114, E119, E120, E121, E125, E126, E127, E128), resulting in 90 channels for the subsequent analyses. An illustration of the electrodes' distribution can be found below.

Figure 3. *HydroCel Geodesic Sensor Net channel distribution.*

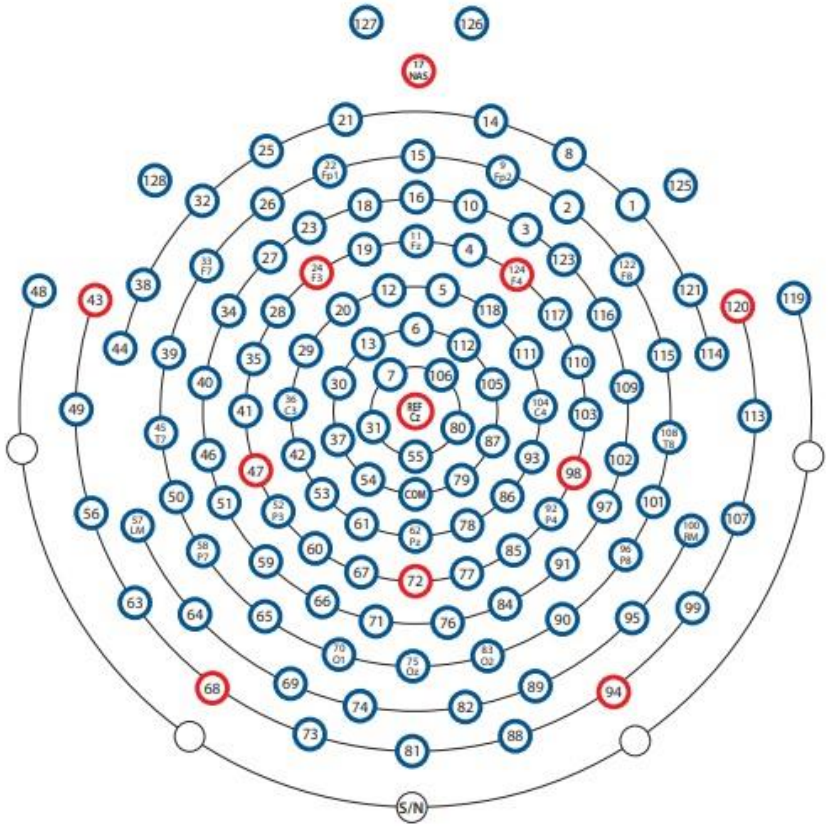


Figure retrieved from EGI User Manual.

2.1.4. Epoching

Events were then imported and segmented into bin-based epochs. Those varied depending on the components being analysed, with different timeframes and stimuli being analysed. A detailed description of the creation of epochs for each ERP component is found below.

2.1.4.1. ERN

As an error-related component, epochs for the ERN are response-locked on trials when an error has been committed. Epochs ranged from -200ms to 400ms, with timepoint 0ms as the erroneous response. Baseline correction was performed from -200ms to 0ms. Mean amplitudes were calculated between 0 and 100 ms at electrode Fz, following visual inspection and in accordance with previous literature (Riesel, 2019).

2.1.4.2. Pe

The Error Positivity epochs followed the same structure as the ERN, being also response-locked to errors. Data was segmented between -200 ms (pre-response) to 400 ms, with a baseline correction from -200ms to 0ms. Mean amplitudes were calculated between 200 and 400 ms at electrode Pz, following visual inspection and in accordance with previous literature (Endrass et al., 2010).

2.1.4.3. RP

Finally, the Readiness Potential was response-locked to Go trials, which require a movement. Since this is an ERP that measures motor preparation, the signal is expected prior to 0ms (response), therefore baseline correction was performed in the positive range, from 0ms (response) to 200ms. Data segmentation was performed from -200ms to 200ms. Mean amplitudes were calculated between -100 and 0 ms at electrode Cz, following visual inspection and in accordance with previous literature (Dayan et al., 2014; Wen et al., 2018).

2.1.5. Channel cleaning, re-referencing, and artifact removal

After segmenting the data into epochs, data was cleaned with the EEGLAB plugin 'clean_rawdata', which detects and excludes channels and portions of data with low signal-to-noise ratio. Channels were considered for removal if they presented a flat line (no signal being recorded) for 10s or more and/or if the line noise exceeded 5 standard deviations (likely to not constitute brain signal). Removed channels were then interpolated (a process in which signal is estimated based on neighbouring electrodes), ensuring that every dataset remained with 90 electrodes.

Data were then re-referenced to average, a traditional step in ERP analyses that ensures that positive and negative currents will sum to 0 as per Ohm's law (Jackson & Bolger, 2014). This is particularly important given the nature of ERPs, which consist of differences in potential between recording points (Luck, 2005).

Finally, artifacts introduced by the pre-processing steps were detected following ERPLAB's functions. Four major sources of artifacts were targeted at this stage.

2.1.5.1. Sample-to-sample voltage threshold

The purpose of this function is to detect sudden shifts in voltages between one sample and the one immediately following it and reject segments of data that exceed the threshold set. The function was applied throughout the epoch and in every channel, detecting voltage shifts above 50μV.

2.1.5.2. Moving window peak-to-peak threshold

This step is applied in order to remove eye blinks, one of the strongest sources of noise on EEG data (Luck, 2005), from the dataset. Eye blinks have a distinctive feature from ERPs, presenting different polarities above and below the eye when they occur. For this reason, it is relatively straightforward to isolate those by searching for the most positive and the most negative peaks in an epoch, which will likely consist of blinks. The threshold was set at 300μV and searched for blinks in all channels for the length of the epoch.

2.1.5.3. Blocking

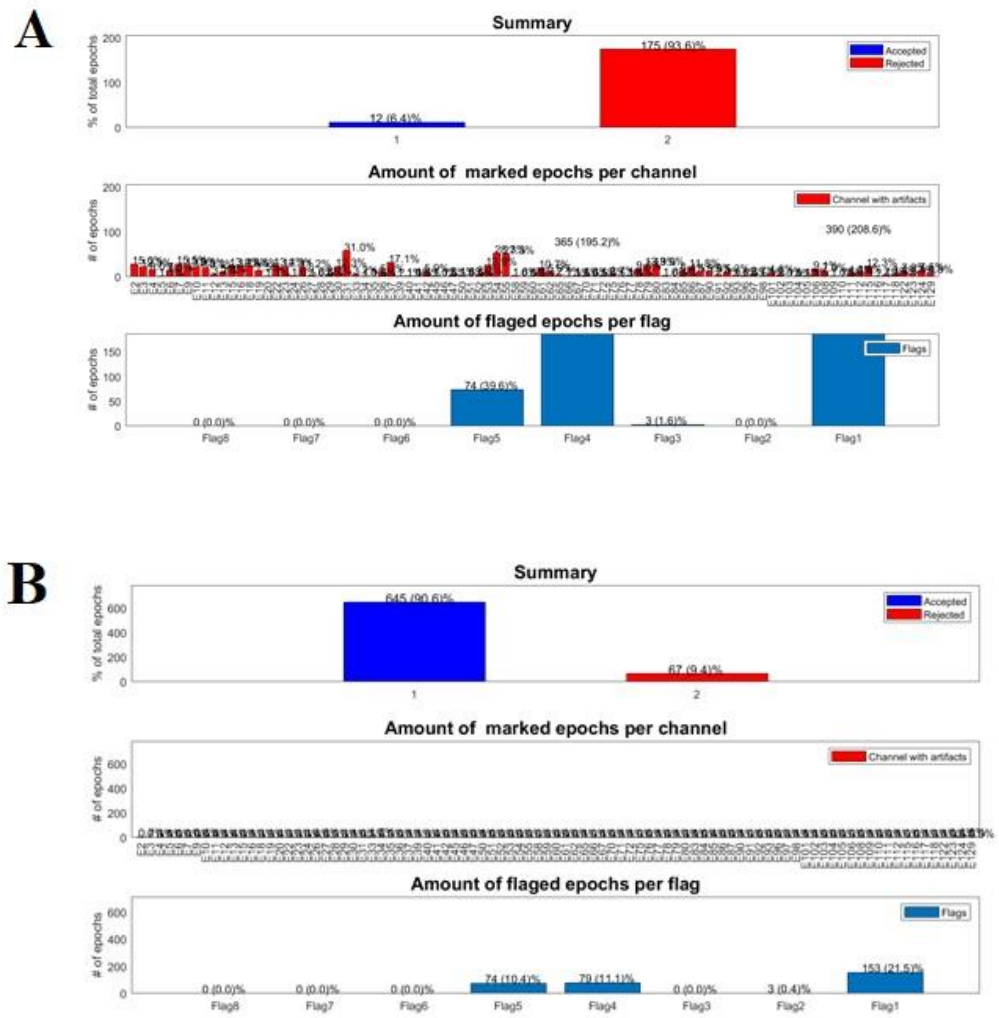
Blocking refers to instances in which the EEG signal becomes a 'flat line', not recording brain activity. To remove those, a function was employed, searching for periods of time above or equal to 100ms where blocking occurred. Plus or minus 0.5μV was the threshold chosen, and the entirety of the epoch was scanned.

2.1.5.4. Step-like artifacts

Finally, artifacts caused by saccadic eye movements were detected. Threshold was set at 50μV and the whole duration of the epoch was searched.

Once artifact detection was completed, channels were visually checked prior to artifact rejection. Electrodes that presented more than 20% of the epochs marked for rejection were excluded. In order to keep the dataset homogeneous across participants, consisting of 90 electrodes each, all deleted channels were interpolated once again. This resulted in a second step of artifact detection, following the procedures outlined above and a new visual inspection. Participants that did not fulfil the quality criteria were thus excluded from analyses. Figure 3 depicts an example dataset following first and second artifact rejection step. The top figure (A) consists of a dataset prior to visual inspection of channels, whereas the bottom one (B) represents a dataset where channels were manually rejected and posteriorly interpolated.

Figure 4. *First and second artifact rejection summaries*



3. EEG Data Analyses

Following artifact detection, each participant data were transformed into ERP files, containing an average of trials in all conditions (bins). Those were then submitted to a grand average, comprising data from all participants in a determined condition (i.e. all HV and all response-locked stop trials). Grand averages were then plotted and visually inspected, which enabled the identification of channels and latencies where the amplitudes were maximum for each ERP. Individual amplitudes measured in microvolts were thus obtained based on the visual inspection and previous literature considering a specific channel and time range. EEGLAB and ERPLAB were used at this step.

4. Behavioural paradigms

4.1. Stop-Signal Go/No-Go Task (SSGNG)

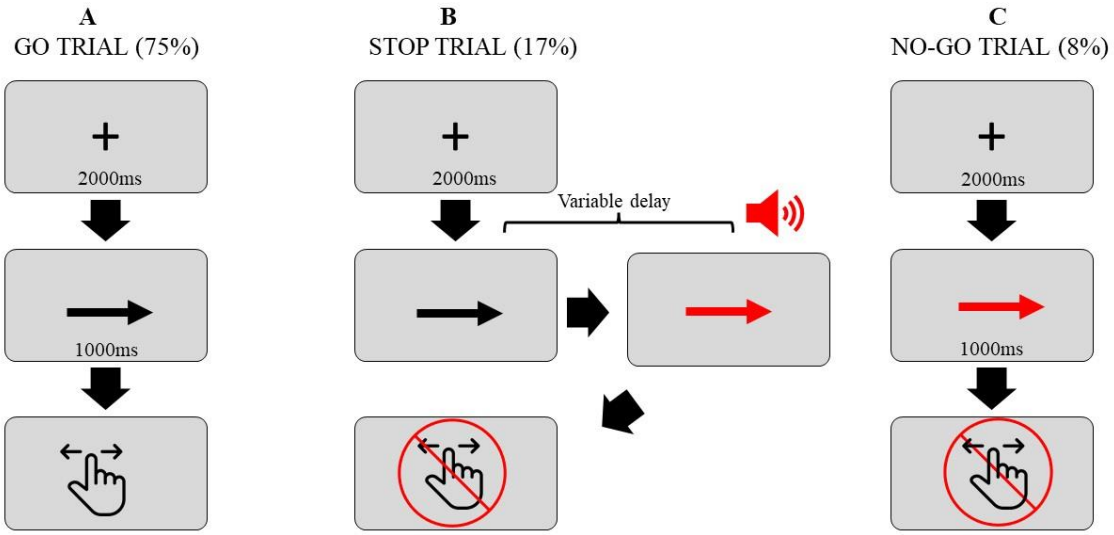
The SSGNG task is a combination of two classic paradigms of behavioural inhibition, the Stop-Signal Task (Lappin & Eriksen, 1966; Logan & Cowan, 1984; Vince, 1948) and the Go/No-Go Task (Gordon & Caramazza, 1982). In this thesis, an adaptation of the task previously used by Ye and colleagues (Ye et al., 2014, 2016) was employed.

In this task, participants see arrows at the centre of the computer screen and must respond either with their left or right hand to the direction of the arrow. Black arrows are considered 'Go' trials, whereas red ones represent trials when one must not press any buttons ('No-Go'). Occasionally, though, black arrows turn red, and an auditory tone is played, consisting of a 'Stop' trial. In those instances, subjects are required to cancel the initiated movement, which is measured by the Stop-Signal Reaction Time (SSRT) parameter (Logan & Cowan, 1984; Verbruggen et al., 2019). The combination of 'No-Go' and 'Stop' trials makes this task rather more comprehensive, since both inhibition and cancellation of actions can be measured (Guo et al., 2018).

The task consisted of six blocks, each containing 80 trials. A short practice block (20 trials) preceded the task and ensured that participants understood the instructions correctly. Both accuracy and speed were emphasised. The distribution of stimuli was predetermined, consisting of 75% 'Go' (360), 8% 'No-Go' (40), and 17% 'Stop' (80) trials. An average inhibition accuracy was also pre stipulated as 50%, maintained through a step up/down tracking algorithm that adjusted the Stop-Signal Delay (SSD) by 50ms. The initial estimate of the SSD was 200ms.

A typical trial consisted of a black fixation cross displayed for 2000ms, followed by the presentation of the stimulus for 1000ms, period in which participants were required to respond, otherwise a new trial would start. Figure 5 depicts a typical 'Go', 'Stop' and 'No-Go' trials.

Figure 5. *Typical trials in the SSGNG task*



Panel **A**. Typical 'Go' trial. Panel **B**. Depiction of a 'Stop' trial. Panel **C**. Representation of a 'No-Go' trial. *Adapted from Ye et al., 2014.*

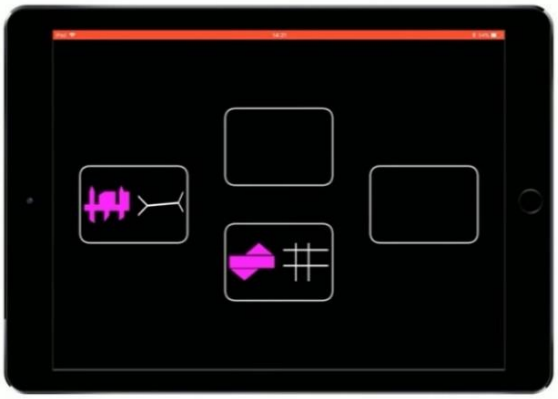
The task was run in MATLAB, and so were data analyses. Variables such as probability of responding to a stop trial, successful go and no-go responses, reaction time, SSD and SSRT are reported in each study. SSRT was calculated using the integration method (Verbruggen et al., 2019). Participants that violated the race model or that presented accuracy in the first or fourth quartiles (<25% or >75%) were excluded from analyses.

4.2. Intra-Extra Dimensional Set-Shifting Task (IED) - Cambridge Neuropsychological Test Automated Battery (CANTAB), Cambridge Cognition

The IED is a widely used and recognised task designed to measure cognitive flexibility (Chamberlain et al., 2007, 2021). Composed of nine stages, it assesses individuals' ability to learn and unlearn rules through feedback, with attentional demands shifting either intra- or extra-dimensionally. Subjects are presented with a pair of compound stimuli comprising exemplars of shape and line perceptual dimensions and required to choose the correct one at each trial. Initially, there is no information on which stimulus should be chosen, so participants must select one and follow feedback. Each compound stimulus consists of two relevant dimensions: shapes and lines. The Intra Dimensional (ID) Shift is specified when contingencies

are reversed and the previous shape, for instance, is no longer rewarded, requiring the subject to attend to the alternative shape. Finally, the Extra Dimensional (ED) shift alters contingencies by switching the rule from shapes to lines, demanding an attentional shift to the previously unrewarded dimension. Main outcome measures are the number of errors throughout the task, number of stages completed, number of errors when ID and ED shifts are specified, and number of trials required to complete the task (Chamberlain et al., 2021). Figure 6 depicts an example of a trial. The task was administered both on CANTAB touch screen devices and on personal laptops.

Figure 6. *Example trial of the IED task.*



Retrieved from the Cambridge Cognition website at *https://www.cambridgecognition.com/cantab/cognitive-tests/executive-function/intra-extra-dimensional-set-shift-ied/*

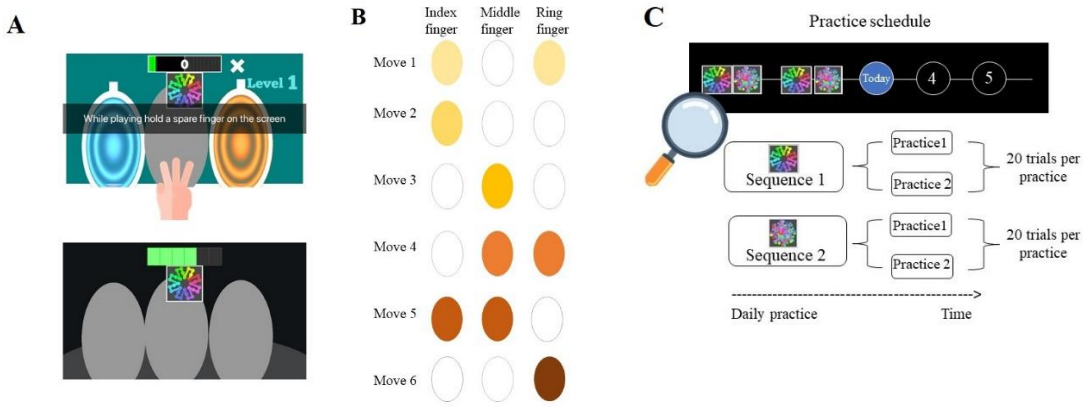
4.3. Mobile application (app) - (Banca et al., 2020)

This app was designed to generate motor habits through sequences of finger tapping movements, randomly generated for each participant. Each sequence is composed of six moves that must be performed by pressing circles on the screen with either the index, middle, or ring finger of the dominant hand, or a combination of two of those fingers. Different levels guide subjects and assist with the learning process, with clues such as sounds and colours. Once participants have mastered the sequences, clues are no longer available, testing real automaticity. Speed and accuracy are rewarded through points that appear on the screen after each trial.

Participants were instructed to learn two sequences, each associated with a symbol. Reward schedules varied in each sequence, being continuous for one and variable for the other (37% of

trials). A practice scheduled represented by a calendar on the screen defined that both sequences should be practised twice daily, for the period of 30 days. A full practice consisted of 20 completed trials, as measured by a loading bar on the top of the screen (Banca et al., 2020). After the month of practice, participants were invited for a second session of testing. Figure 7 illustrates the app.

Figure 7. *Depiction of the app and practice schedule.*



Panel **A**. Top: layout of the app with coloured circles guiding participant. Bottom: App not presenting any clues to guide the sequence. Panel **B**. Example of a sequence. Panel **C**. Daily practice schedule. *Adapted from Banca et al., 2020.*

5. Clinical questionnaires

5.1. Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) - (Goodman et al., 1989)

The Y-BOCS is a widely recognised semi-structured clinical interview to assess the severity of obsessions and compulsions in OCD (Fineberg et al., 2020), being employed both for patient selection for interventions (Tyagi et al., 2019) and for assessing outcomes of treatment (van Westen et al., 2015). It consists of 10 questions, subdivided according to questions relating to ‘obsessions’ and ‘compulsions’, that rate symptoms based on time spent performing them, interference in daily activities, distress caused, resistance, and attempts to control them. Items are rated by a trained clinician/researcher on a scale ranging from 1 (“none”) to 4 (“extremely”). Typical thresholds consider scores above 16 in the clinical range, with most studies including patients that meet this criterion (Storch et al., 2015).

The Y-BOCS checklist (Goodman et al., 1989) is another instrument that assesses OCD symptoms, though focusing on dimensions of the disorder. It consists of a list of common obsessions and compulsions subdivided into categories (aggressive, contamination, sexual,

hoarding/saving, religious, need for symmetry, somatic, and miscellaneous obsessions; cleaning/washing, checking, repeating, counting, ordering, hoarding/collecting, and miscellaneous compulsions), that are rated based on their past or current presence, indicating primary OCD dimension.

5.2. Montgomery- Åsberg Depression Rating Scale (MADRS) - (Montgomery & Åsberg, 1979)

The MADRS is a ten-item semi-structured interview that measures depressive symptoms, using the previous 7 days of the participant's life as reference (Montgomery & Åsberg, 1979). Designed to be more sensitive to changes caused by antidepressants than the Hamilton Rating Scale (Hamilton, 1960), it is conducted by a trained clinician/researcher and scored on a scale ranging from 0 to 6, with higher scores indicating higher levels of depression. Classical thresholds stipulate scores higher than six as being out of the normal range.

5.3. Mini International Neuropsychiatric Review (MINI) – (Sheehan et al., 1998)

This structured diagnostic interview aims to assess the presence of psychiatric disorders through "Yes" or "No" questions. It is conducted by a trained clinician/researcher and facilitates the identification of comorbidities and the confirmation of the primary diagnosis.

5.4. Modified Mini Screen (MMS) - (OASAS, 2002)

The MMS is a 22-item structured interview, developed to assess mood, anxiety, and psychotic disorders through "Yes" or "No" questions. Questions endorsed by participants should then be further explored via the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998).

6. Self-report measures

6.1. Obsessive-Compulsive Inventory (OCI) - (Foa et al., 1998)

This questionnaire comprises 42 items subdivided in 7 subscales, namely: (i) washing; (ii) checking; (iii) doubting; (iv) ordering; (v) obsessing; (vi) hoarding; and (vii) neutralising. A 5-point likert-scale ranging from 0 ("not at all") to 4 ("extremely") is used to rate each item. Higher scores are, thus, indicative of higher OCD symptomatology. The scale presents good psychometric properties (internal consistency, test-retest reliability, and discriminative and convergent validity) (Foa et al., 1998).

Due to recent criticism, though, total scores were calculated based on the 12-item version, which discards the hoarding and neutralising items (Abramovitch et al., 2021). The final questionnaire assesses four OCD dimensions (washing, checking, ordering, and obsessing) and demonstrates good to excellent psychometric properties (Abramovitch et al., 2021).

6.2. Sheehan Disability Scale (SDS) - (Sheehan, 1983)

The SDS is a widely used short self-report scale developed to measure functional impairment in psychiatric disorders. It assesses three main domains, namely: (i) social life; (ii) work life; and (iii) family life. Each of those is rated by the participant from 0 to 10, with higher scores indicating higher disability. Ratings from each dimension are then summed to achieve the final score.

6.3. State-Trait Anxiety Inventory (STAI-S and STAI-T) - (Spielberger et al., 1983).

These questionnaires measure state (STAI-S) and trait (STAI-T) anxiety, each comprising 20 items that are rated through a 4-point Likert scale ranging from 1 (“not at all”) to 4 (“very much so”). The state version assesses levels of anxiety at the very moment that the participant is completing the questionnaires, whereas the trait version rates how the individual generally feels. Higher scores indicate higher levels of anxiety on both scales. This instrument presents good psychometric properties (Spielberger, 1989).

6.4. Intolerance of Uncertainty Scale (IUS) - (Buhr & Dugas, 2002; Carleton et al., 2007)

The IUS is a self-report questionnaire developed to measure how acceptable an individual finds the possibility of a negative event occurring (Carleton et al., 2007). It was originally designed in 1994 (Freeston et al., 1994) in French, and translated and validated to the English language in 2002 (Buhr & Dugas, 2002). Both versions include 27 items, further subdivided into four or five factors. Items are rated on a 5-point Likert scale, ranging from 1 (“not at all characteristic of me”) to 5 (“entirely characteristic of me”). Criticism and poor fit of the multifactorial model (Sexton & Dugas, 2009) resulted in a short version composed of 12 items (Carleton et al., 2007) and subdivided into two factors only. The first refers to the idea that uncertainty should be avoided at all costs (Prospective Anxiety), whereas the second factor measures the idea that uncertainly makes one unable to act (Inhibitory Anxiety) (Carleton et al., 2007; Sexton & Dugas, 2009). Both versions were used in this thesis and the bifactorial model was applied.

6.5. Padua Inventory – Washington State University Revision (PI-WSUR) - (Burns et al., 1996)

The Padua Inventory (PI, Sanavio, 1988) is the most commonly used self-report measure of compulsivity (Hook et al., 2021), being mostly employed for the study of OCD. This questionnaire has been revised and adapted several times, resulting in a shorter version with 39 items organised in five subscales (obsessive thoughts about harm to self/others; obsessive impulses to harm self/others; contamination obsessions and washing compulsions; checking compulsions; and dressing/grooming compulsions). Items are rated on a 5-point Likert scale (0 = "not at all", to 4 = "very much"). Higher scores indicate higher symptomatology.

6.6. Creature of Habit Scale (COHS) - (Ersche et al., 2017)

The COHS is a self-report questionnaire developed to assess habitual behaviour, aiming at disentangling routine and automaticity (Ersche et al., 2017). It is composed of 20 items, rated on a 5-point Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree"). Results are obtained by summing the items, with higher scores suggesting more reliance on habitual behaviour.

6.7. Habitual Tendencies Questionnaire (HTQ) - (Ramakrishnan et al., 2022)

This questionnaire measures habitual tendencies in the general population through 11 items that ask about behaviours, attitudes, beliefs, and thinking styles related to habits (Ramakrishnan et al., 2022), being further subdivided into three factors (preference for regularity, aversion to novelty, and compulsivity). The scale is rated on a 7-point Likert scale, ranging from 1 ("strongly disagree") to 7 ("strongly agree"), with higher scores indicating higher habitual tendencies.

6.8. Self-Control Scale (SCS) - (Tangney et al., 2004)

The SCS was designed with the intention of measuring one's ability to override urges and impulses, break habits, and preserve self-discipline. It comprises 36 items, rated on a Likert scale ranging from 1 ("not at all like me") to 5 ("very much like me"). Higher scores indicate higher levels of self-control (Tangney et al., 2004).

6.9. Habitual Self-Control Questionnaire (HSCQ) - (Schroder et al., 2013)

This questionnaire assesses goal-directed behaviour and persistent goal pursuit, represented by items that measure self-control and healthy behaviours despite challenging scenarios

(Schroder et al., 2013). The 14 items are rated on a Likert scale ranging from 1 (“disagree strongly”) to 5 (“agree strongly”), with higher scores indicating higher self-control.

6.10. Big Three Perfectionism Scale (BTPS) - (Smith et al., 2016)

The BTPS is a measure of perfectionism, a personality trait commonly associated with OCD (Pozza et al., 2019; Wu & Cortesi, 2009). It assesses three higher-order global factors (rigid perfectionism, self-critical perfectionism, and narcissistic perfectionism) through 45 items rated on a 5-point Likert scale ranging from 1 (“disagree strongly”) to 5 (“agree strongly”). Higher scores represent stronger perfectionism traits (Smith et al., 2016).

6.11. Edinburgh Handedness Inventory (EHI) - (Oldfield, 1971)

This scale measures laterality, an essential component of brain analyses (Kourtis & Vingerhoets, 2016; Ocklenburg et al., 2019; Shadli et al., 2021), through items concerning everyday activities (i.e. brushing teeth, throwing a ball). Participants are asked to choose their preferred hand for each of those tasks and to mark the chosen hand twice for any item in which a strong preference exists. Scores are then summed for all eight activities, ranging from -400 to 400 (-50 = always left; -25 = usually left; 0 = no preference; 25 = usually right; and 50 = always right) indicating laterality.

6.12. National Adult Reading Test (NART) - (Nelson & Willison, 1991)

The NART is a widely recognised and used measure of intelligence, which correlates to IQ scores as predicted by the Wechsler Adult Intelligence Scales (WAIS, Wechsler, 1955, 1981, 2008). It was originally developed in 1982 for the British language and consists of a list of 50 words that do not abide by phonetic rules, resulting in previous knowledge prerequisite (Nelson, 1982). This instrument has been revised a number of times, in accordance with new versions of the WAIS (Bright et al., 2018; Nelson & Willison, 1991). In this thesis, the IQ calculations were based on the 1991 version (Nelson & Willison, 1991), which has the revised version of the WAIS (WAIS-R, Wechsler, 1981) as reference.

7. Statistical analyses

Parametric tests were utilised following the assumptions of normality and homogeneous variances, tested respectively by the Shapiro-Wilk and Levene's tests. In case of breached assumptions, non-parametric equivalents of the tests were applied. Differences between groups were measured through independent-sample t-tests (Student and Mann-Whitney, for parametric and non-parametric testing, respectively) when two or less variables were being assessed, and through Analyses of Variance (ANOVA) when three or more variables were present. Paired-sample t-tests (Student or Wilcoxon, for parametric and non-parametric purposes, respectively) were applied to verify differences within participants' groups. Relationships between variables were measured through correlations (Pearson for parametric testing and Spearman for non-parametric assessment). Individual chapters describe the analyses applied.

CHAPTER 3 – NEUROCOGNITIVE PROFILE OF OBSESSIVE-COMPULSIVE DISORDER AND MATCHED CONTROLS

Time travels at different speeds for different people.

I can tell you who time strolls for, who it trots for,

who it gallops for, and who it stops cold for.

As you like it, Act II, Scene 2

William Shakespeare

1. Introduction

Despite the common sense and the grammatical inaccuracy that "everyone is a bit OCD" (Fennell & Boyd, 2014; MacMaster & Rosenberg, 2021), individuals with and without Obsessive-Compulsive Disorder (OCD) present differences in genetic (Grünblatt, 2021), chemical (Biria et al., 2021), neural (Robbins et al., 2019), cognitive (Vaghi, 2021), behavioural (Chamberlain et al., 2005; Gillan & Robbins, 2014), and affective status (Goodwin, 2015).

Albeit still unclear, the causation of OCD seems to be multifactorial, sharing both nature (Grünblatt, 2021; Mahjani et al., 2021) and nurture (Pauls et al., 2014) elements. For instance, endophenotype studies suggest common abnormal mechanisms between individuals with OCD and their unaffected first-degree relatives (Chamberlain et al., 2007; Vaghi, 2021), which poses the question as to why some people are more at risk of developing the disorder than others.

Whilst unable to conclusively answer this question and given the incipient longitudinal research (Pinto et al., 2006), cross-sectional trials can provide important information regarding baseline functioning in individuals with and without OCD. Understanding basic deficits sheds light on underlying mechanisms of the condition, contributing not only to the discovery of target sites for intervention, but to the development of efficacious treatments as well (Insel, 2014).

As pillars of basic research, endophenotypes can be defined as heritable intermediate phenotypes, bridging the gap between genotypes and behavioural manifestations of a condition

(Gottesman & Gould, 2003). As measurable biomarkers of risk for the development of diseases (Beauchaine, 2009), endophenotypes have been extensively studied in a plethora of psychiatric conditions, with OCD being amongst them (Bzdok & Meyer-Lindenberg, 2018; Juli et al., 2021; Roffman, 2019).

Six main neurocognitive endophenotypes have been identified hitherto in Obsessive-Compulsive Disorder, namely: i) planning – associated to dorsolateral prefrontal cortex (dlPFC) and putamen reduced connectivity ; ii) response inhibition – related to supplementary motor area (SMA) overactivation; iii) action monitoring – linked to anterior cingulate cortex (ACC) overactivation; iv) decision-making – related to orbitofrontal (OFC) dysfunction; v) working memory – related to frontoparietal dysfunction; and vi) cognitive flexibility – associated with ventrolateral prefrontal cortex (vlPFC) and caudate reduced connectivity (Bari & Robbins, 2013; Chamberlain & Menzies, 2009; de Vries et al., 2014; de Wit et al., 2012; Marzuki et al., 2020; Menzies et al., 2007; Riesel, 2019; Vaghi, Vértes, et al., 2017; Vaghi, 2021; Zhang et al., 2015). In this study, given the nature of the paradigms employed, cognitive flexibility, inhibition, and action-monitoring will be discussed in further detail.

Cognitive flexibility refers to the ability to adjust behaviour and/or thinking as a result of changes in the environment and feedback (Chamberlain et al., 2021). Essential for an adaptive life, this executive function has been reported as abnormal in numerous studies of OCD and related disorders (Chamberlain et al., 2021; Vaghi, 2021), with patients demonstrating higher rigidity (Chamberlain et al., 2007, 2021).

A robust and reliable measure of cognitive flexibility can be obtained with the Intra-Extra Dimensional Set-Shifting Task (IED, Cambridge Neuropsychological Test Automated Battery (CANTAB), Cambridge Cognition) (Robbins et al., 1998). In this paradigm, participants are required to choose the appropriate alternative amongst two either simple or compound stimuli, which present lines and shapes as relevant dimensions (Chamberlain et al., 2021). Initial stages of the task assess participants' abilities in discriminating between simple stimuli, such as shapes, for instance. Once rules are learned, contingencies are reversed, testing individuals' capabilities of adjusting behaviour accordingly and switching to the new rule. Although these initial stages already engage flexible behaviour, notable deficits in OCD have been reported later in the task, specifically when subjects are required to shift attention extra-dimensionally (Chamberlain et al., 2021). Indeed, Chamberlain and colleagues (2021) have reviewed the literature, carrying out a meta-analysis of the application of the task in OCD, and suggested that Extra-Dimensional (ED) shift deficits are a robust finding in OCD, with medium to large effect sizes, not attributable to age or IQ differences. The authors propose that cognitive

inflexibility, hence, is at the core of OCD symptomatology and might explain patients strains in suppressing the repetitive cycle of obsessions and compulsions (Chamberlain et al., 2021).

A second endophenotype with clear contributions to the maintenance of OCD symptoms, response inhibition can be defined as the ability to suppress prepotent responses in favour of goal-directed actions (Bari & Robbins, 2013; Chambers et al., 2009). This cognitive function is crucial for everyday functioning, and inhibitory deficits, also known as impulsivity, are considered the core of several psychiatric disorders (Bari & Robbins, 2013).

Functional Magnetic Resonance Imaging (fMRI) studies suggest the engagement of cortical-striatal-thalamic-cortical (CSTC) circuits in inhibition (Robbins, 2007; van Velzen et al., 2014), a circuitry consistently shown to be abnormal in OCD (Robbins et al., 2019). Particularly, brain regions such as the anterior cingulate cortex (ACC), the pre–supplementary motor area (pre-SMA), the inferior frontal gyrus (IFG), and the basal ganglia are thought to be responsible for the inhibitory deficits seen in OCD (Aron et al., 2014; Bari & Robbins, 2013; Riesel, 2019; Rubia et al., 2010; Tyagi et al., 2019; van Velzen et al., 2014).

Classic and robust measures of inhibitory control include the Stop-Signal (SST) (Lappin & Eriksen, 1966; Logan & Cowan, 1984; Vince, 1948) and the Go/No-Go (GNG) (Gordon & Caramazza, 1982) tasks. In those paradigms, response inhibition is measured through the ability to suppress motor responses following ‘stop’ signals or the presentation of a ‘no-go’ stimulus, which represents a cue that shall not be attended. Different inhibitory process are activated in the SST and GNG, namely response cancellation (the ability to deter an already initiated movement) and response suppression (the capacity to prevent a motor response from initiating) (Guo et al., 2018). Typical findings of the SST suggest longer reaction-times required by participants with OCD to inhibit responses, as measured by the Stop-Signal Reaction Time (SSRT), and higher probability of responding to ‘stop’ trials (Mar et al., 2022). Electroencephalographic (EEG) evidence, conversely, indicate enhanced action tendencies in OCD, as measured by the Readiness Potential (RP) (Cunnington et al., 2003; Dayan-Riva et al., 2021; Deecke & Kornhuber, 1978). This Event-Related Potential (ERP) represents a marker of motor preparation and is thought to be generated in the Supplementary Motor Area (SMA) (Cunnington et al., 2003; Nguyen et al., 2014), hence its utility as a neural underpinning of inhibitory control (Dayan et al., 2017; Morand-Beaulieu et al., 2021; Takashima et al., 2019).

A third and final endophenotype of relevance for the current study is action monitoring. This function refers to one’s ability to evaluate action outcomes and adapt behaviour accordingly, essential aspects of an adaptive life (Nieuwenhuis et al., 2005; Riesel et al., 2015). Rooted in the ACC, a brain region hosting a long-standing debate regarding its function as

home to cognitive control (Behrens et al., 2007; Kennerley et al., 2006) or conflict monitoring (Botvinick et al., 2004; Botvinick, 2007). Most importantly, though, is the plethora of evidence suggesting action monitoring deficits in OCD, both in adults and paediatric samples (Marzuki et al., 2020), which could explain enhanced levels of perfectionism (Nedeljkovic & Kyrios, 2007; Pozza et al., 2019) in this population.

Another endophenotype of OCD, Error-Related Negativity (ERN) is the most well-established marker of action monitoring (Gillan et al., 2017; Perera et al., 2019; Riesel, 2019; Weinberg, Dieterich, et al., 2015). This ERP consists of a negative deflection in the EEG signal, peaking between 50 and 100 ms after the commission of an error in speeded reaction-time tasks (Falkenstein et al., 1991; Gehring et al., 1993). Evidence suggests that the ERN is generated in the ACC, the same region thought to generate another ERP, the Error-Positivity (Pe) (Bellato et al., 2021; Endrass et al., 2008, 2010; Herrmann et al., 2004). This component represents error awareness and affective evaluation of errors (Jansen & de Bruijn, 2020; Ullsperger et al., 2014), with higher amplitudes indicating higher awareness of mistakes (Falkenstein et al., 2000; Wessel, 2012; Wessel et al., 2011). Evidence suggests that both components are abnormal in OCD, corroborating a hyperactivation of ACC (Robbins et al., 2019) and exaggerated action monitoring in the disorder (Gillan et al., 2017; Marzuki et al., 2020; Perera et al., 2019; Riesel et al., 2015; Vaghi, 2021).

In order to establish basal differences between patients with OCD and healthy volunteers, this study investigated the three ERPs above mentioned (RP, ERN, Pe) through a Stop-Signal Go/No-Go task (SSGNG). Additionally, cognitive flexibility was measured via the IED task, and OCD symptomatology was assessed with the Y-BOCS. Depression scores, as measured by the Montogmery-Åsberg Depression Rating Scale (MADRS), alongside ratings of intolerance of uncertainty and anxiety were also obtained. It was hypothesised that individuals with OCD would differ from control participants in all measures, and that higher amplitudes of ERN and RP would correlate with a longer SSRT and a higher probability of responding to stop signal, respectively.

2. Methods

2.1. Participants

Given the nature of this study, which combines samples from two distinct settings (“NHS trial” – see Chapter 4, and "the Cambridge study" – see Chapter 5), participants were recruited somewhat differently (see Chapter 2 - Methods). The final sample of this study,

therefore, comprised 67 (n=40 from NHS trial) subjects with OCD and 44 healthy volunteers (HV), matched by age and gender. Since medication was not an exclusion criterion for participants in the OCD group, the vast majority of individuals were taking psychotropic drugs. The most common ones were Selective Serotonin Reuptake Inhibitors (SSRI), namely: (i) sertraline (N=20); (ii) escitalopram/citalopram (N=9); (iii) fluoxetine (N=8); (iv) paroxetine (N=4); and (v) non-specified SSRI (N=4). Alternative medications included: (i) venlafaxine (N=1); (ii) pregabalin (N=1); (iii) clomipramine (N=1); (iv) olanzapine (N=1); (v) quetiapine (N=3); (vi) benzodiazepines (N=1); (vii) zolpidem (N=1); (viii) beta blockers (N=1); (ix) non-specified medication (N=1). Fifteen participants were unmedicated. For a review of inclusion/ exclusion criteria, please refer to chapter 2. Table 1a in the results section depicts demographic characteristics of both samples.

2.2. Materials and procedure

Upon completion of the screening phase and acceptance into the study, participants were invited to attend the testing session, either at the Highly Specialised OCD Clinic at Welwyn Garden City, Hertfordshire (for the NHS trial), or at the Herchel-Smith Building for Brain and Mind Sciences (HSB), part of the University of Cambridge ("Cambridge Study"). Prior to the session, though, participants of both groups completed the Montogmery-Åsberg Depression Rating Scale (MADRS) and individuals with OCD were additionally interviewed with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) by a trained researcher or clinician.

On the day preceding the testing session, participants received a reminder of the experiment and instructions to avoid caffeine and alcohol for a minimum of 4h before taking part in the study, and to avoid cosmetic products that could impact electroencephalographic (EEG) recordings, which would be observed by the researcher the following day. Upon arrival for data collection, participants signed the informed consent form and only then proceeded to the experimental phase. The testing session had an approximate duration of 2h, which comprised about 45 minutes of participant preparation for EEG recordings (applying gel and checking impedances), followed by the Stop-Signal Go/No-Go Task (SSGNG – see Chapter 2 for a full description of the task). Once the EEG net was removed, participants would also complete the Intra-Extra Dimensional Set-Shifting Task (IED – see Chapter 2 for details), the National Adult Reading Test (NART – Chapter 2) and the self-report questionnaires, namely the Intolerance of Uncertainty Scale (IUS) and the state version of the State-Trait Anxiety Inventory (STAI-S). At the end of the session, participants in the ‘Cambridge study’ would be

reimbursed for their time and applicable travel/accommodation expenses. Patients pertaining to the NHS trial were not monetarily compensated but received psychological treatment (see Chapter 4 for details).

3. Results

Given the difference in recruitment and testing setting between OCD samples, results are presented both combining participants and separately for the 'NHS trial' and 'Cambridge study'.

3.1. Demographic and clinical characteristics results

Table 1a depicts demographic and clinical characteristics of healthy volunteers (HV) and participants in the combined OCD group.

Table 1a. *Demographic and clinical characteristics of OCD patients and matched healthy controls*

	HV (n= 44)	OCD (n= 67)	t	df	p
Gender ratio (male/female)	18/26	23/44	$X^2 = 0.494$	1	0.482
Age	34.2 (13.6)	34.8 (11.7)	-0.25	108	0.8
YBOCS	0.0	24.9 (5.7)	-	-	-
MADRS	5.3 (4.2)	16.7 (9.7)	-8.16	96	**<0.001***
IUS	24.2 (8.3)	41.9 (8.3)	10.45	102	**<0.001***
STAI-State	27.3 (6.6)	44.7 (12.5)	-9.03	97	**<0.001***

* $p < 0.05$ level (2-tailed)

OCD: Obsessive-compulsive disorder; HV: Healthy volunteers; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; MADRS: Montgomery–Åsberg Depression Rating Scale; IUS: Intolerance of Uncertainty Scale; STAI-S: The State-Trait Anxiety Inventory-State.

Results comparing both OCD samples are depicted in Table 1b.

Table 1b. *Demographic and clinical characteristics of OCD patients in the NHS and Cambridge samples*

	NHS (n= 40)	CAMBRIDGE (n= 27)	t	df	p
Gender ratio (male/female)	12/28	11/16	X^2=0.825	1	0.364
Age	38.5 (11.7)	29.4 (9.6)	3.3	64	**0.002**
YBOCS	26.7 (4.7)	22.1 (6.2)	3.4	64	**0.001**
MADRS	15.95 (8.7)	18 (11.1)	-0.82	64	0.41
IUS	44.1 (7.36)	38.8 (8.75)	2.66	64	**0.01**
STAI-State	49.2 (12.6)	38.2 (9.3)	3.88	64	**< .001**
IQ	106.7 (9.1)	110.8 (6.3)	-2.02	62	**0.048**

* $p < 0.05$ level (2-tailed)

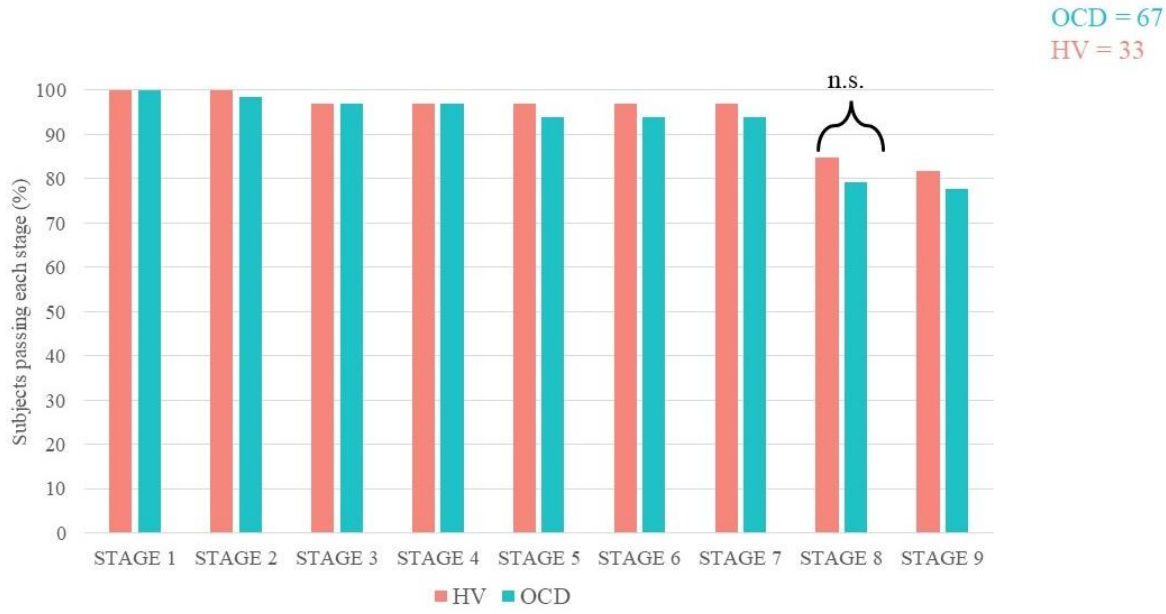
Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; MADRS: Montgomery–Åsberg Depression Rating Scale; IUS: Intolerance of Uncertainty Scale; STAI-S: The State-Trait Anxiety Inventory-State.

3.2. Behavioural paradigms

3.2.1. Intra-Extra Dimensional Set Shifting Task (IED)

Results of the IED are illustrated in Figure 1, representing the percentage of participants attempting each stage of the task. Of particular interest, stage 8 constitutes the extra-dimensional shift of the task, when participants must attend to the lines rather than the previously reinforced shapes.

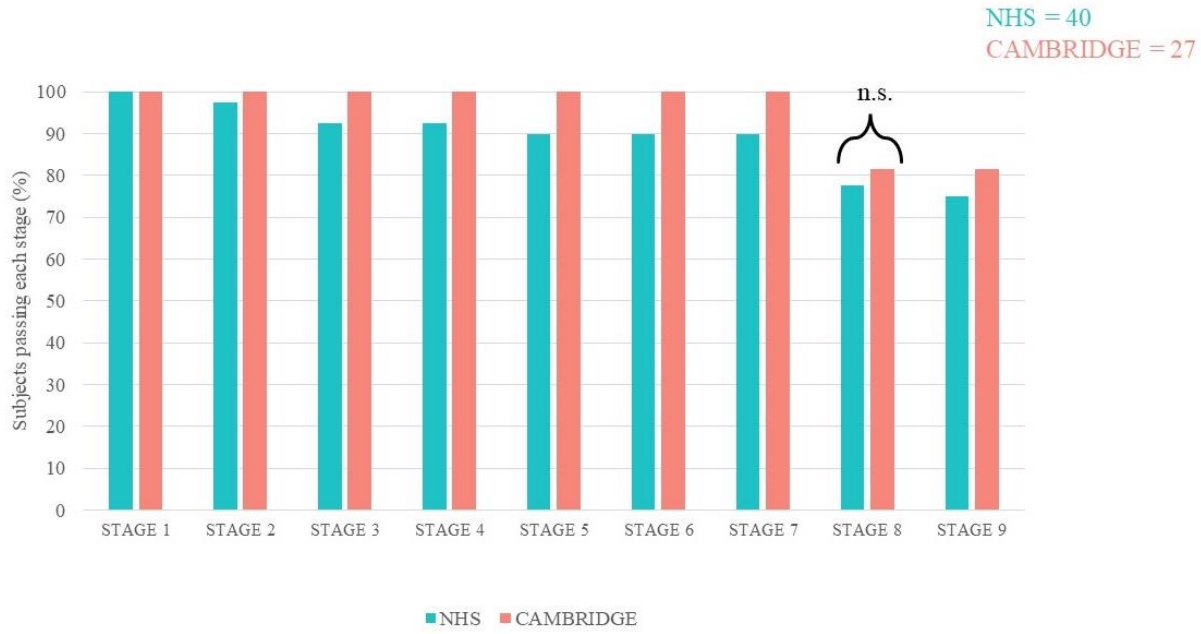
Figure 1a. *IED stages comparing HV and OCD*



n.s.: not significant (p>.05).

A non-parametric independent samples t-test was used to calculate differences between groups on the Extra-Dimensional Shift (EDS – stage 8) stage of the task, given that the Shapiro-Wilk test indicated non-normal distributions ($p<0.01$). The Mann-Whitney test for the ED errors indicated no differences between groups (Mann-Whitney U=1027.5, $n1$=33, $n2$=67, p=0.567, d=-0.07, two-tailed). Mean and standard deviation for the HV group were (M=11.9, SD=30.4) and for OCD (M=17.3, SD=39.2).

Figure 1b. *IED stages comparing both OCD samples*



n.s. not significant (p>.05).

Results of the Extra-Dimensional Shift (stage 8) of the IED task did not show a significant difference between the two OCD groups (Mann-Whiney U= 594.000, *n*1=40, *n*2=27, p=0.49, d=0.1, two-tailed). Means and standard deviations for the NHS and Cambridge samples were M=23.17(49.3) and M=8.52(10.68), respectively.

3.2.2. Stop-Signal Go/No-Go Task (SSGNG)

Table 2a depicts the results of the SSGNG task.

Table 2a. *Stop Signal Go/No-Go Task results*

	HV (n= 42)	OCD (n= 61)	U	p	d
Probability of responding to stop (%)	48.4 (7)	52.5 (6)	809.50	**0.002**	-0.37
Probability of responding to No-Go (%)	8.3 (10)	13.3 (16)	1052.00	0.121	-0.18
Probability of error on Go (%)	4.2 (15)	5.2 (13)	1003.00	0.062	-0.22
Correct Go Reaction Time (ms)	468.48 (315.12)	403.25 (185.6)	1536.00	0.09	0.2
SSD (ms)	249.17 (271.12)	184.73 (163.44)	1493.00	0.156	0.165
SSRT (ms)	200.98 (33.74)	200.91 (34.51)	1051.00	0.92	-0.01

* p < 0.05 level (2-tailed). Mann-Whitney test used.

As can be seen in Table 2a, results indicated that patients presented higher probability of responding to the stop signal, suggesting impaired response inhibition and an inability to cancel already initiated actions.

Results comparing the performance of both OCD samples on the SSGNG task are presented in Table 2b.

Table 2b. *Stop Signal Go/No-Go Task results for OCD samples*

	NHS (n= 35)	CAMBRIDGE (n= 26)	U	p	d
Probability of responding to stop (%)	52.8 (4)	52.1 (8)	459.50	0.95	0.01
Probability of responding to No-Go (%)	13.2 (15)	13.4 (17)	462.50	0.92	0.016
Probability of error on Go (%)	7.2 (17)	2.5 (2)	516.00	0.38	0.134
Correct Go Reaction Time (ms)	397.04 (172.65)	411.61 (205)	455.00	1	0
SSD (ms)	185.88 (142.83)	183.19 (190.69)	517.00	0.37	0.136
SSRT (ms)	199.49 (27.09)	202.95 (43.63)	304.00	0.21	-0.199

* $p < 0.05$ level (2-tailed). Mann-Whitney test used.

As shown in Table 2b, patients from different samples did not differ in any behavioural measures, confirming the deficits in stopping actions as linked to the diagnosis of OCD.

3.3. Electroencephalographic results

Grand averages of each ERP for both HV vs OCD and NHS vs Cambridge patients, alongside scalp topographies, are presented in Figures 2.1, 2.1.1, 2.2, 2.2.1, 2.3, and 2.3.1. Black circles indicate the electrodes used for the analyses of each ERP.

Figure 2.1. *ERN HV vs OCD*

A significant difference was found between groups (Mann-Whitney U=1549.000, *n*1=42, *n*2=60, p=0.05, d=0.23, two-tailed), with the OCD group obtaining a mean of -3.57(SD=5.9) and the HV group presenting a mean of -0.63(SD=4.93). Confirming the original hypothesis, patients did, indeed, present more enhanced ERN amplitudes than healthy volunteers.

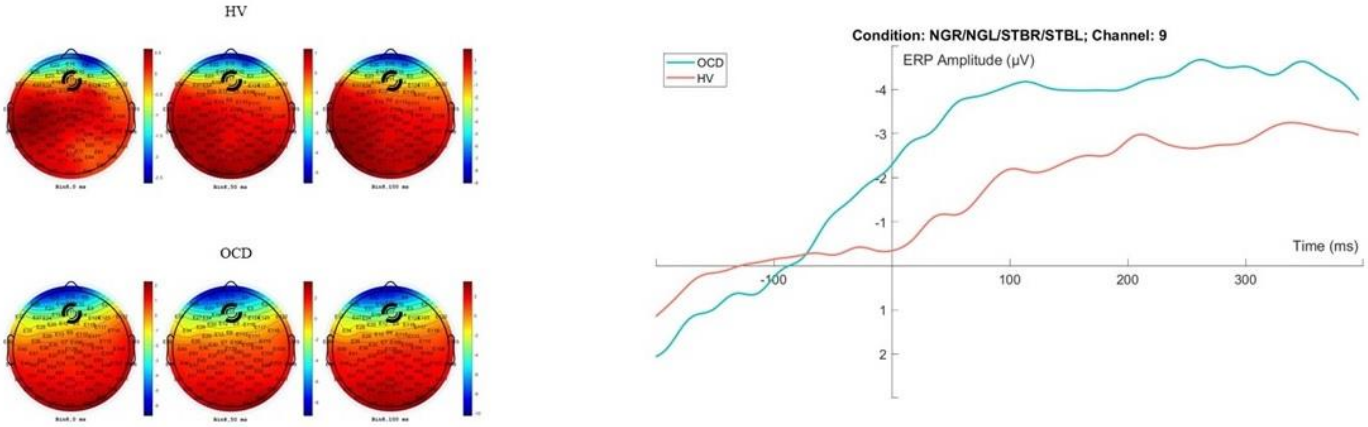


Figure 2.1.1. *ERN NHS vs Cambridge*

ERN amplitudes were significantly enhanced in the Cambridge sample (Mann-Whitney U=634.000, *n*1=33, *n*2=27, p=0.005, d=0.42, two-tailed). Means and standard deviations were M=-2.11(4.73) for the NHS sample and M=-5.36(6.73) for Cambridge participants.

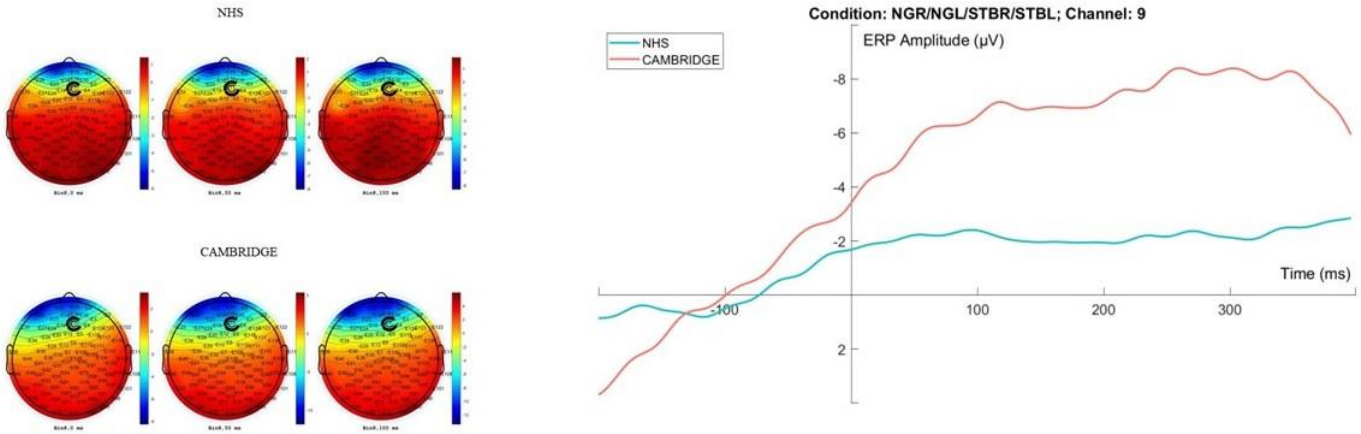


Figure 2.2. *Pe HV vs OCD*

Given the fact that variances were not equal (Levene's p=0.039), the Mann-Whitney test was used. No significant differences were found between groups for the Error Positivity (Mann-Whitney U=1139.000, *n*1=42, *n*2=60, p=0.413, d=-0.1, two-tailed). Mean amplitudes for HV were M=0.99(SD=2.9) and for OCD M=2.6(SD=8).

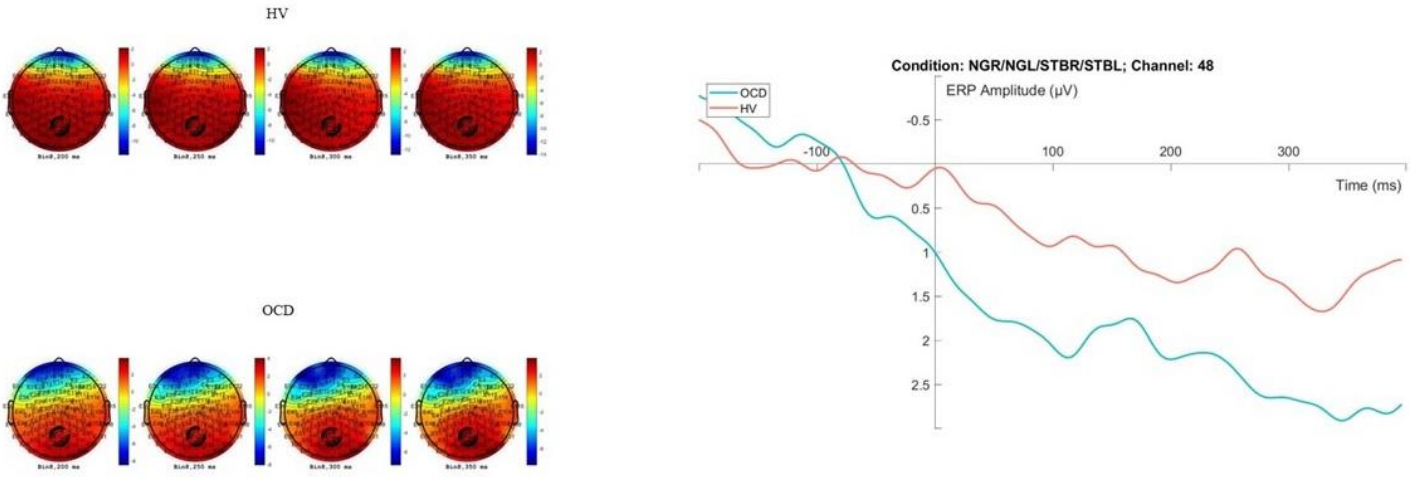


Figure 2.2.1. *Pe NHS vs Cambridge*

Patients did not differ in Pe amplitudes (Mann-Whitney U=336.000, *n*1=33, *n*2=27, p=0.106, d=-0.25, two-tailed). Means for the NHS group were M=2(9.7) and for the Cambridge sample M=3.24(5.2).

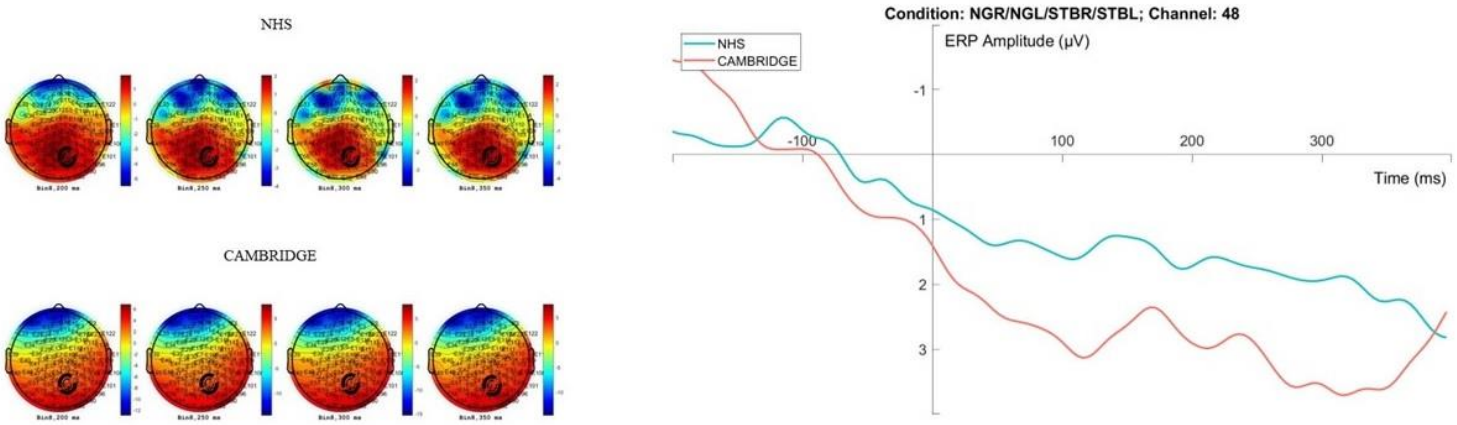


Figure 2.3. *RP HV vs OCD*

The Mann-Whitney test revealed a significant difference between groups (Mann-Whitney U=1664, *n*1=44, *n*2=61, p=0.037, d=0.24, two-tailed), with patients presenting enhanced RP amplitudes. Mean amplitudes for HV were M=-0.44(SD=0.98) and for OCD M=-0.745 (SD=0.965).

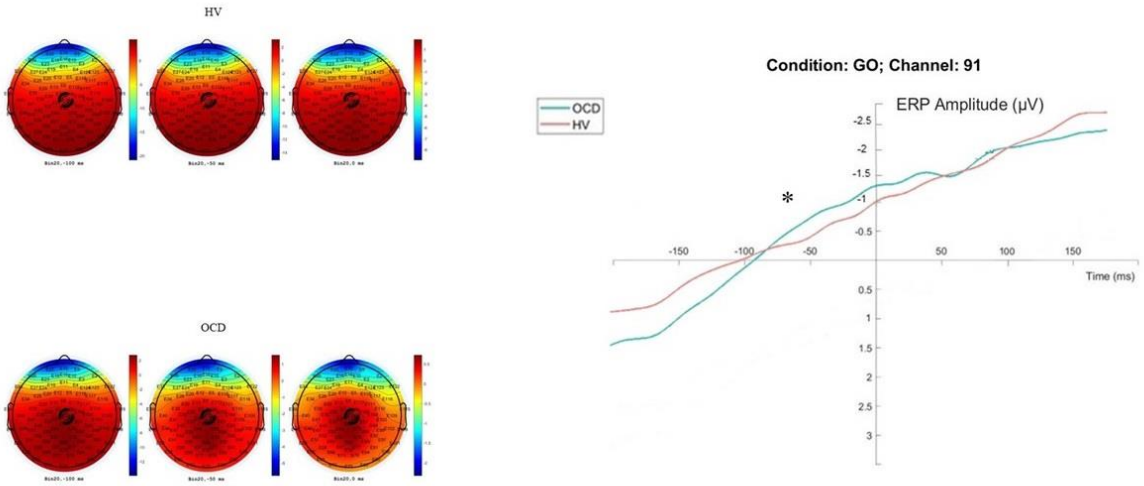
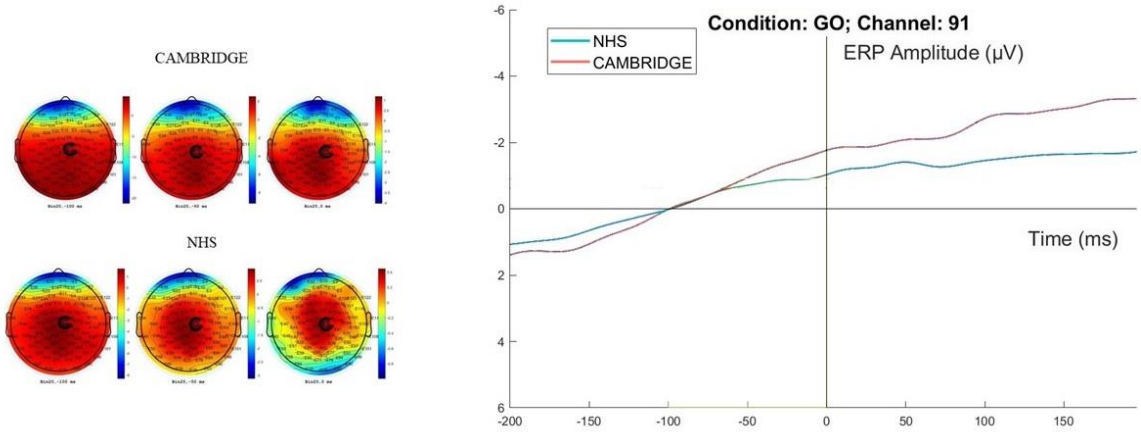


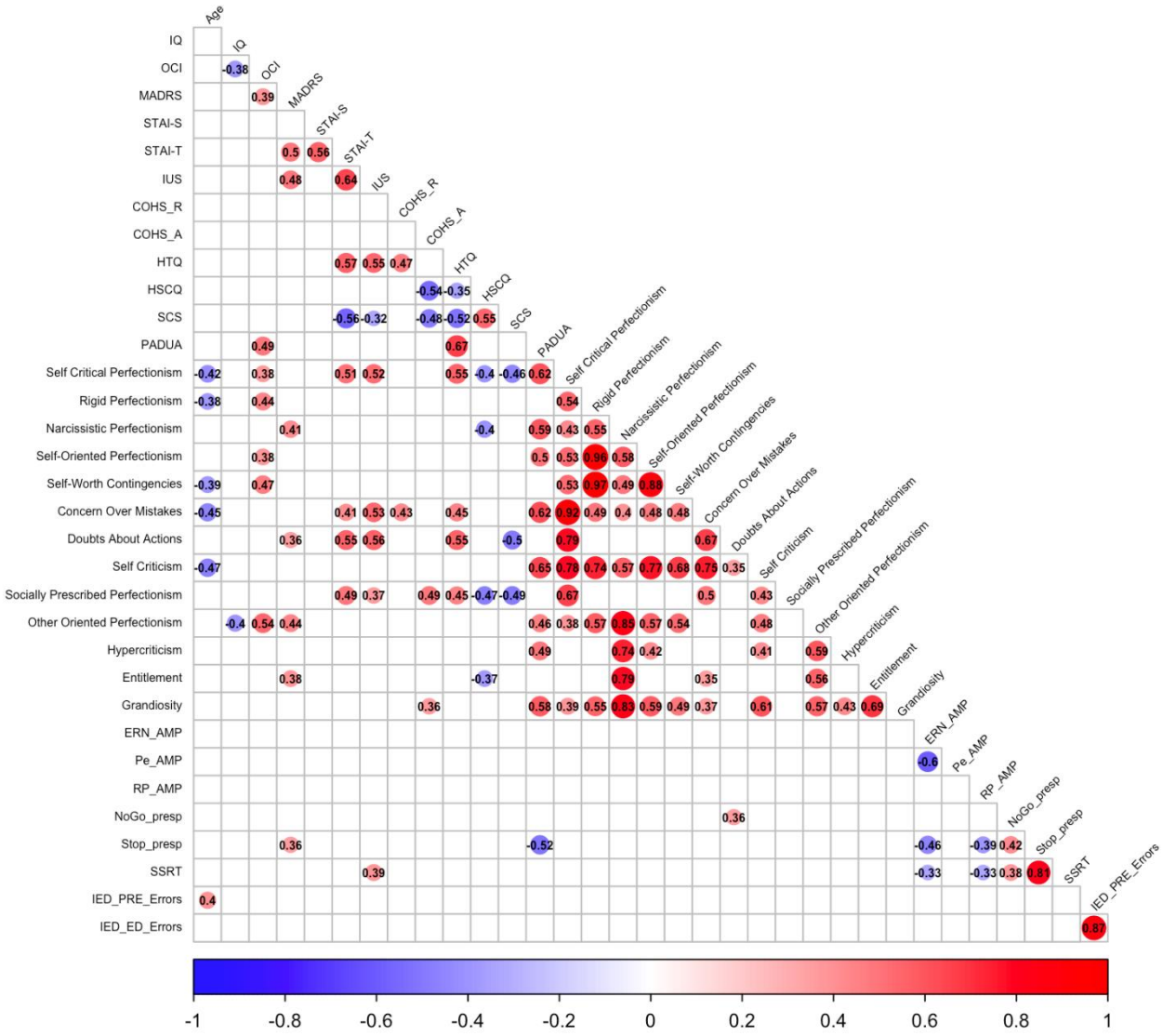
Figure 2.3.1. *RP NHS vs Cambridge*

No significant differences were found between both patient groups regarding RP amplitudes (Mann-Whitney U=519.000, *n*1=34, *n*2=27, p=0.39, d=0.13, two-tailed). Means were M=-0.62(0.67) and M=-0.91(1.24) for the NHS and Cambridge samples, respectively.



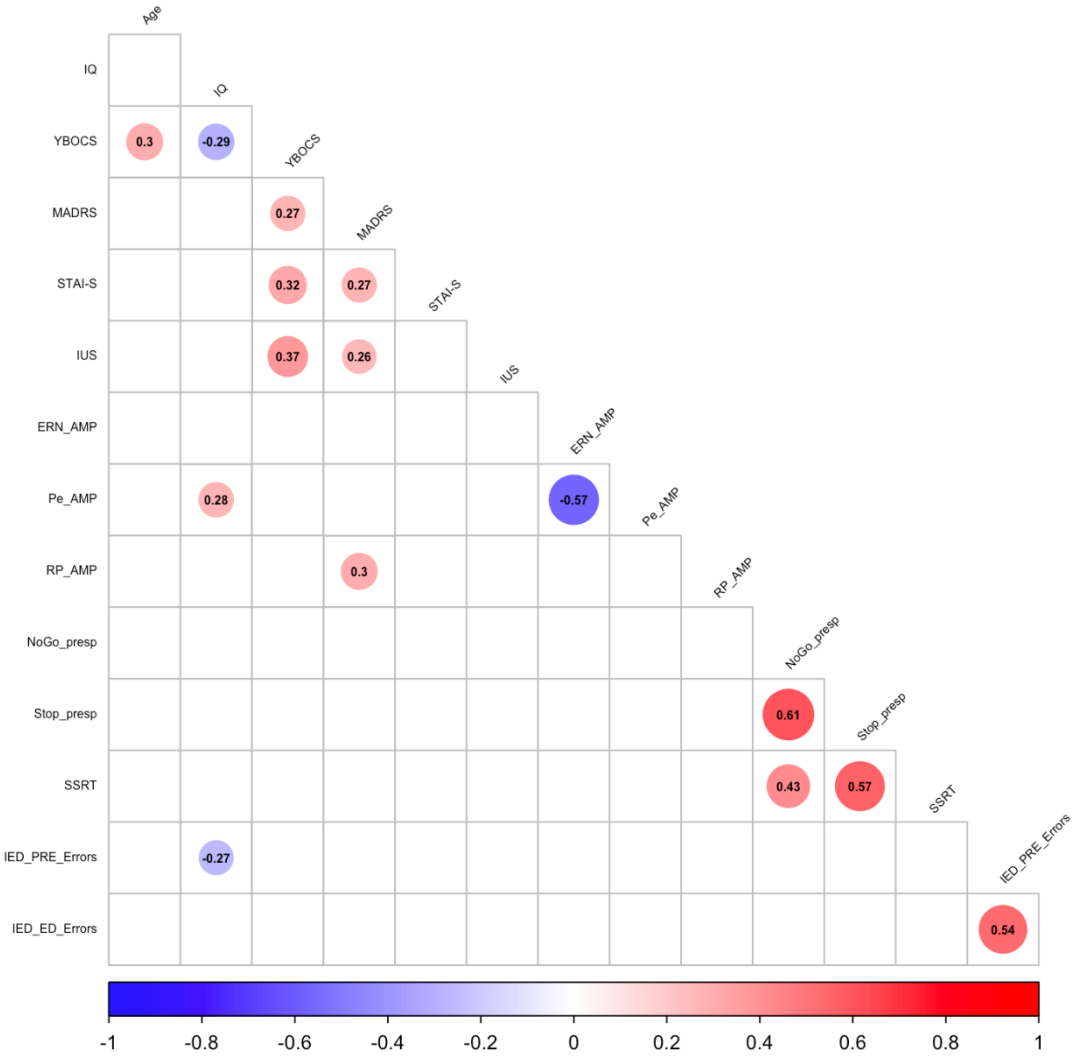
3.4. Correlations

3.4.1. HV



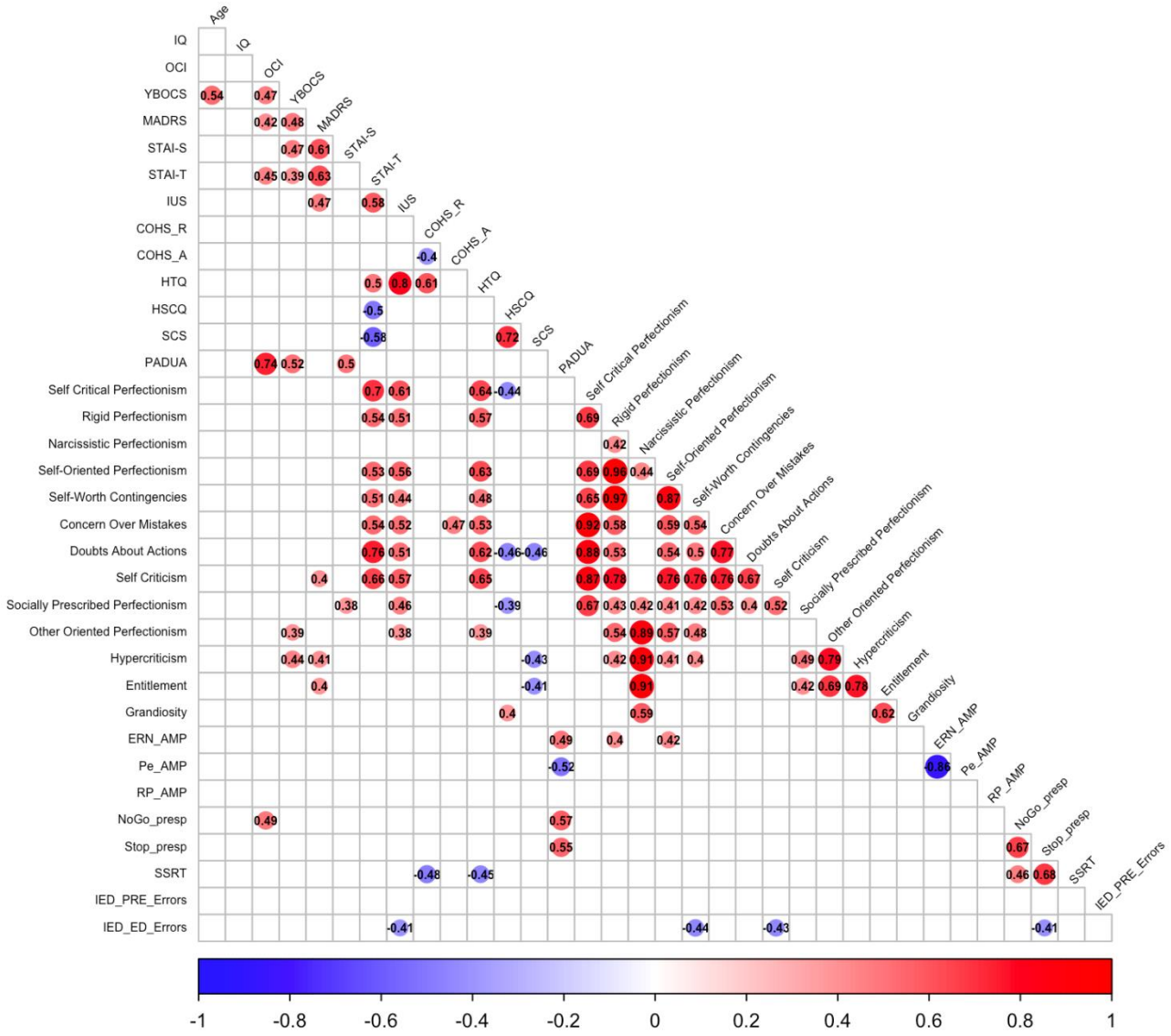
OCI: Obsessive-Compulsive Inventory; COHS-R: Creature of Habit Scale-Routine; COHS-A: Creature of Habit Scale-Automaticity; IUS: Intolerance of Uncertainty Scale; HTQ: Habitual Tendencies Questionnaire; HSCQ: Habitual Self-Control Questionnaire; SCS: Self-Control Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; STAI-S: The State-Trait Anxiety Inventory- State; STAI-T: The State-Trait Anxiety Inventory- Trait; ERN_AMP: Amplitude ERN; Pe_AMP: Amplitude Pe; RP_AMP: Amplitude RP; NoGo_presp: probability of responding to NoGo; Stop_presp: probability of responding to Stop; SSRT: Stop-Signal Reaction Time; IED_PRE_Errors: Pre-ED errors IED; IED_ED_Errors: EDS errors IED.

3.4.2. OCD samples combined



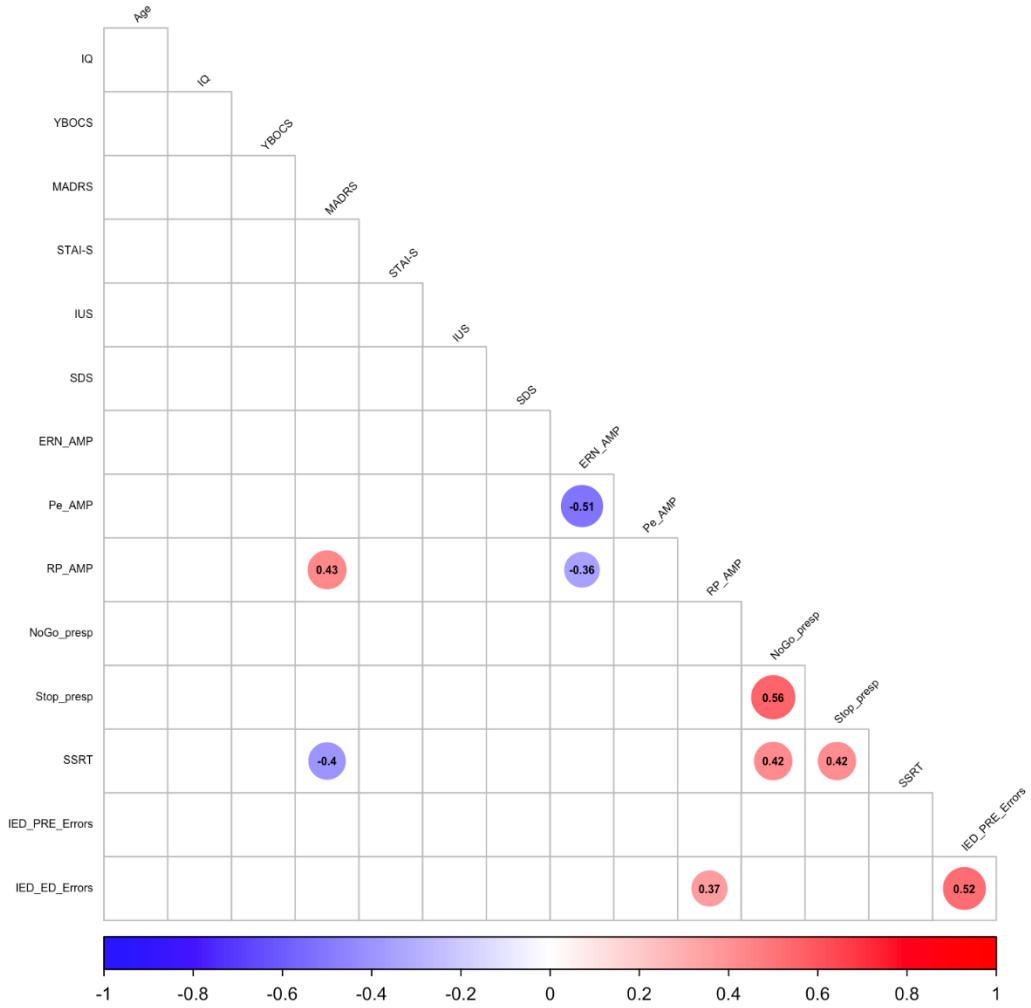
YBOCS: Yale-Brown Obsessive Compulsive Scale; IUS: Intolerance of Uncertainty Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; STAI-S: The State-Trait Anxiety Inventory-State; ERN_AMP: Amplitude ERN; Pe_AMP: Amplitude Pe; RP_AMP: Amplitude RP; NoGo_presp: probability of responding to NoGo; Stop_presp: probability of responding to Stop; SSRT: Stop-Signal Reaction Time; IED_PRE_Errors: Pre-ED errors IED; IED_ED_Errors: EDS errors IED.

3.4.3. OCD – Cambridge sample



YBOCS: Yale-Brown Obsessive Compulsive Scale; OCI: Obsessive-Compulsive Inventory; COHS-R: Creature of Habit Scale-Routine; COHS-A: Creature of Habit Scale-Automaticity; IUS: Intolerance of Uncertainty Scale; HTQ: Habitual Tendencies Questionnaire; HSCQ: Habitual Self-Control Questionnaire; SCS: Self-Control Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; STAI-S: The State-Trait Anxiety Inventory- State; STAI-T: The State-Trait Anxiety Inventory- Trait; ERN_AMP: Amplitude ERN; Pe_AMP: Amplitude Pe; RP_AMP: Amplitude RP; NoGo_presp: probability of responding to NoGo; Stop_presp: probability of responding to Stop; SSRT: Stop-Signal Reaction Time; IED_PRE_Errors: Pre-ED errors IED; IED_ED_Errors: EDS errors IED.

3.4.4. OCD – NHS sample



YBOCS: Yale-Brown Obsessive Compulsive Scale; IUS: Intolerance of Uncertainty Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; STAI-S: The State-Trait Anxiety Inventory- State; SDS: Sheehan Disability Scale; ERN_AMP: Amplitude ERN; Pe_AMP: Amplitude Pe; RP_AMP: Amplitude RP; NoGo_presp: probability of responding to NoGo; Stop_presp: probability of responding to Stop; SSRT: Stop-Signal Reaction Time; IED_PRE_Errors: Pre-ED errors IED; IED_ED_Errors: EDS errors IED.

As can be seen on the heatmaps, correlations followed expected directions in the HV group, with higher depression and intolerance of uncertainty being associated with poorer performance on the SSGNG task. As for the combined OCD group, age was associated with higher YBOCS symptoms, a common finding in epidemiological studies (Zheng et al., 2021). Furthermore, IQ was negatively associated with Pre-ED errors, suggesting that older participants present higher difficulties in learning the task. Intelligence was additionally correlated with awareness of errors in the OCD group, as demonstrated by higher Pe amplitudes in higher IQ individuals. Interestingly, a positive association between RP amplitudes and

MADRS (i.e. lower action tendencies associated to higher depression) was found, potentially highlighting the role of motor retardation in depression (Buyukdura et al., 2011). Specific intra-OCD group correlations revealed an inverse association between ERN amplitudes and clinical symptoms, with enhanced error monitoring predicting *lower* symptomatology.

3.5. Summary of findings

- ERN amplitudes were increased in OCD
- RP amplitudes were increased in OCD
- Action stopping was impaired in OCD
- No SSRT differences were found between HV and OCD
- No differences in behavioural flexibility were found between HV and OCD
- IQ correlated with Pe in OCD
- Increased ERN was associated to lower symptomatology and better performance

4. Discussion

This study investigated three neurocognitive endophenotypes (action monitoring, response inhibition, and cognitive flexibility) in a large sample of patients with OCD and matched healthy volunteers using electroencephalographic, behavioural, and clinical measures. It was expected that groups would differ both in neural and behavioural expression of these mechanisms, consolidating their roles as markers of the disorder.

Indeed, the findings for error-related negativity (ERN) supported the original hypothesis and corroborated previous literature, suggesting enhanced performance monitoring in OCD (Gillan et al., 2017; Perera et al., 2019; Riesel, 2019; Riesel et al., 2015). Nevertheless, contrary to preliminary predictions, the error positivity (Pe), a component that follows the ERN and has been associated with error awareness (Endrass et al., 2010; Falkenstein et al., 2000; Wessel, 2012), did not significantly differ between groups, although there was a suggestion of higher amplitudes in OCD. This result, however, is not unprecedented, and several studies have reported Pe amplitudes in OCD that are similar to those found in control subjects (Endrass et al., 2008, 2010; Endrass & Ullsperger, 2014; Riesel et al., 2011; Ruchsow, Grön, et al., 2005). In addition, no correlations were found between these two ERPs and symptom severity in the OCD group, which might reflect the ERN and Pe specificity for monitoring actions and recruiting cognitive control to maintain adequate performance, a result shared by a plethora of

studies (Endrass et al., 2008; Hajcak et al., 2005; Lei et al., 2015; Nieuwenhuis et al., 2005; Riesel et al., 2014). Interestingly, the compiled OCD sample showed correlations between IQ and amplitudes of the Pe, suggesting that higher error awareness is associated with higher levels of intelligence. This result seems to be corroborated by literature suggesting the role of the anterior cingulate cortex (ACC) in not only detecting errors, but signalling the need for cognitive control and compensatory behaviours (Botvinick et al., 2001; Botvinick, 2007a, 2007b; Botvinick et al., 2004). In fact, evidence suggests that stronger error signals are associated with more effective remedial behaviour (Gentsch et al., 2009), as it appears that the ACC engages the dorsolateral prefrontal cortex (dlPFC) and recruits top-down regulation (García et al., 2022). This could explain why, in this study, the Cambridge OCD sample, although presenting significantly enhanced ERN amplitudes when compared both to HV and to the NHS participants, showed numerically higher performance, significant higher IQ, and significantly lower clinical symptoms than the NHS sample, results further demonstrated by a positive correlation between ERN amplitudes and PADUA scores (i.e. the higher the OC symptoms, the blunter the ERN) on this sample. The ERN, thus, seems to act as a defensive mechanism, recruiting cognitive control and ensuring successful performance adaptation (Banica et al., 2021; Riesel et al., 2012; Weinberg et al., 2012).

Differences between groups were also found concerning behavioural measures, specifically revealed by a higher probability of patients to respond to stop signals in the Stop Signal Go/No-Go task, a robust marker of impaired inhibitory control consistently reported in OCD (Bari & Robbins, 2013; Mar et al., 2022; McLaughlin et al., 2016). Surprisingly, though, no differences were found between HV and OCD in the Stop-Signal Reaction Time (SSRT) measure, contrary to a large body of evidence that suggests longer latencies in patients with OCD (Mar et al., 2022). This finding, nonetheless, may be interpreted by referring to the healthy volunteers, which exhibited significant negative correlations between ERN amplitudes and both probability of responding to stop signals and SSRT. Post-error slowing refers to a frequently seen strategy engaged to adapt behaviour and ensure successful performance on subsequent trials (Gehring et al., 1993). Increased performance monitoring associated with non-impaired behavioural measures in the HV group suggests a speed-accuracy trade-off, a common phenomenon in tasks that emphasise both mechanisms (Desender et al., 2019; Grützmann et al., 2014; Heitz, 2014). In addition, longer SSRTs were positively correlated with intolerance of uncertainty in this group, corroborating previous literature that has demonstrated the role of uncertainty and confidence in evidence accumulation (Banca, Vestergaard, et al., 2015; Marzuki et al., 2021). Interestingly, no differences were found

between groups concerning probability to respond to No-Go stimuli, further confirming the differential mechanisms between action inhibition and action cancellation (Guo et al., 2018). Nonetheless, no correlations were found between ERN/Pe and behavioural measures in OCD.

Results for the readiness potential (RP) may also shed light into the relationship between speed and errors. Amplitudes of this ERP were significantly larger (i.e. more negative) in OCD patients than in HV, adding to a body of evidence reporting enhanced action tendencies in OCD (Dayan et al., 2014, 2017; Dayan-Riva et al., 2021; Morand-Beaulieu et al., 2021). The RP is thought to be generated in the pre-SMA and SMA (Cunnington et al., 2003; Kornhuber & Deecke, 2016), a region also implicated in the ERN (Grützmann et al., 2016, 2022; Hochman et al., 2009; Iannaccone et al., 2015) and in response inhibition (Weigard et al., 2019). Indeed, it appears that increased functional connectivity between the pre-SMA and the IFG may be particularly relevant for the pathophysiology of impaired inhibitory control in OCD (Tomiyama et al., 2021). These results are further supported by the significant negative correlations between RP amplitudes (since the RP is a negative component, more positive amplitudes suggest weaker signal) and both SSRT and probability of responding to stop signal in the control group, reinforcing the notion that higher control of actions is necessary for adaptive, goal-directed performance (Bari & Robbins, 2013; Gillan et al., 2011; Hardwick et al., 2019; Mar et al., 2022).

Finally, the third predisposing factor investigated in this study, cognitive flexibility, did not differ between groups, contrary to the original hypothesis. The strong correlation between ED errors and Pre-ED errors in the healthy sample suggests that the control group had difficulties in the learning stages of the task, which would undeniably impact their ability to perform adequately when the extra-dimensional shift occurred. Nevertheless, no differences were found between groups concerning Pre-ED errors, which hinders the ability to conclusively address this hypothesis.

Importantly, this study presents limitations that should be addressed. Firstly, it is necessary to note that the OCD sample was composed of participants from two different studies (see Chapters 4 and 5 for details). Participants enrolled in the NHS trial had registered for research coupled with psychological treatment, whereas those in the ‘Cambridge study’ were volunteers receiving monetary compensation for their participation. It is possible, thus, that motivation to engage in research and compliance differed between both OCD groups and the control group, since financial compensation has been linked to biased enrolment (Resnik, 2015). Additionally, results suggested that both OCD groups, albeit not differing in behavioural performance, did manifest dissociated neuroclinical profiles, with the Cambridge group

presenting significantly higher IQ, lower age, and clinical symptoms (YBOCS, MADRS, STAI-S, IUS), and larger ERN. However, statistical analyses did not reveal an impact of age or any of the remaining measures on the overall results. Furthermore, the different research settings, albeit with the same procedure and equipment, might have introduced artifacts in the electroencephalographic recordings (Jiang et al., 2019). Attempts to minimise those were undertaken with a thorough pre-processing pipeline (see Chapter 2), but the extent to which signals were impacted remains unclear. Finally, although the OCD sample presented a heterogeneous profile, particularly regarding medication, the effect of those psychiatric drugs was not expected to impact the neural recordings significantly, with a myriad of studies reporting low interference of medication on ERP (de Bruijn et al., 2004, 2006; Endrass et al., 2010; Riesel et al., 2011; Stern et al., 2010). Nevertheless, studies with unmedicated samples are necessary to elucidate if these abnormal mechanisms are conclusively present in OCD.

Despite these limitations, this study provided support for the response inhibition and action monitoring predisposing factors previously reported in OCD (Vaghi, 2021). Moreover, the considerable patient sample size makes it one of the largest OCD studies using electroencephalography, with the largest being conducted in 2014 and comprising 72 adult patients (Riesel et al., 2014). Finally, the corroboration of enhanced action tendencies in OCD, as measured by the readiness potential (Dayan et al., 2014, 2017; Dayan-Riva et al., 2021; Morand-Beaulieu et al., 2021), sheds light on the importance of taking the motor components of OCD into account for the development of new treatments (Szalai, 2019).

CHAPTER 4 – HABIT-REVERSAL TREATMENT FOR OBSESSIVE-COMPULSIVE DISORDER

How use doth breed a habit in a man!

The Two Gentleman of Verona, Act V, Scene 4

William Shakespeare

1. Introduction

Often associated with negative behaviours, such as smoking and overeating, or positive ones, as exercising and flossing (Poldrack, 2021), the capacity for habitual control has enabled preservation of energetic and cognitive resources in favour of performing higher-order tasks (Eilam et al., 2006; Fentress, 1976; Poldrack et al., 2005). Eternalised by Daniel Kahneman in his book *'Thinking, Fast and Slow'* (Kahneman, 2011), the definition of System 1 as a fast, unconscious, and automatic instance is rather analogous to the definition of habitual or model-free behaviour, which opposes the slow, conscious, reflective, and voluntary System 2 (Daw et al., 2011; de Wit & Dickinson, 2009; Robbins & Costa, 2017).

Habits are thus an integral part of human (and other animal) life (Eilam et al., 2006; James, 1890; Poldrack, 2021), promoting easier and faster decision-making given their characteristics of routine and automaticity (Ersche et al., 2017; Robbins & Costa, 2017). The definition of habits, albeit the focus of effervescent debate (Robbins & Costa, 2017), seems to have kept its early concept of automatic responses triggered by stimuli (i.e. S-R associations) (James, 1890), in much the same way as Thorndike's Law of Effect (Thorndike, 1927; Thorndike & Bruce, 2017). Indeed, habits can be described as behaviours performed autonomously of the goal (Banca et al., 2020; Dickinson & Weiskrantz, 1985; Lingawi et al., 2016), although some authors argue that they can be defined as previous goal-directed behaviours that were practised to the point where they reached automaticity (Bargh, 1994; Wood & Rünger, 2016). Unfortunately, though, it appears that habits can become maladaptive as well, in uncertain environments or situations when goals change (Gillan et al., 2011). For

instance, if previously it was adaptive and goal-directed to consume as many calories as possible in case on the next day food was not available, modern men can no longer rely on this habit, risking serious health issues associated with obesity. Learning how to adapt and when to allow the goal-directed system to regulate behaviour is as crucial an ability as preserving cognitive resources through habits (Gillan, 2021; Gillan et al., 2011; Poldrack et al., 2005). Habits can, thus, become rigid and inflexible and, due to their automatic and unconscious nature, significantly impair functioning and quality of life (Voulougouris et al., 2009; Gillan, Kosinski, et al., 2016).

Obsessive-Compulsive Disorder (OCD), a condition marked precisely by an imbalance between goal-directed and habitual behaviours (Gillan, 2021; Gillan et al., 2011; Gillan, Kosinski, et al., 2016; Graybiel & Rauch, 2000; Robbins & Costa, 2017), can offer insight as to the consequences of overreliance on habitual behaviour and treatment targets (Lee et al., 2019). Indeed, international guidelines for the treatment of OCD have established a combination of Cognitive-Behavioural Therapy (CBT) and Exposure-Response Prevention (ERP), referred as Treatment as Usual (TAU), as first-line strategies (Koran et al., 2007; National Institute for Health and Care Excellence [NICE], 2005), with superior results to treatment with medication alone (Foa et al., 2005; Patel et al., 2021).

Two theories have been proposed to explain the reasons behind ERP efficacy, namely emotional processing theory (EPT) and inhibitory learning (Tryon, 2005). Whilst the former assumes that ERP works by activating a ‘fear structure’ (Patel et al., 2021) and providing alternative outcomes to the ones feared by the individual (i.e. proof that one does not harm loved ones by not keeping objects symmetrically aligned) until fear is attenuated, the latter operates by strengthening inhibitory learning of safe associations (Apergis-Schoute et al., 2017). In any case, ERP seems to work through a process of preventing a previously reinforced and automatic behaviour from taking place, in a manner akin to breaking a habit (Hezel & Simpson, 2019; Kalanthroff et al., 2018).

Despite being the 'gold-standard' of OCD treatment, evidence from remission studies suggests that TAU is only effective in approximately 50% of the cases (Fineberg et al., 2015; Mataix-Cols et al., 2016; Patel et al., 2021). Particularly, some patients will drop out of treatment interventions due to beliefs that they are ‘too difficult’ (Mancebo et al., 2011), or that the anxiety provoked by ERP is ‘too intense’ (Franklin et al., 2000; Mantione et al., 2014). It is imperative, therefore, to improve patient adherence to treatment, in order to ameliorate the quality of life of patients with this highly debilitating disorder (Asnaani et al., 2017; Ruscio et al., 2010).

Amongst new strategies proposed to address this issue, Habit-Reversal Treatment (HRT) has recently been gaining increasing attention and interest (Lee et al., 2019; Shephard et al., 2021). Established already as a treatment option for tic disorders, trichotillomania, and 'habit disorders' (Azrin & Nunn, 1973; Bate et al., 2011; Chamberlain et al., 2009; Deckersbach et al., 2006; van de Griendt et al., 2013), this evidence suggests that a logical next step would be to employ HRT in OCD itself (Dillenburger, 2006; Fineberg et al., 2020; Lee et al., 2019; Shephard et al., 2021; Sulkowski et al., 2013; Toffolo & Saxena, 2019). This HRT technique relies on multi-component behaviours, namely: (i) recording; (ii) awareness training; (iii) competing-response practice; (iv) habit-control motivation; and (v) generalisation training (Azrin & Nunn, 1973; Dillenburger, 2006; Lee et al., 2019). It seems particularly effective in cases when premonitory urges precede the compulsions, such as tics or symmetry/ordering (Lee et al., 2019; Shephard et al., 2021).

A possible explanation for the efficacy of HRT in urges comes from brain imaging studies (Balleine et al., 2007; Banca, Voon, et al., 2015; Dickinson & Balleine, 1993; Graybiel, 1998; Yin et al., 2006). Areas implicated in habit formation include what is called 'the OCD circuit', composed by the cortico-basal ganglia network (Graybiel & Rauch, 2000). More specifically, the striatum (its anterior portion, the caudate) and the putamen seem to be overactive in OCD (Graybiel & Grafton, 2015; Graybiel & Rauch, 2000; Menzies et al., 2008; Robbins et al., 2019; Wood & Rünger, 2016). Incidentally, one neuroimaging study has reported significantly reduced activity in the putamen following HRT (Deckersbach et al., 2006). It is not surprising, hence, that patients with enhanced motor compulsions would benefit more from a treatment comprising HRT, considering basal ganglia's long-standing implication in motor functions (Graybiel & Grafton, 2015).

Given the 'motor' component of OCD, it is plausible to hypothesise that individuals with the disorder will also demonstrate increased action tendencies, as measured by the *Bereitschaftspotential*, or Readiness Potential (RP) (see Chapter 3 for further details), in light of the evidence for increased RP in tic disorders (Duggal & Nizamie, 2002; van der Salm et al., 2012) and Parkinson's disease (Dick et al., 1989; Georgiev et al., 2016). Albeit being generated in the pre-Supplementary Motor Area (pre-SMA) (Takashima et al., 2019; Yazawa et al., 2000), this brain region receives afferent input from the basal ganglia (Dick et al., 1989), providing a measure of basal ganglia activity by proxy.

To test these hypotheses, the current study evaluated two samples of patients with OCD who joined a NHS feasibility trial at the Highly Specialised OCD clinic, based in Welwyn Garden City, Hertfordshire. Patients were randomly assigned to TAU (CBT + ERP) or HRT

and completed clinical and self-report measures, a cognitive flexibility paradigm, and a behaviour task of inhibitory control coupled with electroencephalographic (EEG) recordings, at baseline and after six weeks (either six sessions of TAU or daily HRT practice). HRT consisted of a mobile application developed by Banca and colleagues (Banca et al., 2020) in which subjects were instructed to learn two novel sequences of finger tapping movements, similarly to playing keys on a piano (see Chapter 2 for details). Due to the ritualistic and rigid nature of the sequences, analogous to a compulsion without the anxiety component, it was predicted that it would be beneficial as the 'competing-response practice' of HRT, inducing a new, non-maladaptive habit that could attenuate compulsive behaviour. In addition, it was hypothesised that patients assigned to HRT would present diminished amplitudes of RP at midpoint, enhanced goal-directed behaviours, and higher self-reported quality of life, considering that rigid habitual behaviour is identified as one of the primary symptoms in OCD (American Psychiatric Association, 2013).

2. Methods

2.1. Participants

Thirty patients with OCD completed baseline and midpoint stages of the treatment trial and are, therefore, considered in this study. Participants were referred by their local **(**Hertfordshire) mental health teams (Community Mental Health Services (CMHS) or Improving Access to Psychological Therapies (IAPT)) and invited to take part in the feasibility trial. An experienced clinical psychologist would then assess individuals to ensure eligibility for the study through a detailed demographic questionnaire, the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), the Yale-Brown Obsessive Compulsive Scale (Y-BOCS - both checklist and rating scale) (Goodman et al., 1989), and the Montgomery- Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) (see Chapter 2 for details of the questionnaires). Patients that did not fit inclusion criteria were re-referred to their local teams and preserved their position on the waiting list for standard NHS treatment. Inclusion criteria were: (i) having OCD as a diagnosis confirmed using the MINI; (ii) have minimum OCD symptom severity score of 17 based on the Y-BOCS rating scale; (iii) maintaining formulation dose of medication unchanged for 16 weeks prior to the study and for the total duration of the trial; (iv) be aged 18 to 65 years old; (v) have adequate use of the English language to understand the study documentation and participate in the rating assessments; and (vi) be capable of consenting to the study. Patients would be excluded if: (i)

they fit criteria for Severe Major Depressive Disorder with a score of at least 35 as measured by the MADRS; (ii) severe suicidal ideation, as measured by a score of 4 or greater on the relevant question of the MADRS; (iii) there was presence of past or present psychotic episodes; (iv) they met DSM-5 criteria for substance abuse or dependence; and (v) there was presence of severe physical impairments affecting eyesight or motor performance. Considering the clinical nature of the study, the vast majority of patients were medicated as follows: (i) sertraline (N=8); (ii) fluoxetine (N=3); (iii) citalopram (N=3); (iv) escitalopram (N=1); (v) paroxetine (N=2); (vi) non-specified SSRI (N=3); (vii) clomipramine (N=1); (viii) quetiapine (N=2); (ix) olanzapine (N=1); (x) mirtazapine (N=1); (xi) aripiprazole (N=1); (xii) amitriptyline (N=1); (xiii) venlafaxine (N=1); and (xiv) pregabalin (N=2). Nine patients were unmedicated. Table 1 in the results section depicts demographic and clinical characteristics of both patient groups.

2.2. Materials and procedures

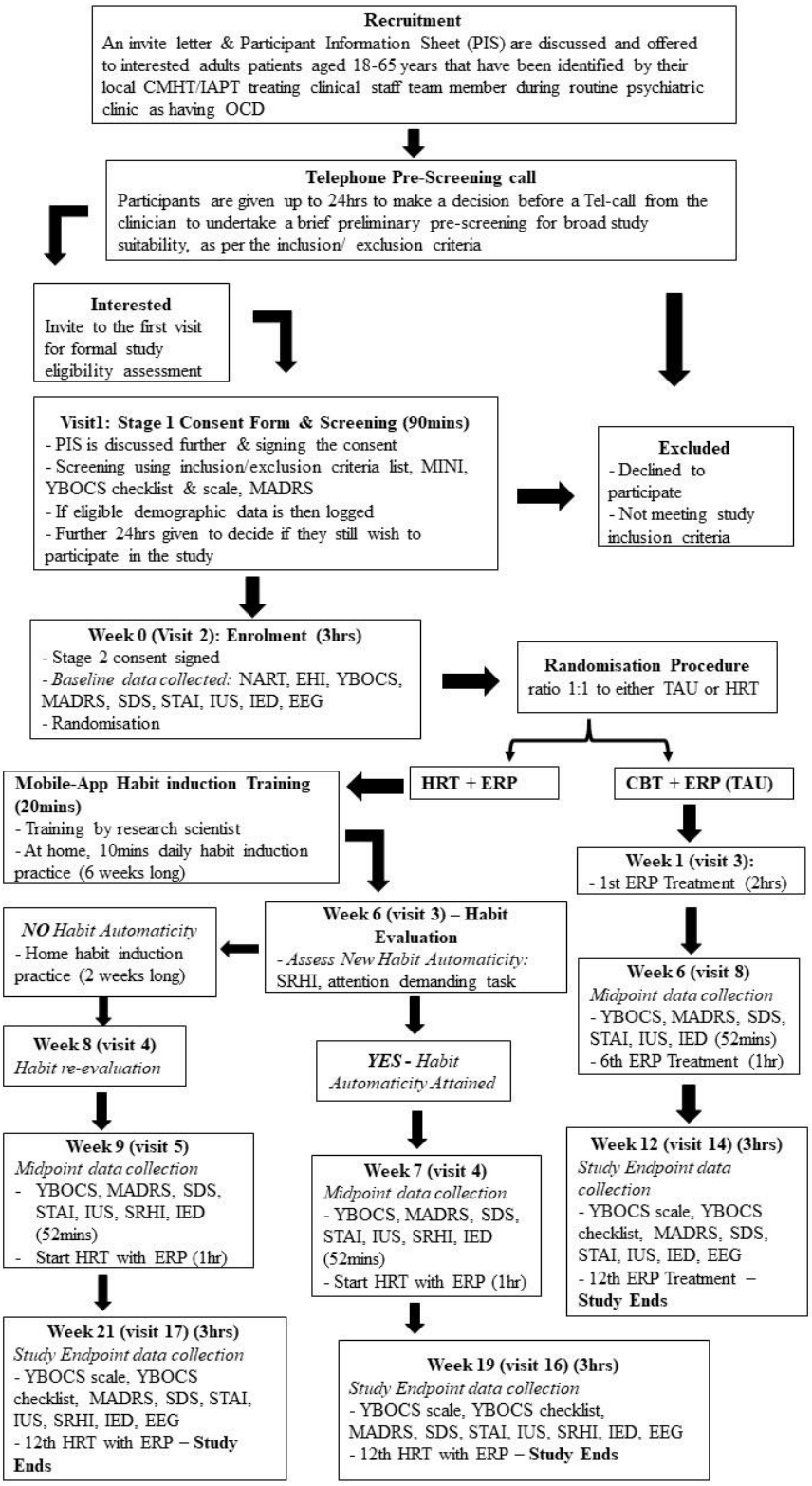
Following successful screening, patients were invited for a baseline assessment at the Highly Specialised OCD clinic in Welwyn Garden City, Hertfordshire. Prior to the session, a trained clinician assessed participants' scores on the Y-BOCS rating scale and on the MADRS. Following the assessment, the research administrator randomised patients to either TAU or HRT through a software. The researcher was notified about the output of randomisation, nonetheless, the clinician was kept blind, to avoid bias. Baseline testing consisted of completing self-report measures of intolerance of uncertainty (IUS-12) (Carleton et al., 2007), quality of life as measured by the Sheehan Disability Scale (SDS) (Spielberger et al., 1970) (Sheehan, 1983), state anxiety through the STAI-S (Spielberger et al., 1970), and handedness as assessed by the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). Additionally, patients would be tested on the National Adult Reading Test (NART) (Nelson & Willison, 1991) by the researcher. Behavioural paradigms included the Intra-Extra Dimensional Set-Shifting Task (IED) (Cambridge Neuropsychological Test Automated Battery (CANTAB), Cambridge Cognition) and the Stop-Signal Go/No-Go (see Chapter 2 for details of these measures), which was performed whilst EEG signals were being recorded. Finally, the researcher informed participants of the outcome of the randomisation and, if applicable, trained them on the mobile application (Banca et al., 2020) used for HRT.

Participants in both groups were invited for a midpoint assessment after 6 weeks, which corresponded to either six sessions of TAU, or six weeks of daily HRT training. This practice was regularly monitored by the researcher online, and participants received emails reminding

them of the training if everyday practice was not achieved. Once again, prior to the second testing session, participants completed the Y-BOCS and the MADRS with the blind researcher. Subjects in the HRT group were additionally tested to ensure that automaticity was obtained in the mobile application, an essential component of a successful habit-reversal treatment. If automaticity was not obtained, patients were requested to practice the new habit for an additional two weeks, when they returned for midpoint assessment.

The second testing was identical to baseline, with the exception of the EHI and NART, which required no re-testing. Following the session, patients in the TAU group would complete the remaining six weeks of treatment, whereas HRT participants would receive a full 12-week course of TAU + HRT. At the end of treatment, both groups were re-assessed in an endpoint session, where the same measures were repeated. Given the fact that this study is still ongoing, solely data from baseline and midpoint are presented in this chapter. A flowchart depicting the stages of the study can be found below.

Figure 1. *Flowchart of HRT feasibility trial*



3. Results

3.1. Baseline comparisons

3.1.1. Demographic and clinical data

Demographic and clinical characteristics of both patient groups are depicted in Table 1.

Table 1. *Baseline demographic and clinical characteristics of TAU and HRT patients*

	TAU (n= 17)	HRT (n= 13)	t	df	p
Gender ratio (male/female)	3/14	5/8	$X^2 = 1.63$	1	0.2
Age	43.89 (10.67)	34.54 (10.91)	-2.35	28	**0.026**
YBOCS	26.35 (5.38)	26.77 (4.47)	0.22	28	0.82
MADRS	17.06 (8.76)	13.08 (7.95)	-1.28	28	0.21
IUS	43.18 (7.63)	45.15 (8.9)	0.65	28	0.52
STAI-State	47.41 (11.8)	49.46 (15.53)	0.41	28	0.68
SDS	21.3 (5.3)	19.3 (6.1)	-0.95	28	0.35
IQ	105.8 (7.45)	109.51 (10.6)	1.09	26	0.28

* $p < 0.05$ level (2-tailed)

TAU: Treatment As Usual; HRT: Habit-Reversal Treatment; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; MADRS: Montgomery–Åsberg Depression Rating Scale; IUS: Intolerance of Uncertainty Scale; STAI: The State-Trait Anxiety Inventory; SDS: Sheehan Disability Scale; IQ: Intelligence Quotient.

As can be seen in Table 1, groups solely differed in age, with HRT participants being significantly younger than those in the TAU group. This was caused by the software utilised by the NHS, which did not account for age. Subsequent analyses, therefore, were conducted using age as a control variable.

3.1.2. Stop-Signal Go/No-Go Task

Table 2 reports the performance on the SSGNG task for HRT and TAU participants. As can be seen, no group differences were found.

Table 2. *Stop Signal Go/No-Go Task results*

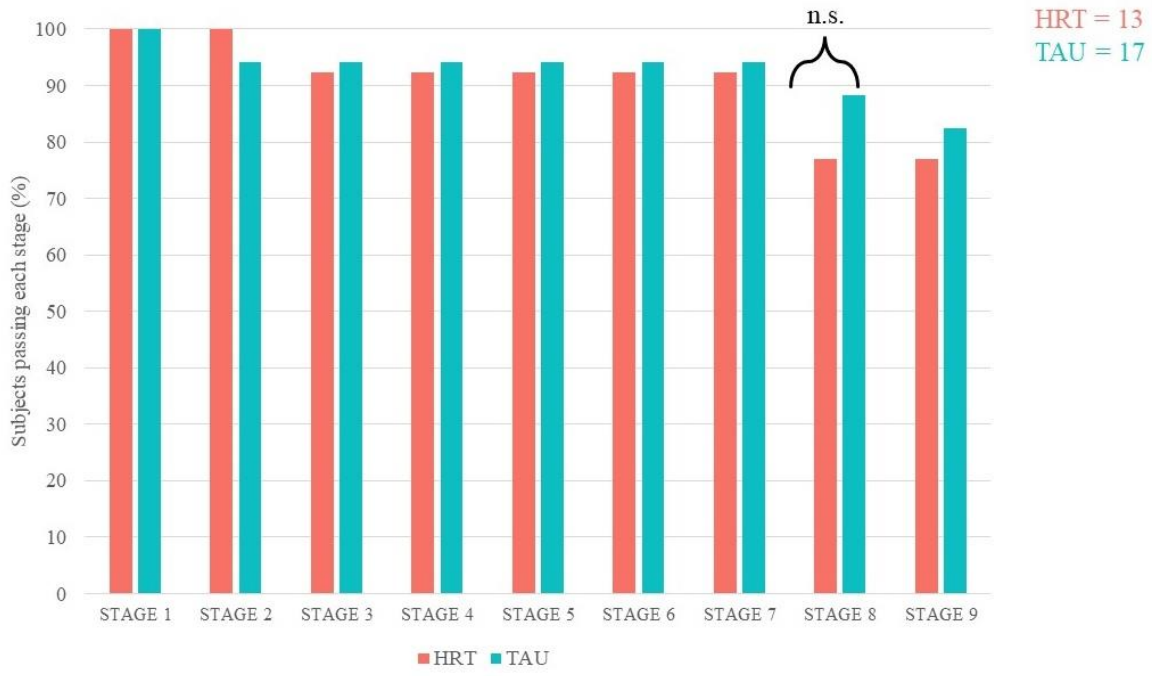
	TAU (n= 16)	HRT (n= 11)	t	df	p	d
Probability of responding to stop (%)	52.3 (4)	51.6 (4)	-0.42	25	0.68	-0.16
Probability of responding to No-Go (%)	10.6 (15)	15.4 (16)	0.82	25	0.42	0.32
Probability of error on Go (%)	2.9 (4)	7.6 (14)	1.30	25	0.2	0.51
Correct Go Reaction Time (ms)	431.06 (193.95)	368.87 (105.03)	-0.97	25	0.34	-0.38
SSD (ms)	208.06 (175.04)	155.43 (97.17)	-0.90	25	0.37	-0.35
SSRT (ms)	199.7 (31.18)	208.18 (20.92)	0.76	24	0.46	0.31

* $p < 0.05$ level (2-tailed).

3.1.3. Intra-Extra Dimensional Set Shifting Task

Figure 2 illustrates results of the IED task for both HRT and TAU groups. Statistical analyses did not reveal group differences on the Extra-Dimensional Shift (EDS, Stage 8) stage of the task, with $t(28)=0.19$, p=0.85, d=0.07, two-tailed.

Figure 2. *IED results*

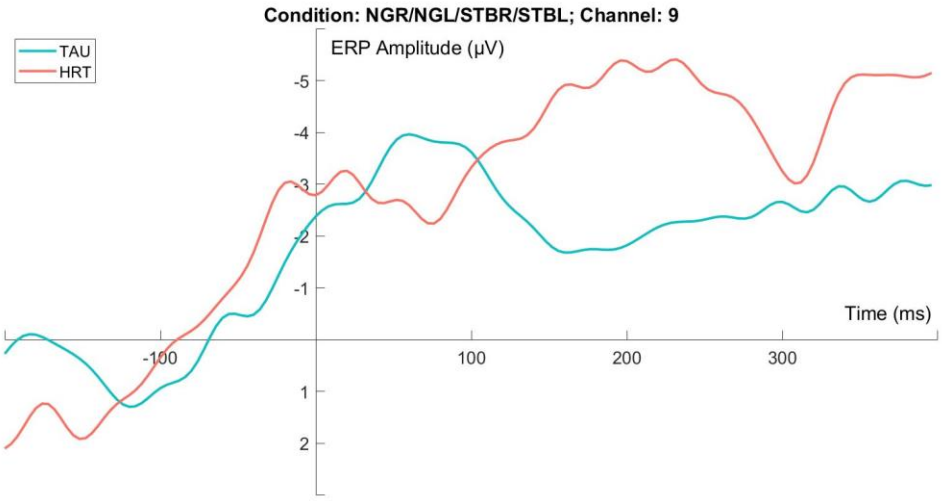


n.s.: not significant p>0.05.

3.1.4. Electroencephalographic results

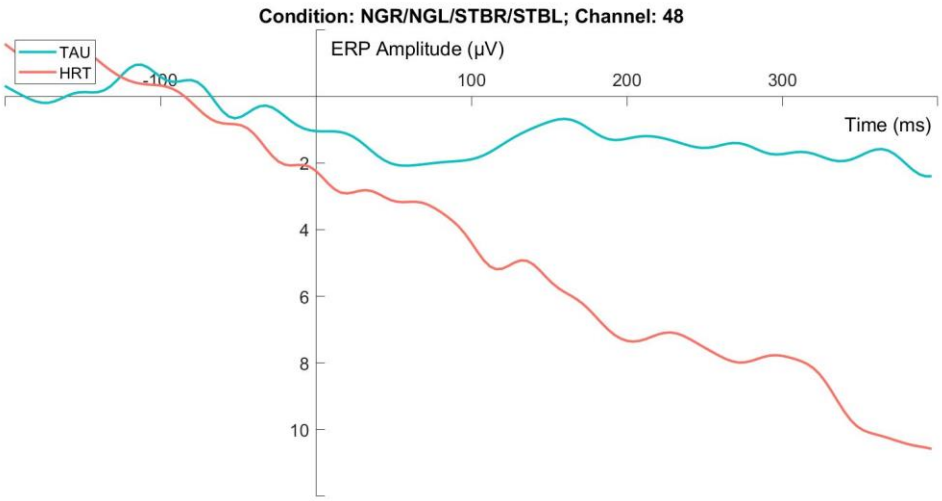
3.1.4.1. ERN

Analyses of the ERN were conducted on electrode Fz (channel 9), considering the mean amplitude between 0ms (erroneous response) and 100ms. Groups did not differ concerning the mean amplitude of ERN $t(15)=0.22$, p=0.83, d=0.11, two tailed. Means and standard deviations for TAU were M= -3.3(3.9) and for HRT M=-2.78(5.3).



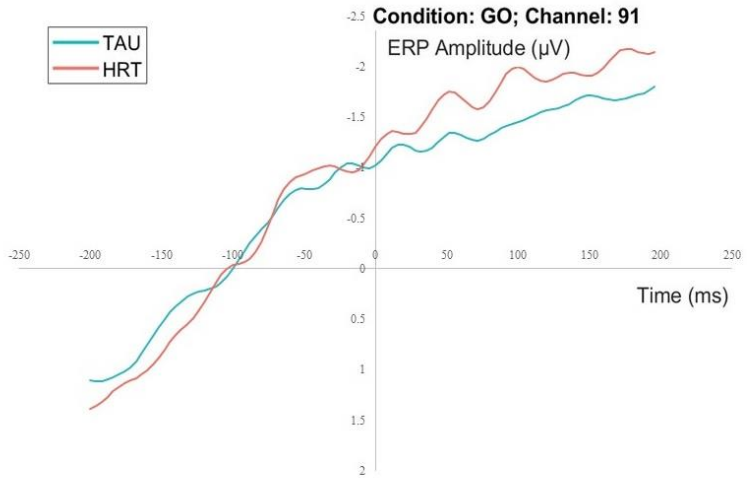
3.1.4.2. Pe

The error positivity (Pe) was calculated as the mean amplitude between 200ms and 400ms following an incorrect response (time 0ms), on electrode Pz (channel 48), where amplitudes were maximal. Statistical analyses did not reveal group differences in this ERP (Mann-Whitney U=29, *n*1=11, *n*2=6, p=0.73, d=-0.12, two-tailed). Means and standard deviations for TAU and HRT were M=1.26(1.7) and M=8.5(21.95), respectively.



3.1.4.3. RP

Finally, the readiness potential was calculated on electrode Cz (channel 91), as the mean amplitude between -100ms and 0ms (response locked) on Go trials, in order to assess motor preparation. Once again, groups did not differ $t(16)= 0.33$, p=0.75, d=0.16, two tailed. Means and standard deviations for TAU and HRT were M=-0.75(0.67) and M=-0.64(0.61) respectively.



3.2. Post-intervention between groups comparisons

3.2.1. Clinical measures

Table 3. *Post intervention clinical characteristics of TAU and HRT patients*

	TAU (n= 17)	HRT (n= 13)	t	df	p
YBOCS	20.65 (5.1)	22.23 (6.58)	0.74	28	0.46
MADRS	12.71 (8.44)	11.77 (6.15)	-0.34	28	0.74
IUS	39.25 (11.51)	43.31 (9.37)	1.024	27	0.31
STAI-State	41.7 (11.68)	44.45 (13.46)	0.68	27	0.5
SDS	19.37 (5.65)	14.38 (8.4)	-1.91	27	0.07

* $p < 0.05$ level (2-tailed)

TAU: Treatment As Usual; HRT: Habit-Reversal Treatment; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; MADRS: Montgomery–Åsberg Depression Rating Scale; IUS: Intolerance of Uncertainty Scale; STAI: The State-Trait Anxiety Inventory; SDS: Sheehan Disability Scale.

No differences between groups were found for the clinical measures.

3.2.2. Stop-Signal Go/No-Go Task

Table 4. *Post intervention Stop Signal Go/No-Go Task results*

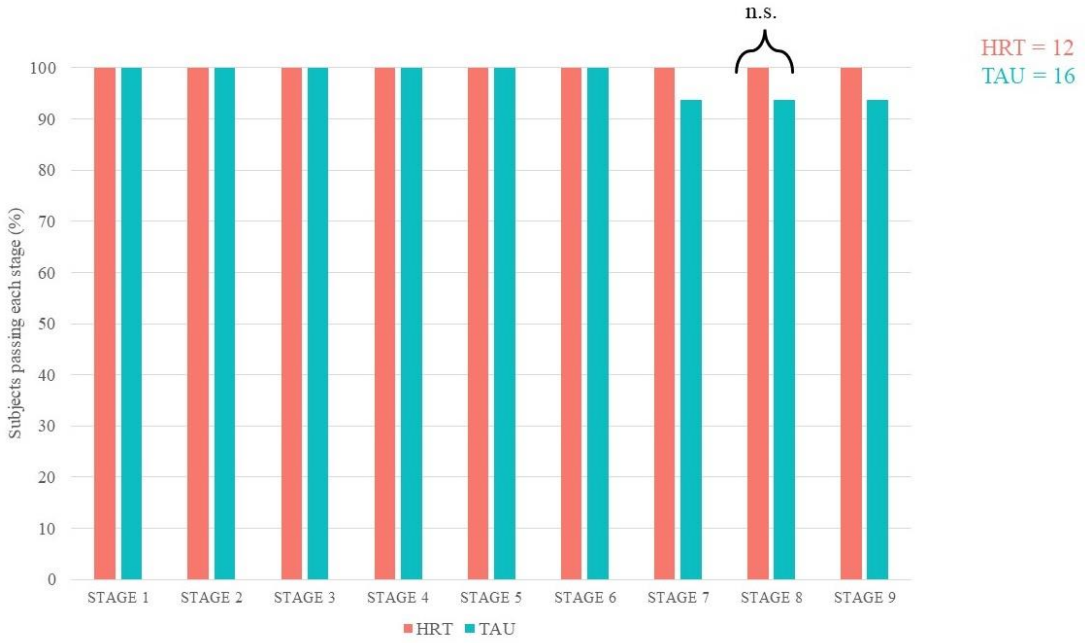
	TAU (n= 12)	HRT (n= 7)	t	df	p	d
Probability of responding to stop (%)	52.2 (5)	52.7 (2)	0.29	17	0.77	0.14
Probability of responding to No-Go (%)	12 (15)	19.8 (19)	1.01	17	0.33	0.48
Probability of error on Go (%)	2.8 (3)	4.8 (4)	1.17	17	0.26	0.56
Correct Go Reaction Time (ms)	453.43 (235.51)	347.63 (90.2)	-1.13	17	0.27	-0.54
SSD (ms)	250.57 (271.66)	137.51 (74.4)	-1.10	17	0.3	-0.51
SSRT (ms)	198.54 (20.35)	197.4 (15.3)	-0.12	16	0.9	-0.06

* $p < 0.05$ level (2-tailed).

As table 4 shows, no group differences were found for performance on the SSGNG task.

3.2.3. Intra-Extra Dimensional Set Shifting Task

Figure 3. *Post-intervention IED results*



n.s.: not significant p>0.05.

Results revealed no group differences on the extra-dimensional shift (stage 8) stage of the IED task $t(26)= -1.07$, p=0.3, d=-0.41, two-tailed.

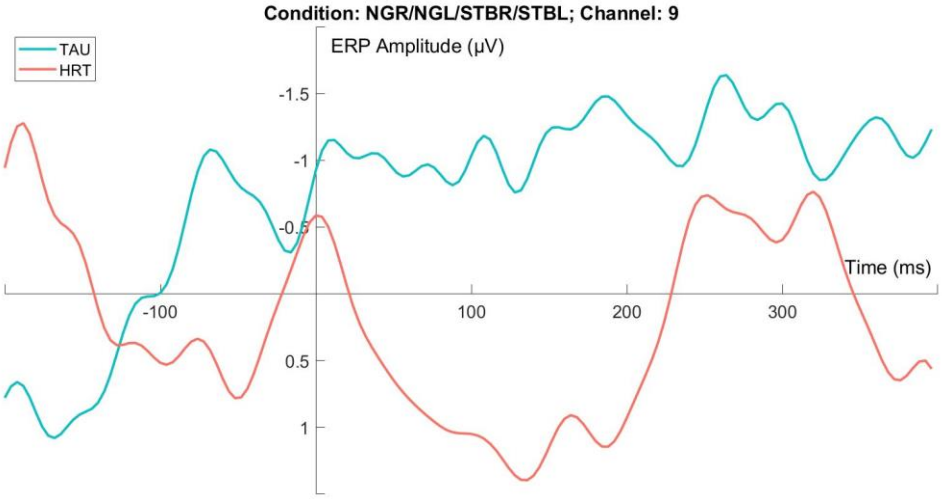
3.2.4. Electroencephalographic results

ERPs were calculated in the same manner as baseline results, considering fixed latencies mean amplitudes in electrodes of interest.

3.2.4.1. ERN

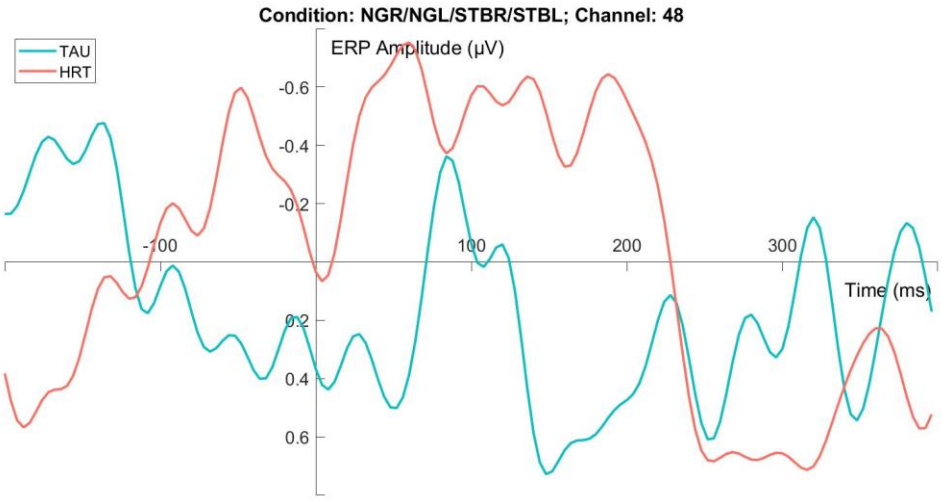
Mean amplitudes from response onset (0ms) to 100ms post-response on electrode Fz (channel 9) indicated no differences between groups $t(15)=1.28$, p=0.22, d=0.65, two-tailed.

Means and standard deviations for TAU and HRT were M=-0.98(2.21) and M=0.47(2.28), respectively.



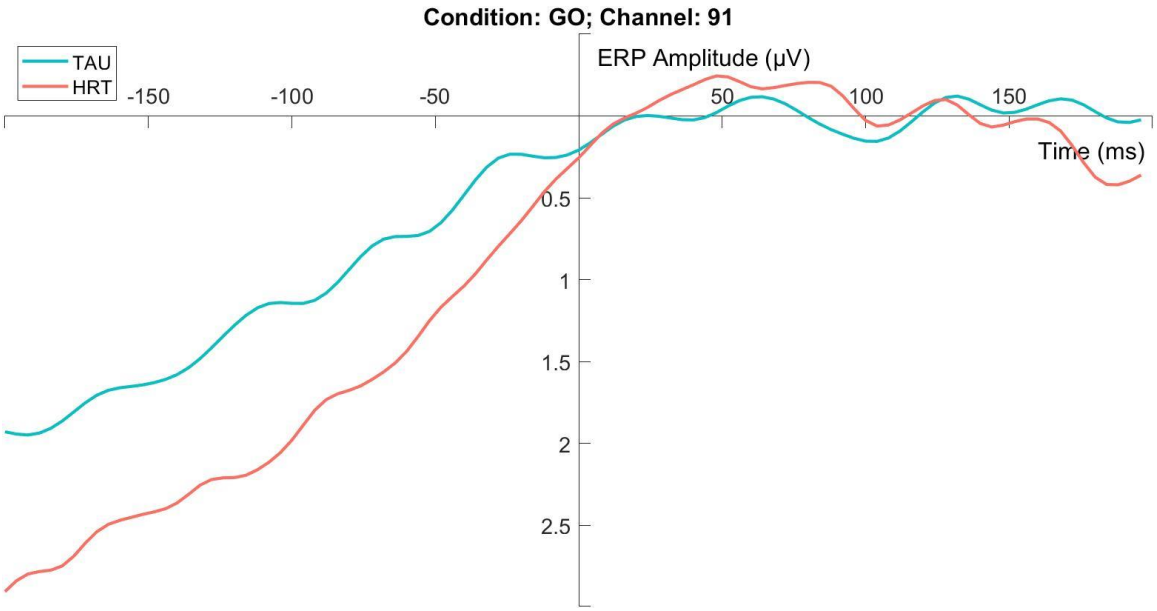
3.2.4.2. Pe

Mean amplitudes from 200ms to 400ms (response-locked) on electrode Pz (channel 48) indicated no differences between groups $t(15)=0.12$, p=0.9, d=0.06, two-tailed. Means and standard deviations for TAU and HRT were M=0.24(3) and M=0.39(1.16), respectively.



3.2.4.3. RP

Mean amplitudes from -100ms to 0ms (response-locked) on electrode Cz (channel 91) indicated no differences between groups $t(16)=0.8$, p=0.43, d=0.41. Means and standard deviations for TAU and HRT were M=0.62(1.55) and M=1.17(0.77), respectively.

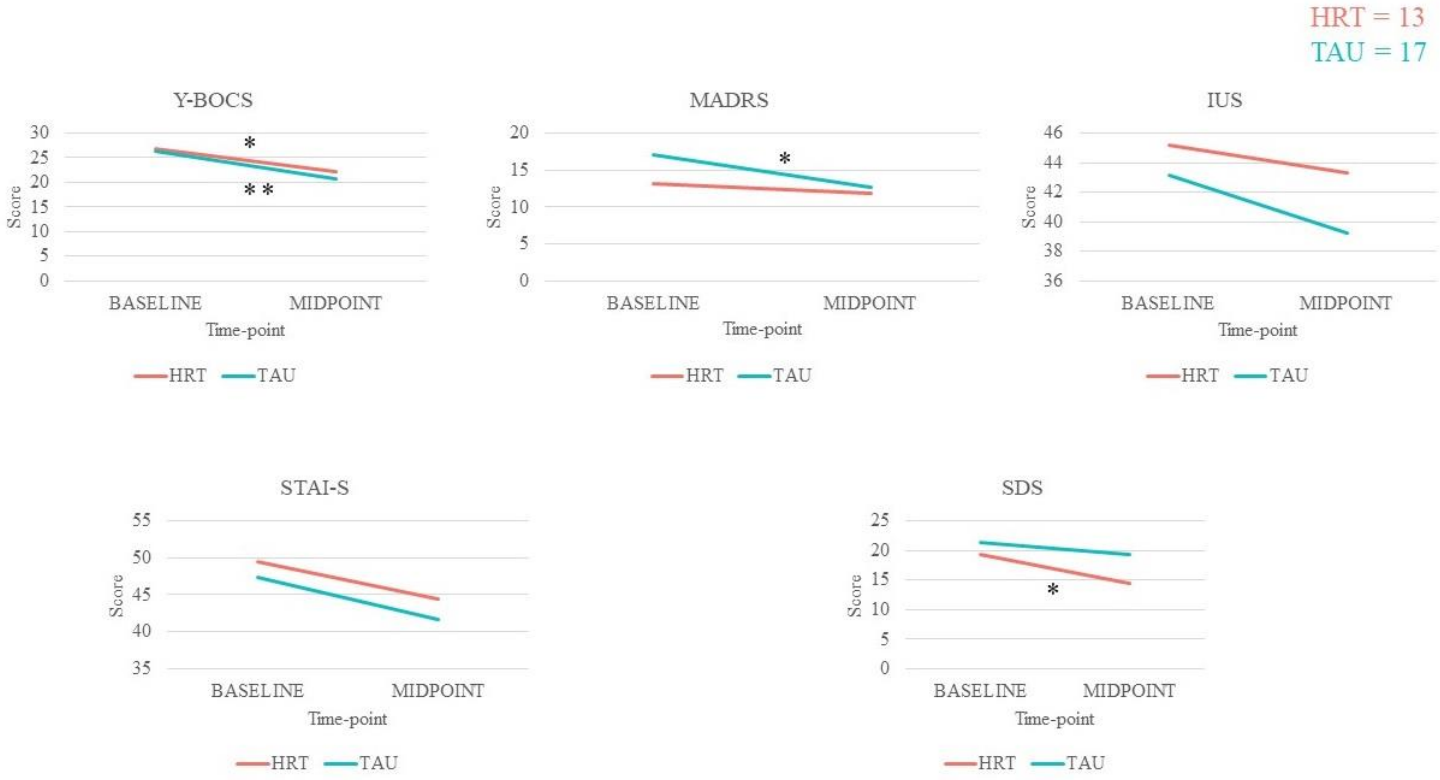


3.3. Post-intervention between and within groups comparisons

3.3.1. Clinical measures

Figure 4 depicts baseline and midpoint scores of clinical measures for both patient groups.

Figure 4. *Baseline vs midpoint comparison for HRT and TAU patients.*



*p < .05; **p < .001

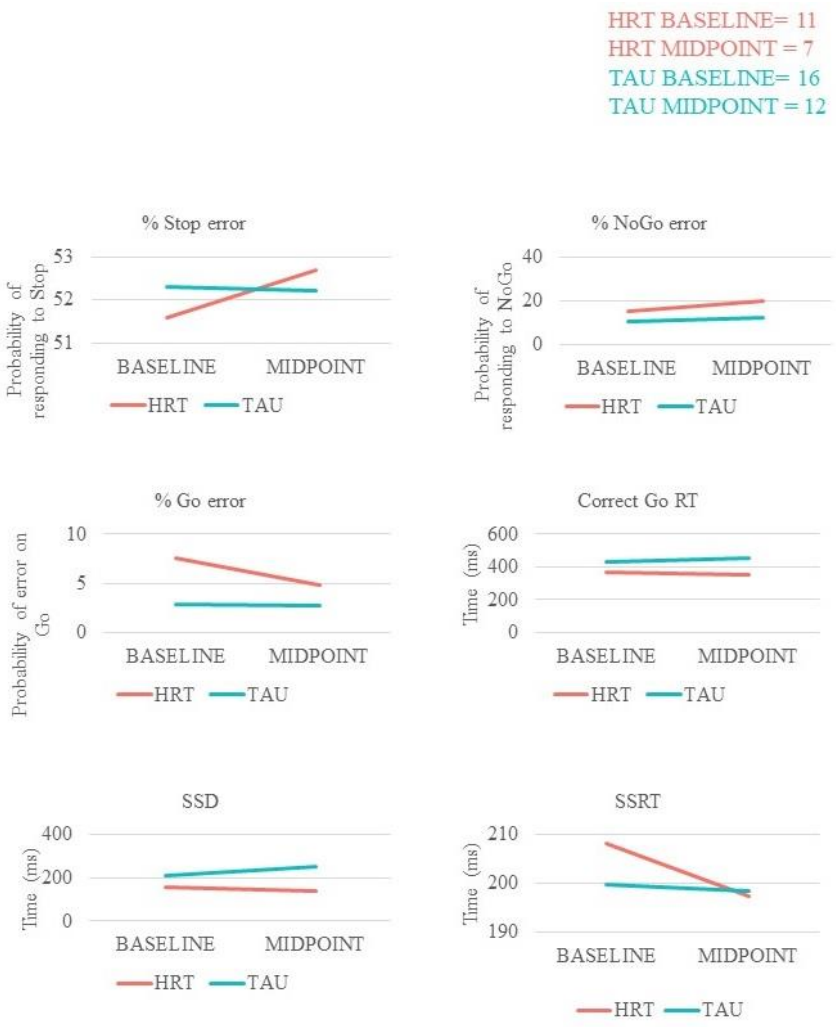
Paired-sample *t* tests revealed significant differences between baseline and midpoint scores of the YBOCS for HRT $t(12)=2.87$, $p=0.014$, $d=0.79$, two-tailed, and TAU patients $t(16)=4.24$, $p<.001$, $d=1.03$, two-tailed. Significant differences were also found on MADRS scores for the TAU group $t(16)=2.87$, $p=0.011$, $d=0.7$, two-tailed. The HRT group, conversely, presented significant differences on SDS scores $t(12)=2.3$, $p=0.04$, $d=0.64$, two-tailed. No other measures revealed significant differences.

Analysis of covariance showed no significant effect of time $F(1,27)=0.36$, $p=0.55$, $\eta^2=0.004$, or any interactions between time, age, or group on YBOCS scores. Alternatively, an interaction between time and age was found for MADRS scores $F(1,27)=7.3$, $p=0.012$, $\eta^2=0.032$. Both STAI-S and IUS revealed no effects of time or any interactions between time, age, or group $F(1,26)=0.24$, $p=0.63$, $\eta^2=0.003$, and $F(1,26)=0.004$, $p=0.95$, $\eta^2= <.001$, respectively. Finally, a significant effect of group was found for SDS scores $F(1,26)=4.95$, $p=0.035$, $\eta^2=0.11$.

3.3.2. Stop-Signal Go/No-Go Task

Figure 5 depicts baseline and midpoint performance on the SSGNG task for both groups.

Figure 5. *Baseline vs midpoint comparison of SSGNG performance for HRT and TAU*

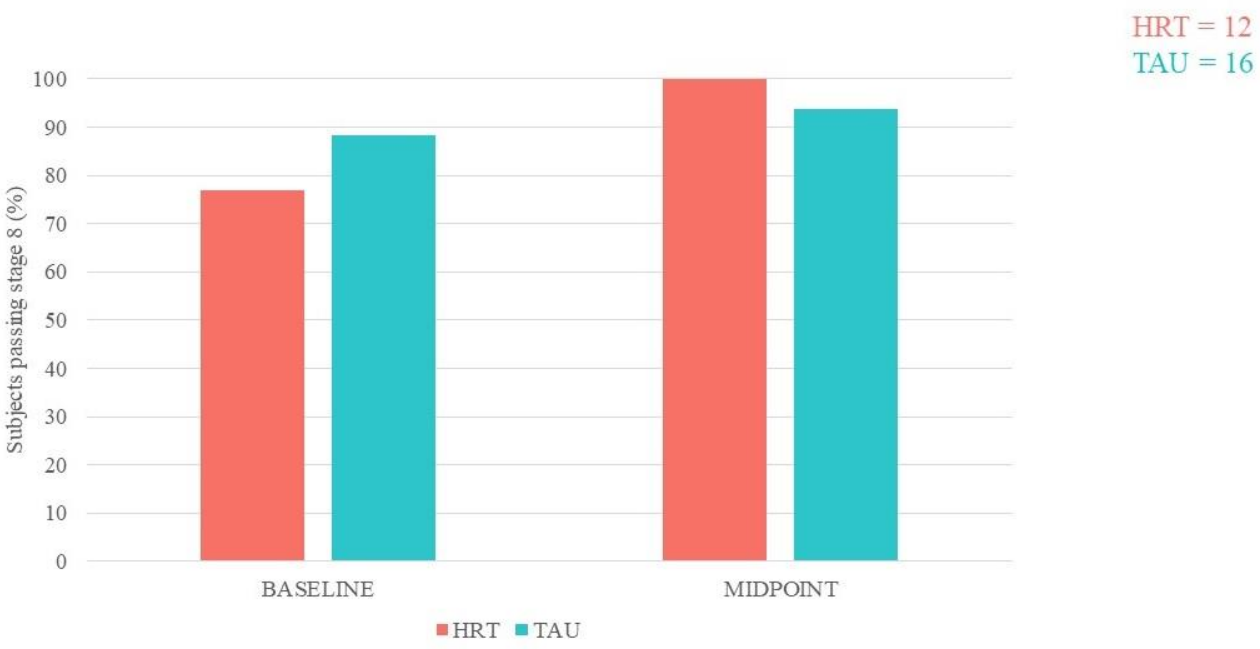


Analysis of covariance solely indicated significant differences on SSRT, with a main effect of age $F(1,14)=15.6$, $p=0.001$, $\eta^2=0.3$. No other effects were found for the remaining variables.

3.3.3. Intra-Extra Dimensional Set-Shifting Task

Results of the Extra-Dimensional Shift (EDS) stage of the IED are shown in figure 6.

Figure 6. *Baseline vs midpoint comparison of EDS for HRT and TAU patients*

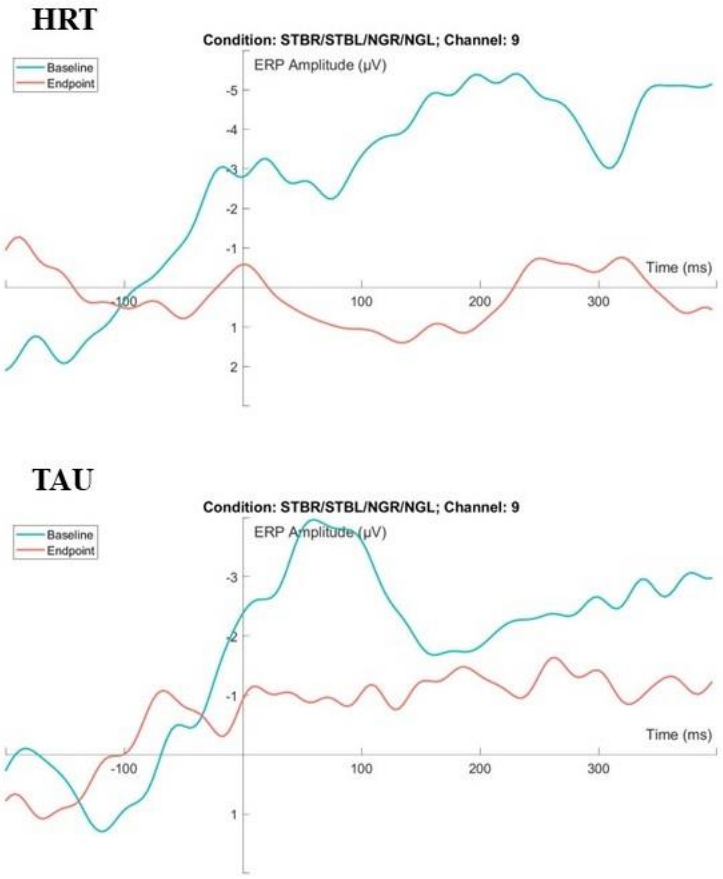


Analysis of covariance indicated a main effect of age between HRT and TAU subjects $F(1,25)=5.6$, $p=0.026$, $\eta^2=0.084$. No interactions between time, age, or group were found.

3.3.4. Electroencephalographic results

3.3.4.1. ERN

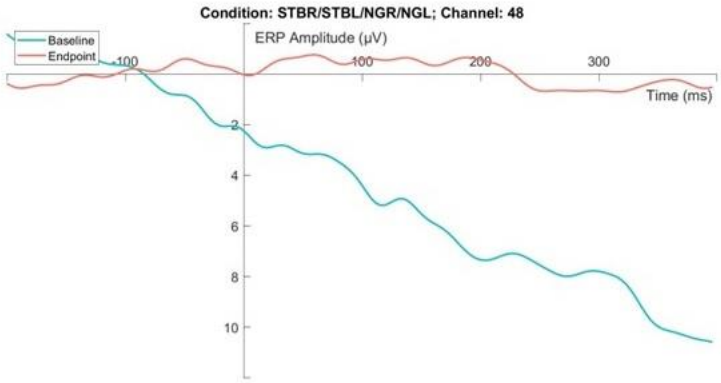
The analysis of covariance revealed a between subjects main effect of age on the amplitudes of the ERN $F(1,14)=6.01$, $p=0.028$, $\eta^2=0.154$. No interactions were found.



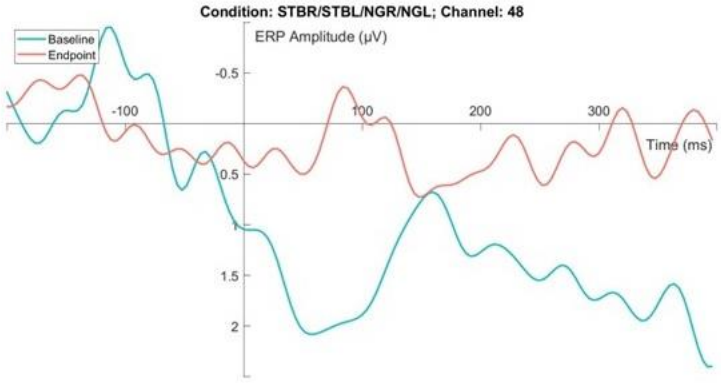
3.3.4.2. Pe

No significant effects or interactions were found for the amplitudes of the error positivity $F(1,14)=0.028$, $p=0.87$, $\eta^2<.001$.

HRT



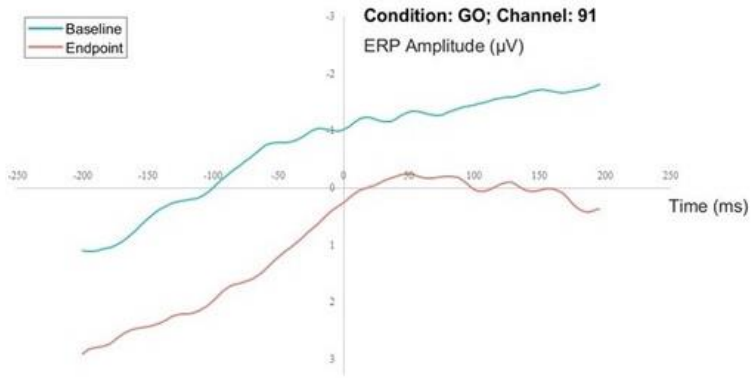
TAU



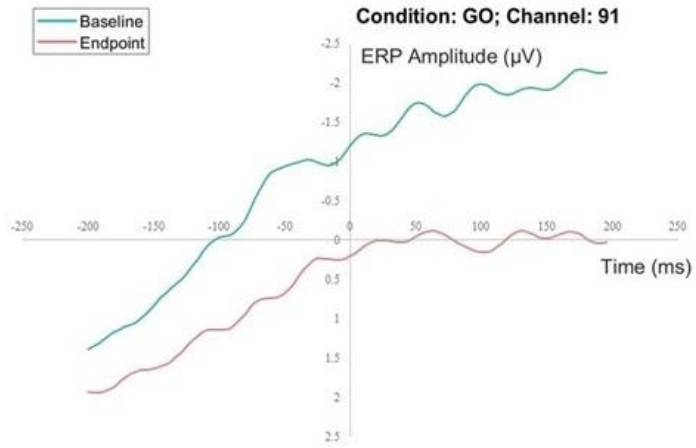
3.3.4.3. RP

Both a main effect of time F(1,15)=24.72, p<.001, η^2=0.31 and an interaction between time and age *F*(1,15)=12.97, p=0.003, η^2=0.16 were found for the readiness potential.

HRT

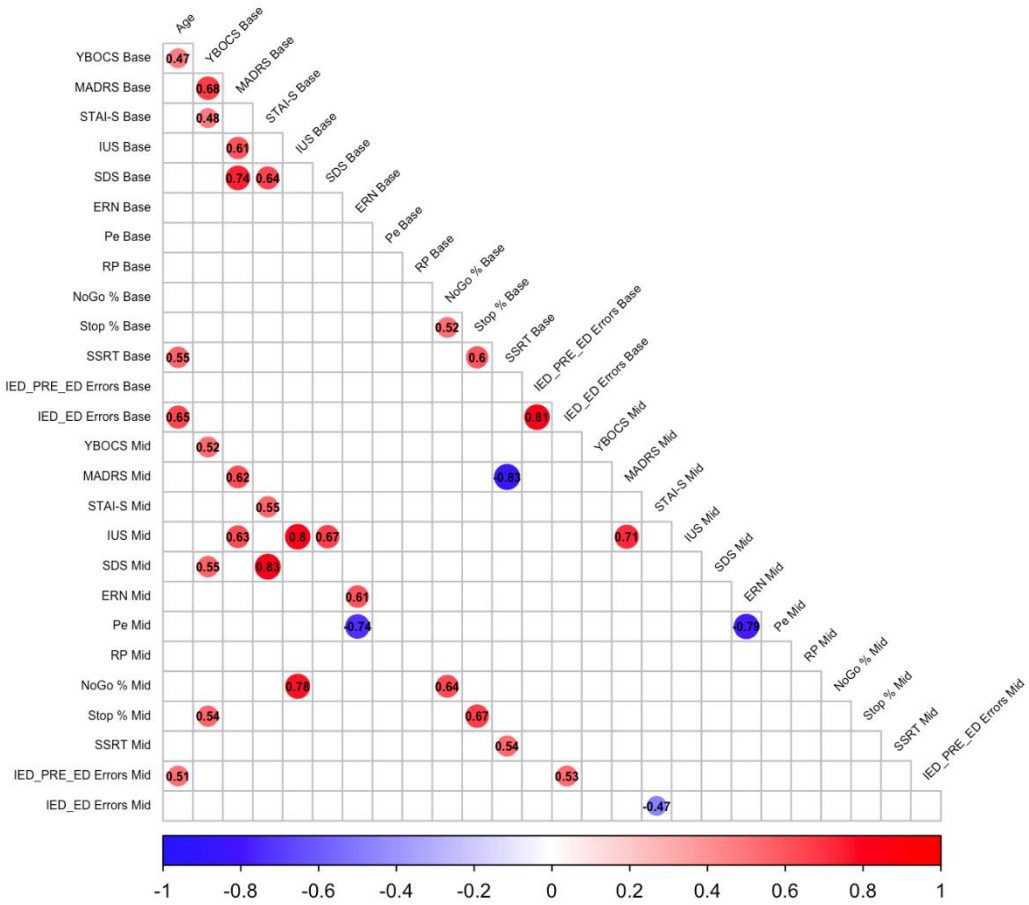


TAU



3.3.5. Correlations

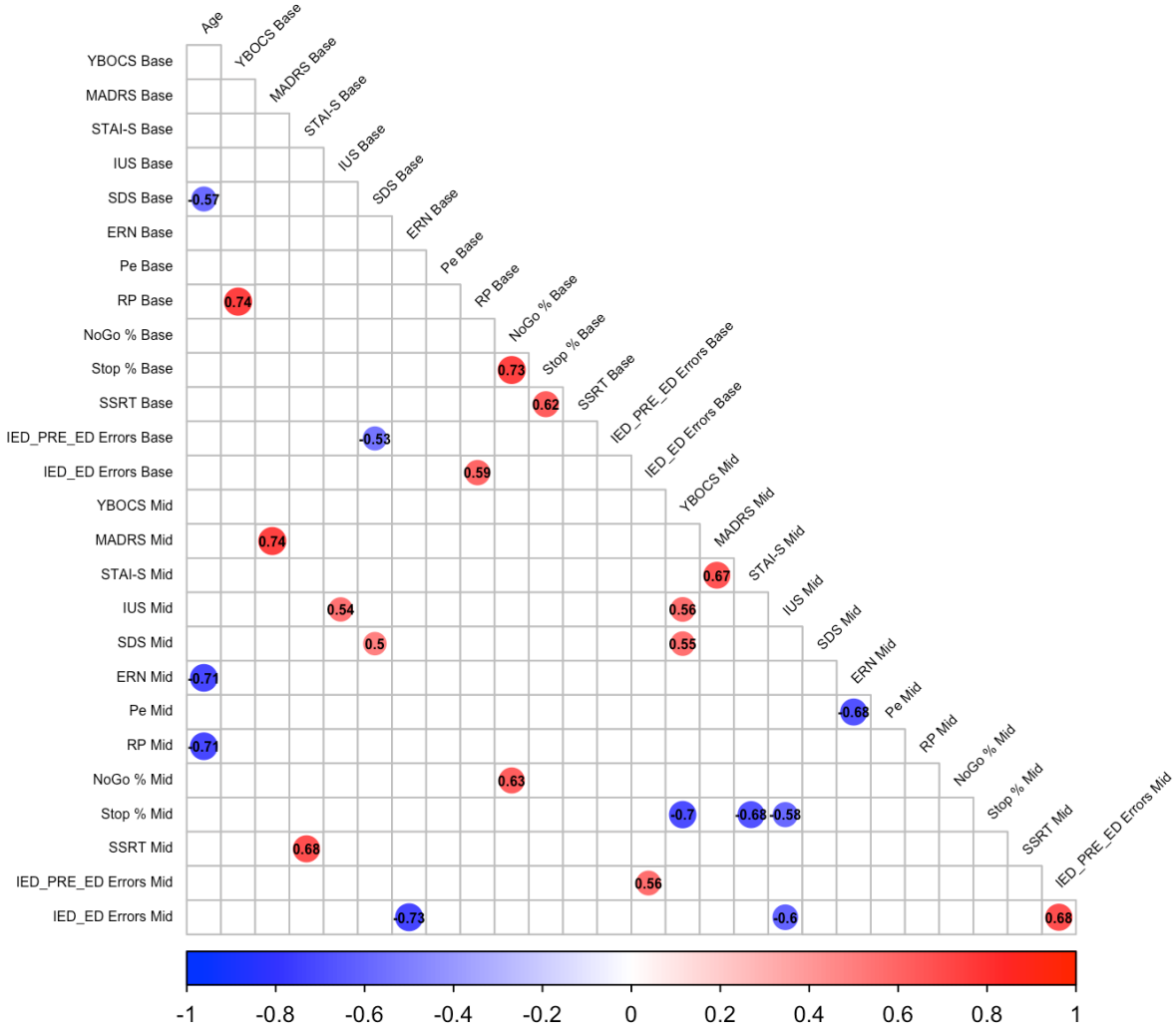
3.3.5.1. HRT



YBOCS: Yale-Brown Obsessive Compulsive Scale; IUS: Intolerance of Uncertainty Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; STAI-S: The State-Trait Anxiety Inventory-State; SDS: Sheehan Disability Scale; ERN_AMP: Amplitude ERN; Pe_AMP: Amplitude Pe; RP_AMP: Amplitude RP; NoGo %: probability of responding to NoGo; Stop %: probability of responding to Stop; SSRT: Stop-Signal Reaction Time; IED_PRE_Errors: Pre-ED errors IED; IED_ED_Errors: EDS errors IED; BASE: baseline; MID: midpoint.

As can be seen on the heatmap, significant correlations were found between YBOCS and performance on the SSGNG and IED tasks, indicating that severity of OCD symptoms is associated to impaired inhibition and cognitive flexibility. Additionally, higher scores on the Sheehan Disability Scale were associated to higher depression, anxiety, and severity of OCD symptoms, suggesting that disability is highly reported in relation to clinical discomfort, rather than behavioural performance.

3.3.5.2. TAU



YBOCS: Yale-Brown Obsessive Compulsive Scale; IUS: Intolerance of Uncertainty Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; STAI-S: The State-Trait Anxiety Inventory-State; SDS: Sheehan Disability Scale; ERN_AMP: Amplitude ERN; Pe_AMP: Amplitude Pe; RP_AMP: Amplitude RP; NoGo %: probability of responding to NoGo; Stop %: probability of responding to Stop; SSRT: Stop-Signal Reaction Time; IED_PRE_Errors: Pre-ED errors IED; IED_ED_Errors: EDS errors IED; BASE: baseline; MID: midpoint.

Correlations for the TAU group indicated strong negative associations between age and disability scores, ERN, and Pe amplitudes, suggesting that older individuals reported less functional impediments and presented more negative ERN (i.e. higher error monitoring) and RP amplitudes (enhanced motor preparation). The readiness potential was also correlated with higher OCD symptomatology, indicating that more severe patients present lower action tendencies. Finally, EDS errors were positively associated to RP amplitudes at baseline and negatively correlated with ERN amplitudes at midpoint, insinuating that higher control of

actions led to more errors at baseline and that EDS impairments at midpoint happened alongside higher error monitoring.

3.4. Summary of findings

- TAU improved symptom severity, depression, and attenuated the RP
- HRT improved symptom severity, quality of life, and attenuated the RP
- No improvement was found for the ERN and the Pe
- Behavioural measures did not improve following intervention
- HRT seems to be a tolerable and efficient treatment for OCD

4. Discussion

The present experiment aimed at investigating the effect of training a novel ritualised behaviour for habit-reversal treatment (HRT) in comparison with participants receiving cognitive-behaviour therapy (CBT) combined with exposure-response prevention (ERP) in OCD. Electroencephalographic, behavioural, and clinical measures were collected at baseline and after 6 weeks of intervention, in order to fully assess the efficacy of the intervention.

Results suggested that participants in the Treatment As Usual (TAU – CBT + ERP) group significantly improved in OCD symptomatology, as measured by the YBOCS, and presented a significant decrease in depression scores as per the MADRS questionnaire. Additionally, the intervention led to a reduction in the mean amplitude of the readiness potential, indicating that TAU can benefit behaviour control by altering motor preparedness neural signatures.

Interestingly, the HRT group also presented lower RP amplitudes following treatment, suggesting a reduction in the pre-SMA and SMA activation (Cavanna et al., 2017; Colebatch, 2007; Deecke, 1987; Deecke & Kornhuber, 1978; Kornhuber & Deecke, 2016). Indeed, research has shown that both CBT and practice of complex motor skills can attenuate the RP, reducing the effort demanded from the SMA (Deecke, 1995; Di Russo et al., 2005; Kristeva, 1984; Morand-Beaulieu et al., 2015, 2018, 2019; Wright et al., 2012). Evidence suggests that the RP is dependent upon complexity and duration of the motor task (Simonetta et al., 1991), which supports the findings of enhanced amplitudes in OCD, given the nature of compulsions (Dayan et al., 2017; Morand-Beaulieu et al., 2021).

Not surprisingly, the RP has not only been identified in the SMA and pre-SMA, but also in the basal ganglia, with one study observing this ERP in the caudate of all subjects (Rektor et al., 2001). Researchers propose that the readiness potential is evoked by pallido-thalamo-

cortical afferents subjected to dopaminergic control (Simpson & Khuraibet, 1987), which could explain its association to habitual behaviour (Graybiel, 1998; Haber, 2014).

A second account on the functional significance of the RP refers to sense of agency (Nahab et al., 2017). This phenomenon, which can be conceptualised as the perception of control over one's actions and their effect on the external world (Haggard, 2017), has been consistently reported as impaired in OCD (Reuven-Magril et al., 2008; Szalai, 2019). The notion of intentional binding is particularly relevant for this (Haggard et al., 2002). It refers to the perception that the temporal delay between the execution of a motor action and its environmental effect is shorter than its actual duration, promoting the feeling of 'I did this!' (Seghezzi & Zapparoli, 2020). In OCD, however, there seems to be a mismatch between actions and expected outcomes, a phenomenon termed 'prediction error' (Murray et al., 2019). The exaggerated prediction errors in OCD might shed light to the abnormal sense of agency seen in the disorder, which consequently affects intentional binding (Haggard et al., 2002). In addition, intentional binding seems to be reflected by the readiness potential and pre-SMA activity (Jo et al., 2014), an area responsible for attributing agency as well (Kühn et al., 2013; Nahab et al., 2017).

Research suggests that the SMA is also implicated in the generation of premonitory urges, the intrusive feeling that an action must be performed, also known as 'motivation-for-action' (Cavanna et al., 2017; Shephard et al., 2021). Whilst voluntary actions elicit binding effects (Haggard et al., 2002), automatic and non-intentional movements produce the opposite perception (Haggard et al., 2002), which corroborates the low sense of agency in OCD (Szalai, 2019). Indeed, premonitory urges seem to be distinct from the neural system implicated in the planning and execution of intentional, instrumental actions (Jackson & Bolger, 2014), adding evidence to the feeling that compulsions are performed involuntarily in OCD, which has been proven in tic disorders (Kwak et al., 2003). Furthermore, research suggests that movements disorders present a dysfunction in the sense of agency network, comprised by the pre-SMA and dlPFC (Nahab et al., 2017), regions highly relevant in the neurobiology of OCD (Graybiel & Rauch, 2000). Interestingly, premonitory urges seem to be preceded by the RP (Cavanna et al., 2017; Karp et al., 1996), which may explain why there is an intensification of the urge when individuals are stopped from performing the action (Kwak et al., 2003). The findings of lower RP following habit-reversal, hence, are not surprising, since premonitory urges seem to be reduced with habituation (Houghton et al., 2017).

Aside from lower RP amplitudes, the HRT group also showed a decrease in YBOCS and SDS scores. Albeit impossible to conclude with certainty, it is unlikely that the decrease of

YBOCS scores would have been caused simply by the passage of time, given the lack of a main effect of time or interactions found in the statistical analyses. It is possible, thus, that the reduction of the urges has affected quality of life and disability perception, which in turn reduced the severity of OCD symptoms. This is further corroborated by the strong correlation between disability and symptom severity found for the HRT group. Conversely, the findings of no improvement in disability for the TAU group seem to reflect the strains imposed by ERP, with high rates of dropout often attributed to the intensity and anxiety caused by the treatment (Franklin et al., 2000; Mantione et al., 2014).

Results from the ERN and Pe corroborated previous research and added evidence to the vast literature on error monitoring as a possible predisposing factor for OCD, impervious to treatment (Gillan et al., 2017; Perera et al., 2019; Riesel, 2019; Riesel et al., 2015, 2019; Vaghi, 2021). The lack of association between these components and clinical measures is also aligned with existing literature, which suggests that the ERN is independent from symptom severity and expression (Endrass et al., 2008; Lei et al., 2015; Riesel et al., 2014). Importantly, anxiety scores not only showed no correlations with ERPs, but also did not improve in any of the groups, challenging the common notion that OCD and error monitoring are driven by anxiety (Hajcak et al., 2003a; Meyer et al., 2012; Riesel et al., 2019).

Behavioural results, on the other hand, did not improve as per the original hypothesis, suggesting that neural changes precede behavioural manifestation. No within or between group differences were found for the SSGNG and IED tasks, albeit the latter revealed anecdotal improvement.

This study, notwithstanding, had limitations that should be considered. Firstly, the Coronavirus Disease (Covid-19) pandemic has significantly impacted data collection, which resulted in patients not assessed with electroencephalographic recordings at midpoint, hindering the ability to draw robust conclusions due to the small sample size. This has also affected the HRT patients more strongly, and the resulting sample was lower in this group. Nevertheless, procedures were adjusted so that the remaining measures could still be collected, minimising the loss of data.

It is important to note that the shift from in-person data collection to online and telephone-based measurements may have impacted the data, although evidence suggests that the IED, for instance, is equally reliable when compared between online and in-person (Leong et al., 2022). Finally, the use of a clinical room for electroencephalographic recordings may have introduced artifacts on the signal (Tatum et al., 2011), albeit attempts to minimise those were made through a careful pre-processing pipeline.

Despite those caveats, this study has been able in a preliminary way to demonstrate the tolerability and efficacy of HRT in OCD in comparison with TAU. Particularly, the findings of symptom improvement in both clinical arms, taken together with lower disability reported solely by the HRT group, shed light on the importance of addressing the regulation of sensorimotor activity in OCD (Morand-Beaulieu et al., 2019).

Given the findings of the study, which comprised two active patient groups, it was imperative to investigate the effects of the novel ritualised behaviour on healthy participants, matched with passive (no-intervention controls). Moreover, the lack of a passive OCD group compared to the HRT one hinders the possibility of addressing placebo and/or passage of time effects. The next chapter, therefore, presents results of a 2 X 2, four group study, investigating the effects of HRT in patients with OCD and matched controls, paired with the relevant passive groups.

CHAPTER 5 – NEUROCOGNITIVE, BEHAVIOURAL, AND SUBJECTIVE IMPACTS OF TRAINING ON A MOBILE APPLICATION IN OCD AND CONTROLS

Until I know this sure uncertainty,

I'll entertain the offered fallacy

The Comedy of Errors, Act II, Scene 2

William Shakespeare

1. Introduction

Hobson et al (2018) have defined rituals as repetitive, non-goal directed actions that are performed with the aim to impact the environment despite lacking a direct connection with it, a definition that could also potentially describe compulsive behaviour. With both constructs sharing rather similar definitions, what is it that makes rituals adaptive and performance-enhancing (Damisch et al., 2010; Dömötör et al., 2016), and compulsions maladaptive and distressful (American Psychiatric Association, 2013)?

Rituals and compulsions, often used as synonyms, are common and natural behaviours that range from 'normal' and 'healthy' to 'abnormal' and 'clinical' (Hobson et al., 2018; Muris et al., 1997). A plethora of theories have been proposed to explain this common dimensionality between healthy and deleterious behaviours, but it seems that the key difference between them refers to belief (Dulaney & Fiske, 1994). Although not only similar in definition, but also in behavioural expression (Graybiel, 2008; Muris et al., 1997), rituals involve superstitious beliefs (i.e. illusory or 'magic' thinking style of applying causality to unrelated events) (Brooks et al., 2016; Hobson et al., 2017), whereas compulsions in Obsessive-Compulsive Disorder (OCD) are often ego-dystonic, with patients being aware of the lack of connection between them and the expected outcomes (Jacob et al., 2014; Vaghi, Luyckx, et al., 2017). Another striking dissimilarity relates to how habitual are these two behavioural responses. Whilst both rituals and compulsions can be performed to relieve anxiety, the former tends to be conducted solely in contexts where a positive outcome is expected (prior to an important football game, for instance) (Dömötör et al., 2016; Schippers & Van Lange, 2006), and the latter occurs based on a stimulus-response (S-R) association (Dickinson & Balleine, 1993; James, 1890; Robbins et al., 2019). Indeed, research suggests that the higher the levels of stress, anxiety, and uncertainty, the more individuals engage in ritualistic behaviour, in an attempt to control the

environment and regulate negative emotions (Brooks et al., 2016; Damisch et al., 2010; Dömötör et al., 2016; Hobson et al., 2017, 2018; Schippers & Van Lange, 2006). Performing rituals, therefore, not only boosts confidence and feelings of self-efficacy (Brooks et al., 2016; Damisch et al., 2010), but also provides a reward in itself, as completing a sequence of rigid motor actions satisfies a natural need for order (Hobson et al., 2018) and allows the individual to regain control of the environment by returning to a state of 'low-entropy', in which the amount of uncertainty is reduced to a manageable level (Hirsh et al., 2012). In OCD, however, compulsions are not associated to positive outcomes (in fact, they tend to be performed to avoid negative ones), lack symbolic meaning, and are solely executed as an attempt to reduce anxiety, which paradoxically increases negative affect (Fradkin et al., 2020; Hobson et al., 2018; Robbins et al., 2012). Finally, a third and crucial distinction between rituals and compulsions relates to voluntary control. Whilst rituals are voluntarily performed to increase confidence and feelings of luck (Brooks et al., 2016; Hobson et al., 2018; Schippers & Van Lange, 2006), compulsions are manifested as intrusive urges that can only be delayed with difficulty, at the expense of great effort (Storch et al., 2015).

Treatment strategies for OCD have, therefore, focused on preventing compulsions from being performed, with Exposure-Response Prevention (ERP) figuring as the ‘gold-standard’ technique (Koran et al., 2007; Patel et al., 2021). Albeit being efficient (Franklin et al., 2000; Hezel & Simpson, 2019), ERP training relies on habituating the individual to the anxiety elicited by the exposure to the feared situation (Tryon, 2005), which is often perceived by patients as extremely intense or intolerable (Mantione et al., 2014; Whittal et al., 2005) and configures a reason for treatment drop-out (Franklin et al., 2000). In light of these challenges, it is imperative to investigate techniques that could function as alternatives to compulsions, although effectively alleviating anxiety.

One potential candidate can be derived from the motor components of OCD. Akin to ritualistic performance, in which completing the rigid and repetitive sequence of actions promotes anxiety relief (Hobson et al., 2018), it would be possible to infer that novel ritualistic behaviours would also generate a soothing effect in OCD by engaging the very motor circuitry responsible for the urges seen in the disorder (Shephard et al., 2021). Tentative evidence for this comes from Habit-Reversal Treatment (HRT) studies (see Chapter 4), reporting that compulsions can be replaced by non-maladaptive habits (Lee et al., 2019), particularly when sensory urges are present (Shephard et al., 2021).

Indeed, a majority of patients with OCD report sensory phenomena (Miguel et al., 2000; Shavitt et al., 2014), which consist of subjective experiences that accompany or precede

compulsions (i.e. urges) (Jackson et al., 2011; Shephard et al., 2021; Stern et al., 2020). In addition, some patients report performing compulsions to achieve a sense of completeness or the 'just right' feeling (Fornés-Romero & Belloch, 2017), compatible with the sensorimotor account of OCD (Ferreira et al., 2017; Miguel et al., 2000; Szalai, 2019). It seems, thus, that completing ritualised behaviours provides rewarding effects on its own (Ferreira et al., 2017; Hobson et al., 2018), rather than serving a purpose of alleviating anxiety or 'bringing luck' (Shephard et al., 2021).

A second rewarding aspect of performing rituals/compulsions relates to intolerance of uncertainty. This key component of OCD (Fradkin et al., 2020; Pinciotti et al., 2021) is closely associated with the need for certainty and control seen in the disorder (Linkovski et al., 2021; Moulding & Kyrios, 2007; Olatunji et al., 2008; Tolin et al., 2003; Wheaton et al., 2010), and has been proposed as an explanation for the maintenance of repetitive behaviours with non-instrumental purpose (Reuven-Magril et al., 2008).

Taken together, evidence suggests that repetitive, ritualistic behaviours may, paradoxically, benefit the treatment of OCD, if performed in a context dissociated from compulsions. Evidence for this has been presented on chapter 4, where two groups of patients receiving either Treatment as Usual (TAU) or Habit-Reversal Treatment (HRT) were assessed, with both decreasing YBOCS scores. That experiment, however, lacked a comparison OCD group receiving no-intervention, therefore hindering robust conclusions regarding the treatments. Additionally, the absence of a control group prevented the evaluation of the effect of rituals in healthy participants. This study, thus, was designed to assess the impact of a mobile application involving rigid and repetitive movements on cognitive, neural, and clinical measures in a sample of patients with OCD and matched healthy volunteers, tested twice over the period of a month. Participants were additionally subdivided in groups training the novel behaviours and groups receiving no-intervention, to account for the effects of passage of time and placebo, a common effect in OCD (Carpenter et al., 2018; Kotzalidis et al., 2019). Importantly, the rigid action sequences were not introduced as rituals, in order to prevent confounding effects of previous beliefs involving those. Prior research has adopted this approach and found that rituals effectively impacted individuals despite belief (Hobson et al., 2017; Norton & Gino, 2014). It was expected that both healthy participants and patients with OCD training the ritualistic behaviours would show improved performances on error-monitoring and motor preparedness measures, as well as on OCD symptomatology, anxiety, and intolerance of uncertainty scores.

2. Methods

2.1. Participants

Thirty healthy volunteers (HV) and thirty-six individuals with OCD completed both sessions of the study. Participants in each group (HV vs OCD) were further subdivided into groups training the mobile application (APP group) and groups receiving no-intervention (NO-APP group). The final sample was, thus, composed of 15 HV-APP vs 15 HV-NO-APP, and 22 OCD-APP (N=13 from the NHS trial – see Chapter 4) vs 14 OCD-NO-APP.

Participants were recruited via posters and social media and invited to complete a screening assessment prior to their participation in the study. Inclusion criteria established that participants: (i) should be aged between 18-65 years; (ii) should have OCD as a primary diagnosis (for the patient group); and (iii) should present scores equal or above 16 on the Y-BOCS rating scale. Exclusion criteria were: (i) presence of neurological disorders or head trauma; (ii) substance abuse (alcohol or recreational drugs); (iii) presence of motor disorders or tics; (iv) presence of epilepsy or use of anticonvulsants; (v) use of psychotropic medication in the healthy volunteers group; and (vi) presence of psychiatric diagnoses in the control group. Screening was conducted by a trained researcher (participants recruited in Cambridge) or by a clinician (patients from the NHS trial), and comprised the Modified Mini Interview (OASAS, 2002) for Cambridge participants, the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) (participants from the NHS trial), the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989), the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979), the Obsessive-Compulsive Inventory (OCI) (Foa et al., 2002) and demographic questions.

Participants in the OCD group were medicated as follows: (i) sertraline (N=11); (ii) fluoxetine (N=4); (iii) citalopram (N=3); (iv) escitalopram (N=2); (v) paroxetine (N=2); (vi) non-specified SSRI (N=2); (vii) clomipramine (N=1); (viii) quetiapine (N=1); (ix) venlafaxine (N=1); (x) pregabalin (N=1); (xi) beta-blockers (N=1); (xii) non-specified medication (N=1). Nine patients were unmedicated. Table 1 depicts the clinical and demographic characteristics of the sample.

2.2. Materials and procedures

Eligible participants were invited for the first session of the study, which had a duration of approximately 2h. Prior to attending the session, though, individuals were asked to comply with the pre-testing instructions (see Chapter 2 for details). Upon arrival for the assessment, all

participants signed the Informed Consent Form and were reassured that they were able to withdraw from the study at any time, with no penalties. The testing initiated solely following agreement to the terms of the Consent Form.

The testing session consisted of the electroencephalographic (EEG) recordings, performed whilst participants undertook the Stop-Signal Go/No-Go Task (SSGNG) (see Chapter 2 for details). Additionally, participants completed the National Adult Reading Test (NART) (Nelson & Willison, 1991), the state form of the State-Trait Anxiety Inventory (STAI-S) (Spielberger et al., 1970), and the Intra-Extra Dimensional Set-Shifting Task (IED) (Cambridge Neuropsychological Test Automated Battery (CANTAB), Cambridge Cognition). Details of these measures can be found in chapter 2.

Finally, participants were assigned either to the 'APP' or to the 'NO-APP' condition. Subjects in the experimental condition were, thus, trained on the mobile application and told that acquiring automaticity on the app was essential prior to the second session. A detailed description of the app can be found in chapter 2.

Training of the participants on the 'APP' condition was monitored daily, and individuals were only invited for the second session if they had complied with the minimum required practices. The second testing session was, therefore, scheduled after a month of daily app training or no intervention.

The session was identical to the previous one, to allow for comparisons between baseline and endpoint, with the exception of a questionnaire completed uniquely by the 'APP' group, assessing their experiences when training the novel behaviours. Data on these qualitative measures are depicted in Figure 16. Additionally, all participants completed a set of self-report questionnaires through Qualtrics, comprising: (i) the trait form of the State-Trait Anxiety Inventory (STAI-T) (Spielberger et al., 1970); (ii) the Big-Three Perfectionism Scale (Smith et al., 2016); (iii) the Intolerance of Uncertainty Scale (IUS) (Carleton et al., 2007); (iv) the Creature of Habit Scale (COHS) (Ersche et al., 2017); (v) the Habitual Tendencies Questionnaire (HTQ) (Ramakrishnan et al., 2022); (vi) the Self-Control Scale (SCS) (Tangney et al., 2004); (vii) the Habitual Self-Control Questionnaire (HSCQ) (Schroder et al., 2013); and (viii) the Padua Inventory (Burns et al., 1996). Detailed descriptions of these measures can be found in chapter 2. Tables 2a and 2b depict data of the self-report questionnaires. Finally, participants in the OCD group completed a second Y-BOCS interview with the trained researcher/clinician, which enabled the assessment of the efficacy of the app.

For a clear understanding of the findings, data will be presented by time-points (baseline and endpoint), and finally by a combination of both. Between-subject analyses (HV vs OCD)

will be reported for baseline and endpoint, in order to illustrate how groups contrasted before and after the intervention. Considering that analyses of variance including the four groups would be uninformative, remaining analyses will focus on within, rather than on between-subject results, as the main goal of this study was to evaluate the impact of the mobile application in HV and OCD samples. A summary of the relevant findings is provided at the end of the results section.

3. Results

3.1. Baseline comparisons

3.1.1. Salient between-group comparisons

Table 1. *Significant baseline clinical, behavioural, and electroencephalographic characteristics of OCD and HV participants*

	HV (n= 30)	OCD (n= 36)	t	df	p
MADRS[a]	5.3 (4.2)	15 (9.5)	160.500	61	**< .001**
STAI-State[a]	27.2 (7)	41.1 (12.7)	114.000	60	**< .001**
STAI-Trait	35.6 (9.7)	56.4 (10.7)	-7.2	48	**< .001**
IUS	22.9 (8.4)	41.2 (9.3)	-8.3	64	**< .001**
OCI-12[a]	3.2 (4.3)	18.4 (8.6)	27.500	51	**< .001**
% Responding to stop signal	48.9 (7.1)	52.4 (5.6)	-2.2	61	**0.03**
ERN amplitude	0.38 (5)	-4.3 (6.7)	3.14	61	**0.003**

* $p < 0.05$ level (2-tailed). [a] Levene's test is significant, therefore equal variances were not assumed.

HV: Healthy volunteers; OCD: Obsessive-Compulsive Disorder; MADRS: Montgomery–Åsberg Depression Rating Scale; IUS: Intolerance of Uncertainty Scale; STAI: The State-Trait Anxiety Inventory; OCI: Obsessive-Compulsive Inventory.

As table 1 shows, patients with OCD and controls differed on most clinical measures, as well as on behavioural performance on the SSGNG task. Patients also exhibited significantly increased ERN amplitudes. No differences were found for the other ERP components or behavioural measures. Subsequent results will focus on intra-group comparisons, to enable the assessment of prior differences between participants.

3.1.2. Baseline within groups demographic and clinical data

Demographic and clinical characteristics of the four groups are depicted in tables 1a (HV) and 1b (OCD).

Table 1a. *Baseline demographic and clinical characteristics of HV-APP and HV-NO-APP participants*

	HV-APP (n= 15)	HV-NO-APP (n= 15)	t	df	p
Gender ratio (male/female)	6/9	5/10	X^2= 0.14	1	0.71
Age	33.87 (13.5)	38.13 (16.21)	0.78	28	0.44
MADRS	3.73 (3.36)	7.25 (4.5)	-2.34	25	**0.03**
STAI-State[a]	24.64 (3.59)	30.17 (8.79)	52.500	24	0.11
STAI-Trait	31.87 (8.75)	40.33 (8.98)	-2.47	25	**0.02**
IUS[a]	20.80 (5.44)	24.93 (10.44)	93.000	28	0.43
OCI-12	3.13 (3.29)	3.33 (5.26)	-0.13	28	0.9
IQ	111.11 (6.18)	114.07 (9.47)	-0.99	27	0.33

* $p < 0.05$ level (2-tailed). [a] Levene's test is significant, therefore equal variances were not assumed.

HV: Healthy volunteers; MADRS: Montgomery–Åsberg Depression Rating Scale; IUS: Intolerance of Uncertainty Scale; STAI: The State-Trait Anxiety Inventory; OCI: Obsessive-Compulsive Inventory.

As can be seen in Table 1a, the HV group was matched in age, gender, and IQ, yet differing on depression and trait anxiety, with the NO-APP group presenting higher scores on these measures.

Table 1b. *Baseline demographic and clinical characteristics of OCD-APP and OCD-NO-APP participants*

	OCD-APP (n= 22)	OCD-NO-APP (n= 14)	t	df	p
Gender ratio (male/female)	8/14	6/8	X^2= 0.15	1	0.7
Age	31.82 (10.47)	31.43 (10.4)	0.11	34	0.91
YBOCS	23.7 (6.17)	22.9 (6.25)	0.39	34	0.7
MADRS[a]	12.3 (7.3)	19.3 (11.13)	95.000	34	0.06
STAI-State[a]	43.3 (14.81)	37.7 (7.82)	181.000	34	0.39
STAI-Trait	56.33 (9.46)	56.43 (11.72)	-0.02	21	0.98
IUS	42.6 (8.9)	38.93 (9.7)	1.16	34	0.25
IQ	110.6 (8.8)	110 (7.4)	0.22	33	0.83

* $p < 0.05$ level (2-tailed). [a] Levene's test is significant, therefore equal variances were not assumed.

OCD: Obsessive-compulsive disorder; Y-BOCS: Yale-Brown obsessive-compulsive scale; MADRS: Montgomery–Åsberg Depression Rating Scale; IUS: Intolerance of Uncertainty Scale; STAI: The State-Trait Anxiety Inventory.

Results of the OCD sample, conversely, showed no differences between APP and NO-APP groups in any of the measures.

3.1.3. Baseline within groups self-report questionnaires

Results of the self-report questionnaires for all groups can be found in tables 2a (HV) and 2b (OCD).

Table 2a. *Self-report questionnaires of HV-APP and HV-NO-APP participants*

	HV-APP (n= 15)	HV-NO-APP (n= 15)	t	df	p
COHS-R	43.93 (9.23)	50.4 (7.02)	-2.16	28	**0.039**
COHS-A	27.67 (8.47)	26.47 (6.21)	0.44	28	0.66
HTQ	32.47 (7.3)	35.92 (10.53)	-1	25	0.33
HSCQ	48.47 (8.38)	49.2 (5.23)	-0.29	28	0.78
SCS	130.53 (15.67)	130 (17.24)	0.09	28	0.93
PADUA	50.89 (10.52)	49.86 (12.16)	0.18	14	0.86

* $p < 0.05$ level (2-tailed).

COHS-R: Creature of Habit - Routine; COHS-A: Creature of Habit - Automaticity; HTQ: Habitual Tendencies Questionnaire; HSCQ: Habitual Self-Control Questionnaire; SCS: Self-Control Scale

Results of the self-report questionnaires indicated significantly higher routine scores for the HV-NO-APP group, with the remaining questionnaires not differing between groups.

Table 2b. *Self-report questionnaires of OCD-APP and OCD-NO-APP participants*

	OCD-APP (n= 9)	OCD-NO-APP (n= 14)	t	df	p
COHS-R	52.8 (9.3)	54.93 (12.44)	-0.44	21	0.66
COHS-A	36.9 (9.43)	35.93 (7.82)	0.27	21	0.79
HTQ	55.7 (6.8)	54.1 (7.4)	0.52	21	0.61
HSCQ	43.6 (9.2)	41.1 (12.32)	0.52	21	0.61
SCS	115 (18.8)	114.4 (21.5)	0.073	21	0.94
PADUA	82.44 (14.45)	90.14 (27.04)	-0.78	21	0.44

* $p < 0.05$ level (2-tailed).

COHS-R: Creature of Habit - Routine; COHS-A: Creature of Habit - Automaticity; HTQ: Habitual Tendencies Questionnaire; HSCQ: Habitual Self-Control Questionnaire; SCS: Self-Control Scale

NB. The sample size of OCD-APP differs from what is mentioned in the introduction (n=22), as the 13 patients from the NHS sample did not complete these questionnaires.

As shown in Table 2b, OCD groups did not differ in any of the measures.

3.1.4. Baseline within groups Stop-Signal Go/No-Go Task

Behavioural results are depicted in tables 3a (HV) and 3b (OCD).

Table 3a. *Baseline Stop-Signal Go/No-Go Task results for HV-APP and HV-NO-APP participants*

	HV-APP (n= 15)	HV-NO-APP (n= 15)	U	df	p	d
Probability of responding to stop (%) [a]	50.3 (3.3)	47.7 (9.3)	113.000	27	0.74	0.08
Probability of responding to No-Go (%) [a]	5.4 (8.1)	12 (11.5)	66.500	27	0.09	-0.37
Probability of error on Go (%) [a]	1.4 (1.4)	2.5 (2.7)	86.000	27	0.43	-0.18
Correct Go Reaction Time (ms) [a]	409.11 (137.81)	615.61 (469.14)	78.000	27	0.25	-0.26
SSD (ms) [a]	185.01 (121.26)	353.33 (407.74)	84.000	27	0.38	-0.2
SSRT (ms) [a]	206.78 (14.75)	197.76 (47.93)	88.000	24	0.88	0.04

* $p < 0.05$ level (2-tailed). [a] Levene's test is significant, therefore equal variances were not assumed.

Table 3b. *Baseline Stop-Signal Go/No-Go Task results for OCD-APP and OCD-NO-APP participants*

	OCD-APP (n= 16)	OCD-NO-APP (n= 14)	t	df	p	d
Probability of responding to stop (%) [a]	52.5 (2.6)	52.9 (8.2)	130.500	28	0.45	0.16
Probability of responding to No-Go (%)	13.9 (13.3)	14.9 (21.4)	-0.15	28	0.88	-0.06
Probability of error on Go (%)	3.3 (3)	2.6 (3)	0.64	28	0.53	0.23
Correct Go Reaction Time (ms)	350.07 (80.47)	401.62 (162.17)	-1.12	28	0.27	-0.41
SSD (ms)	129.48 (75.36)	177.67 (153.19)	-1.11	28	0.27	-0.41
SSRT (ms)	215.6 (20.9)	190.76 (53.18)	1.62	25	0.12	0.62

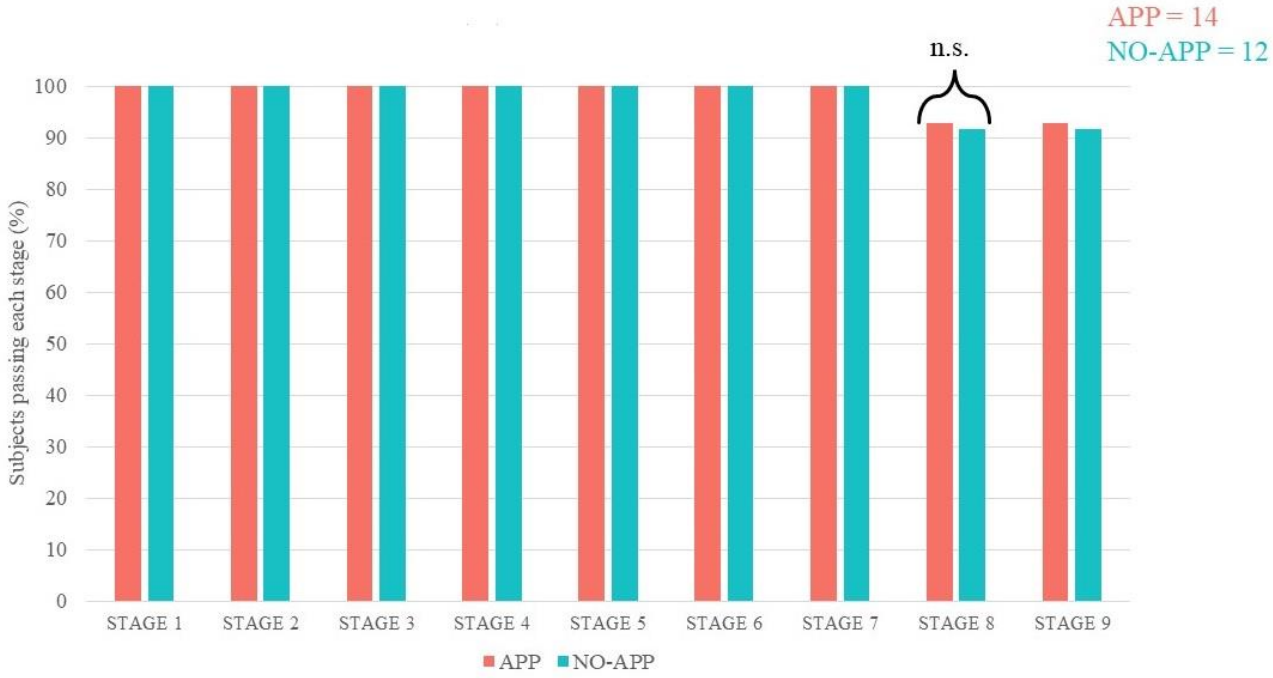
* $p < 0.05$ level (2-tailed). [a] Levene's test is significant, therefore equal variances were not assumed.

As can be seen on tables 3a and 3b, groups did not differ in behavioural performance on the SSGNG task.

3.1.5. Baseline within groups Intra-Extra Dimensional Set Shifting Task

Group performance on the IED task can be found in figures 1a and 1b.

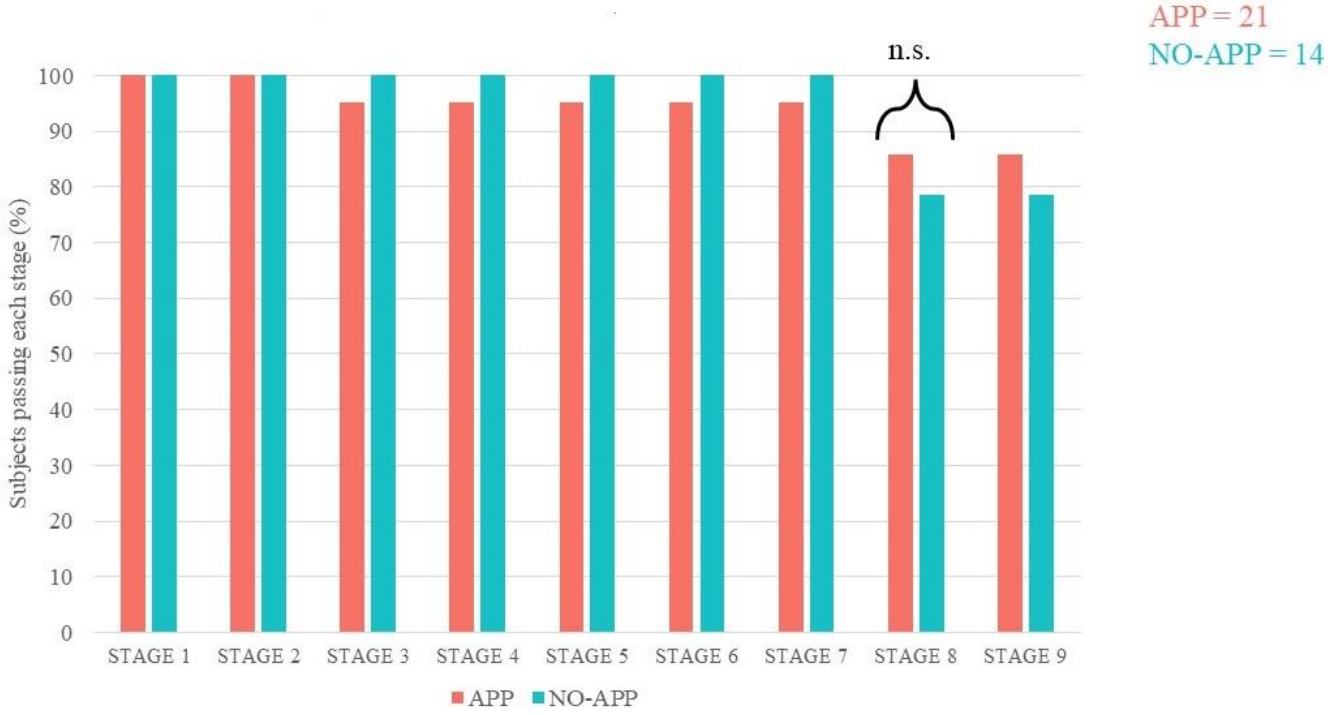
Figure 1a. *Baseline comparison between HV-APP and HV-NO-APP participants*



n.s.: not significant p>0.05.

Independent sample *t* tests revealed no significant differences between groups on the Extra-Dimensional Shift (EDS, stage 8) stage of the task $t(24)= -0.07$, $p=0.94$, $d=-0.03$, two-tailed. Means and standard deviations for the APP group were M=5.21(7.2) and for the NO-APP group M=5.42(6.85).

Figure 1b. *Baseline comparison between OCD-APP and OCD-NO-APP participants*



n.s.: not significant p>0.05.

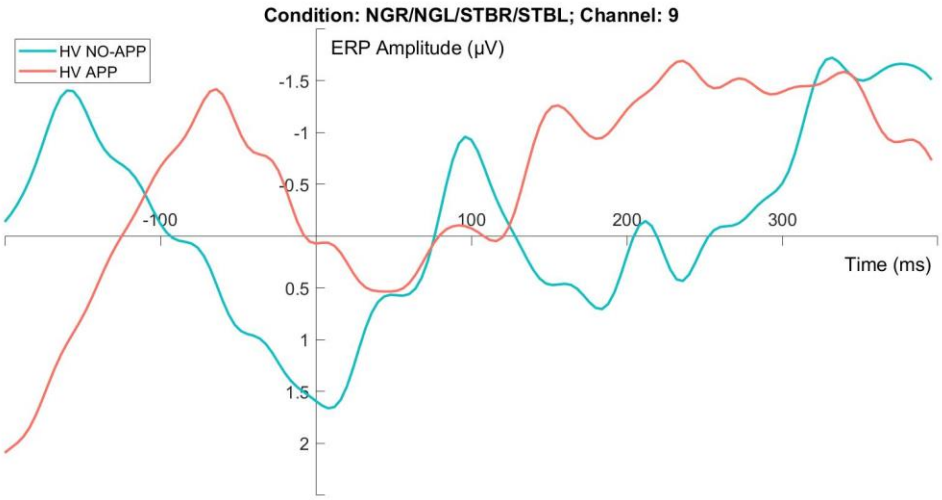
Statistical analyses indicated no differences between groups on the EDS stage $t(34)=0.5$, p=0.62, d=0.17, two-tailed. Means and standard deviations for APP and NO-APP groups were M=14.36(36.9) and M=9.2(11.9), respectively.

3.1.6. Baseline within groups electroencephalographic results

3.1.6.1. ERN

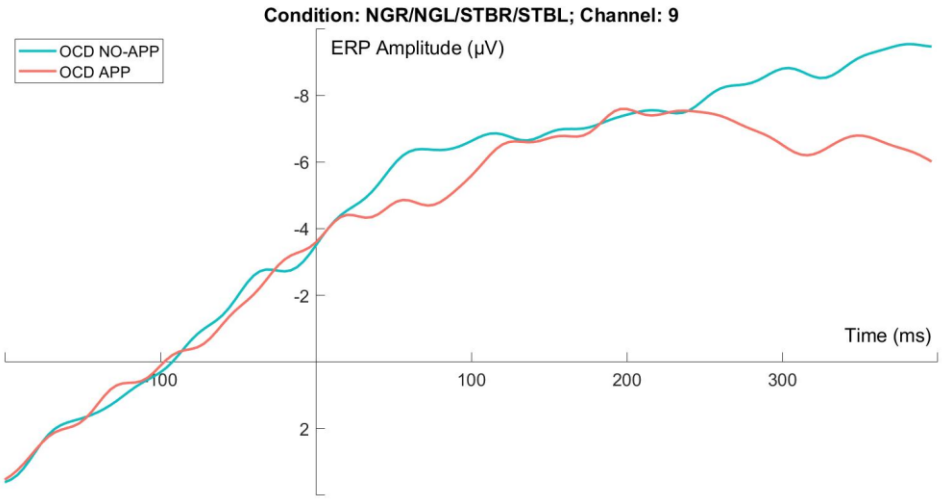
Figures 2a and 2b depict ERN results for HV and OCD samples. Mean amplitudes were calculated using the period between 0ms (erroneous response) and 100ms, on electrode Fz (channel 9).

Figure 2a. *ERN amplitudes of HV-APP vs HV-NO-APP participants*



Independent sample *t* tests did not indicate significant differences between groups on ERN amplitudes *t*(28)= -0.16, p=0.87, d= -0.06, two-tailed. Means and standard deviations for the APP and NO-APP groups were M=0.23(4.17) and M=0.54(5.9), respectively.

Figure 2b. *ERN amplitudes of OCD-APP vs OCD-NO-APP participants*

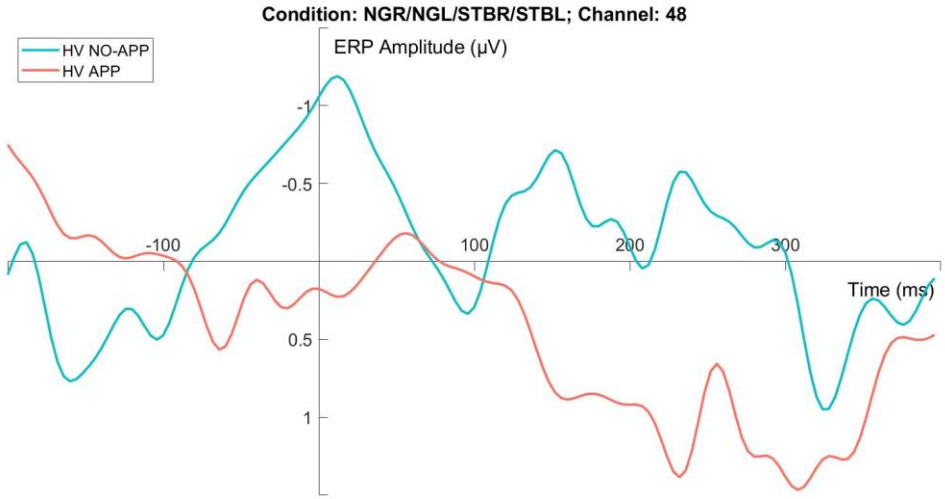


Similarly, the OCD group did not differ on ERN amplitudes *t*(27)=0.35, p=0.73, d=0.13, two-tailed. Means and standard deviations were M=-4.6 (7.7) and M=-5.5(6) for APP and NO-APP participants, respectively

3.1.6.2. Pe

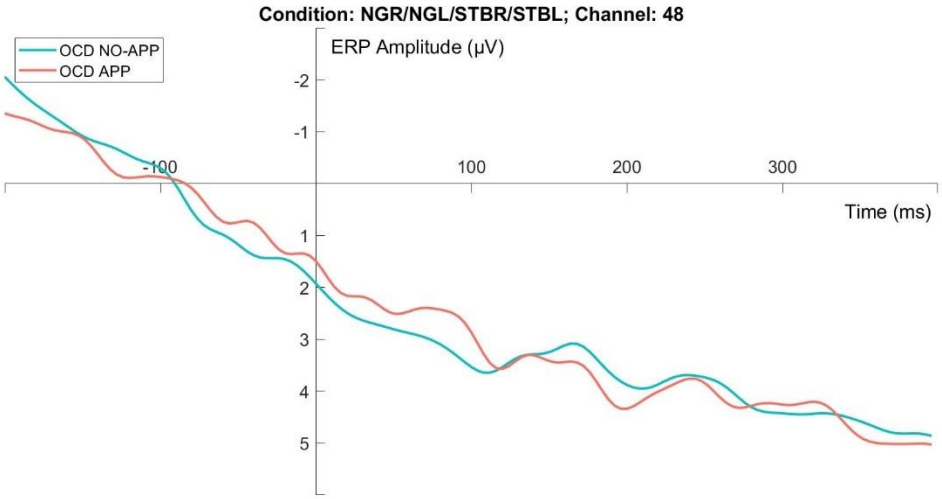
The error positivity was calculated as the mean amplitude between 200ms and 400ms following an incorrect response (locked at 0ms). Amplitudes were extracted from channel 48, which corresponds to electrode Pz. Figures 3a (HV) and 3b (OCD) depict the results.

Figure 3a. *Pe amplitudes of HV-APP vs HV-NO-APP participants*



The independent sample *t* tests did not find differences between both HV groups *t*(28)=0.97, p=0.34, d=0.35, two-tailed. Means and standard deviations were M=1(3.25) and M=0.1(1.8) for APP and NO-APP participants, respectively.

Figure 3b. *Pe amplitudes of OCD-APP vs OCD-NO-APP participants*

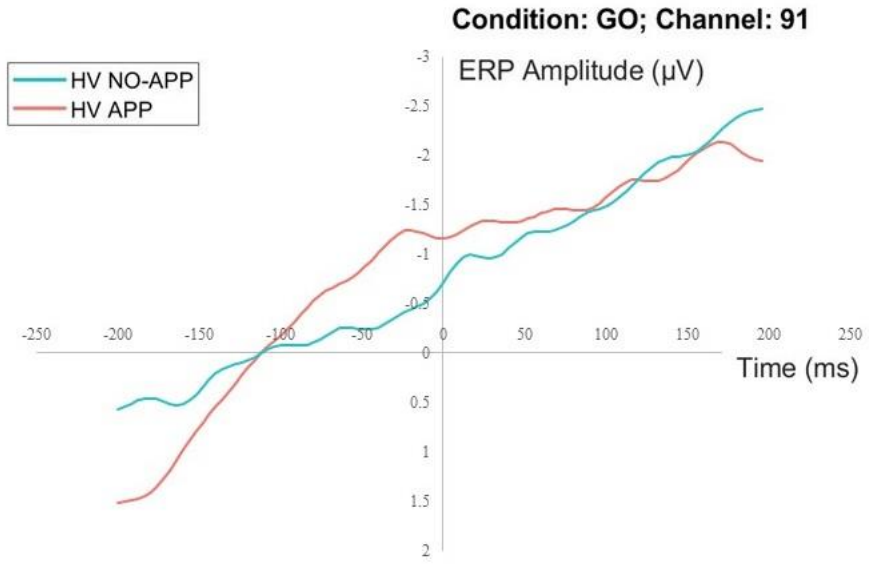


Participants in the OCD-APP and OCD-NO-APP groups did not differ on Pe amplitudes *t*(27)= 0.025, p=0.98, d= 0.01, two-tailed. Means and standard deviations were M=4.38(14.15) and M=4.28(5.43) for APP and NO-APP subjects, respectively.

3.1.6.3. RP

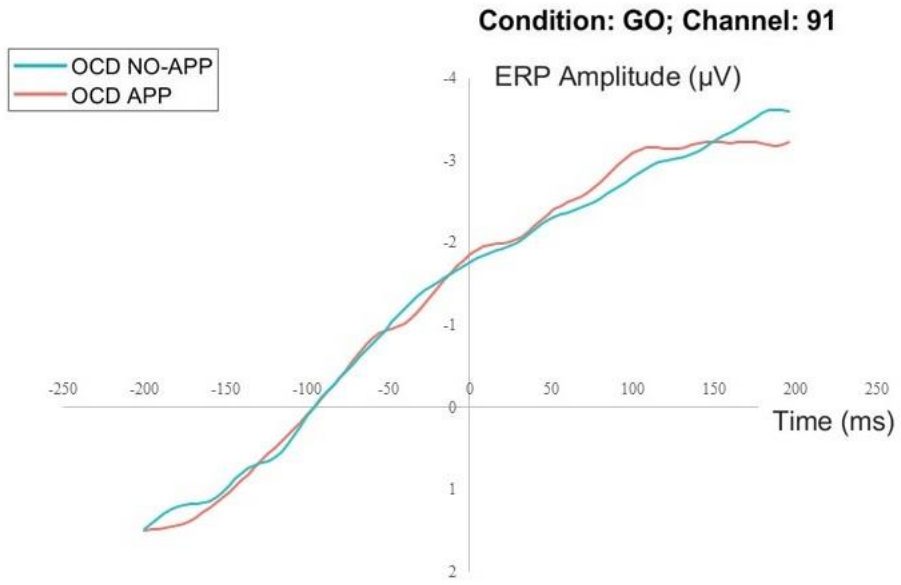
Finally, the readiness potential was calculated as the mean amplitude between -100ms and 0ms (response locked) on 'Go' trials, where a movement is required. Electrode Cz (channel 91) was used to obtain the amplitudes.

Figure 4a. *RP amplitudes of HV-APP vs HV-NO-APP participants*



Statistical analyses did not reveal significant differences between groups, with *t*(28)= -1.33, p=0.19, d= -0.49, two-tailed. Means and standard deviations for the APP and NO-APP groups were M=-0.79(1.17) and M= -0.29(0.87), respectively.

Figure 4b. *RP amplitudes of OCD-APP vs OCD-NO-APP participants*



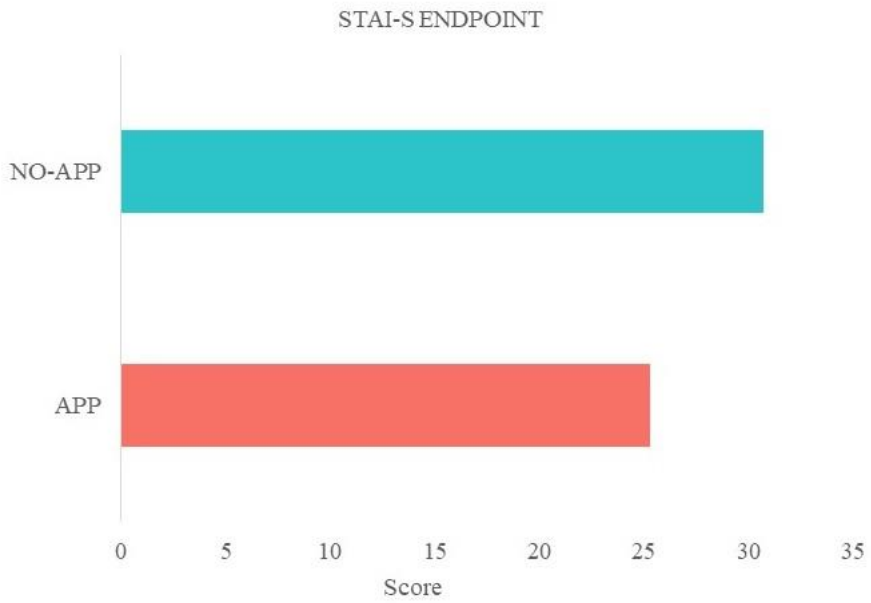
A similar pattern was found for the OCD group, with $t(27)= -0.04$, p=0.97, d=0.014, two-tailed. Means and standard deviations were M=-0.94(1.19) and M= -0.92(1.2) for APP and NO-APP subjects, respectively.

3.2. Post-intervention within groups comparisons

3.2.1. Post-intervention within groups clinical measures

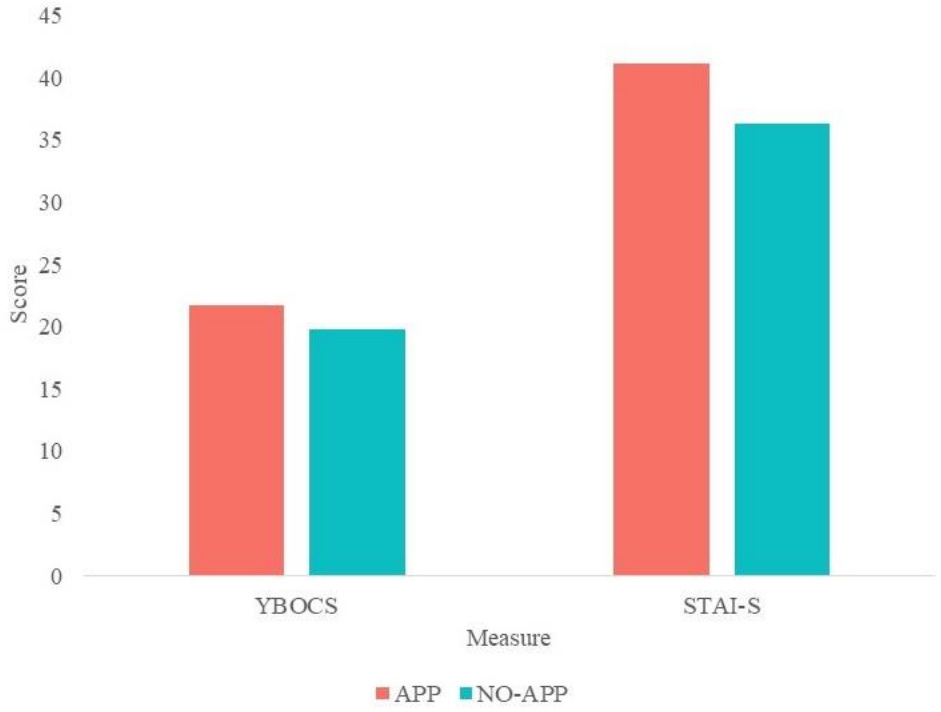
Figures 5a and 5b depict post-intervention data for HV and OCD samples, respectively.

Figure 5a. *Post-intervention clinical data for HV*



Independent sample *t* tests indicated no differences (albeit suggesting a nearly significant result) between APP and NO-APP participants on the State form of the State-Trait Anxiety Inventory $t(25)= -1.98$, $p=0.06$, $d=-0.76$, two tailed. Means and standard deviations for the APP and NO-APP group were M=25.3(5.6) M=30.7(8.8), respectively.

Figure 5b. *Post-intervention clinical data for participants in the OCD group.*



Statistical analyses did not find differences between groups on either YBOCS $t(33)=0.91$, $p=0.37$, $d=0.31$, two-tailed, or STAI-S $t(34)=1.21$, $p=0.23$, $d=0.41$, two-tailed. Means and standard deviations for APP and NO-APP groups on YBOCS were $M=21.76(6.18)$ and $M=19.79(6.48)$ and on STAI-S were $M=41.09(13)$ and $M=36.29(8.8)$, respectively.

3.2.2. Post-intervention within groups Stop-Signal Go/No-Go Task

Post-intervention behavioural results are depicted in tables 4a (HV) and 4b (OCD).

Table 4a. *HV post-intervention Stop Signal Go/No-Go Task results*

	HV-APP (n= 15)	HV-NO-APP (n= 15)	t	df	p	d
Probability of responding to stop (%)	49.4 (7.4)	47.5 (10)	0.59	28	0.56	0.22
Probability of responding to No-Go (%)	4.8 (7.6)	11.1 (10.2)	-1.91	28	0.07	-0.7
Probability of error on Go (%)	1.4 (1.5)	8.9 (23.4)	-1.24	28	0.23	-0.45
Correct Go Reaction Time (ms)	499.98 (313.69)	543.24 (528.19)	-0.27	28	0.79	-0.1
SSD (ms)	272.78 (291.56)	286.75 (386.91)	-0.11	28	0.91	-0.04
SSRT (ms)	190.74 (34.08)	207.38 (30.07)	-1.39	27	0.18	-0.52

* $p < 0.05$ level (2-tailed).

Table 4b. *OCD post-intervention Stop Signal Go/No-Go Task results*

	OCD-APP (n= 16)	OCD-NO-APP (n= 14)	t	df	p	d
Probability of responding to stop (%)[a]	51.8 (2.8)	52.8 (7.1)	116.500	28	0.87	0.04
Probability of responding to No-Go (%)	14.5 (14.3)	11.9 (16.1)	0.48	28	0.64	0.17
Probability of error on Go (%)	3 (3.1)	2.9 (3.1)	0.09	28	0.93	0.03
Correct Go Reaction Time (ms)[a]	346.6 (71.96)	514.7 (384.6)	91.000	28	0.4	-0.19
SSD (ms)[a]	131.16 (62.36)	288.79 (364.04)	106.000	28	0.82	-0.05
SSRT (ms)	204.25 (20.31)	209.27 (43.83)	-0.40	25	0.69	-0.16

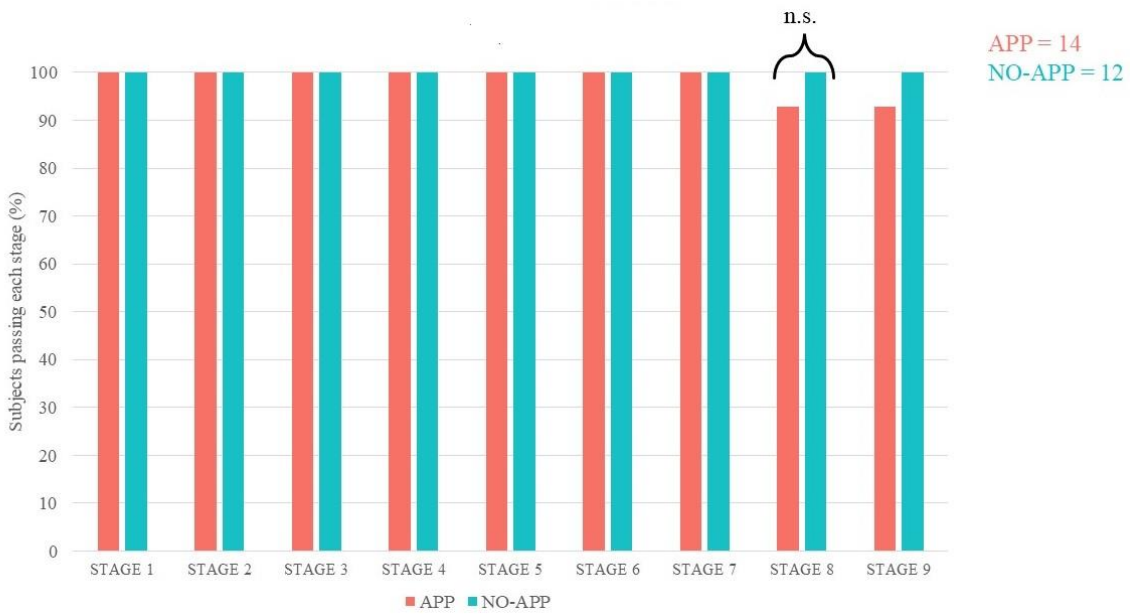
* $p < 0.05$ level (2-tailed). [a] Levene's test is significant, therefore equal variances were not assumed.

As can be seen in Tables 4a and 4b, groups did not differ on behavioural performance post-intervention.

3.2.3. Post-intervention within groups Intra-Extra Dimensional Set Shifting Task

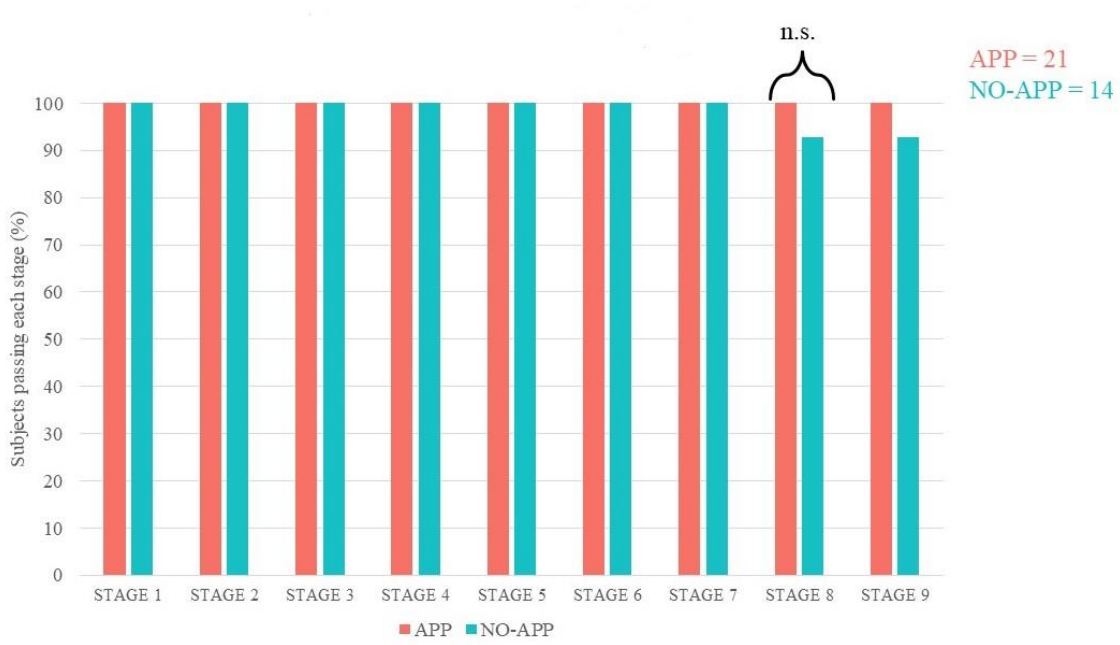
Figures 6a (HV) and 6b (OCD) illustrate IED results post-intervention.

Figure 6a. *HV post-intervention IED results*



Independent sample *t* tests did not reveal significant differences between APP and NO-APP participants on the EDS stage (stage 8), with $t(24)=0.62$, $p=0.54$, d-0.25, two-tailed. Means and standard deviations for APP and NO-APP subjects were M=3.8(6.53) and M=2.55(1.57), respectively.

Figure 6b. *OCD post-intervention IED results*



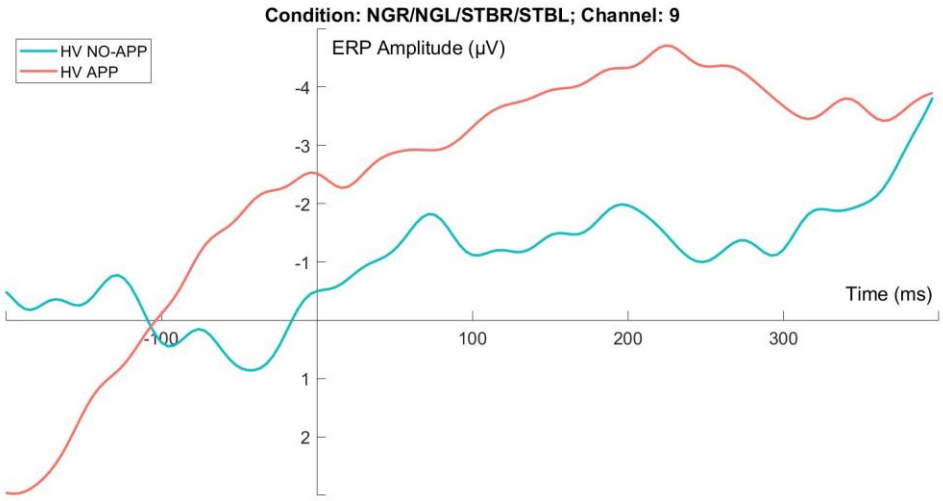
Considering that Levene's test was significant (p=0.037), the Mann-Whitney test was used to assess differences between APP and NO-APP participants on stage 8 (EDS) of the task. Results indicated no differences between groups (Mann-Whitney U=131.500, *n*1=21, *n*2=14, p=0.6, d= -0.11, two-tailed). Means and standard deviations were M=3.29(3.41) and M=5.64(8.85) for APP and NO-APP groups, respectively.

3.2.4. Post-intervention within groups electroencephalographic results

3.2.4.1. ERN

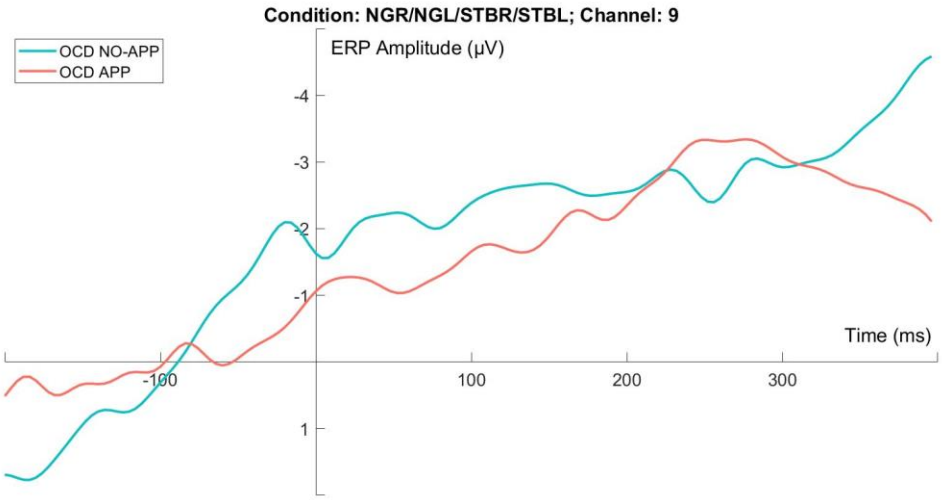
Figures 7a and 7b illustrate ERN results for the HV and OCD samples, respectively.

Figure 7a. *HV post-intervention ERN results*



Independent sample *t* tests indicated no significant differences between HV groups on ERN amplitudes *t*(28)= -0.98, p=0.34, d= -0.36, two-tailed. Means and standard deviations for APP and NO-APP groups were M= -2.76(3.6) and M= -1.15(5.24), respectively.

Figure 7b. *OCD post-intervention ERN results*

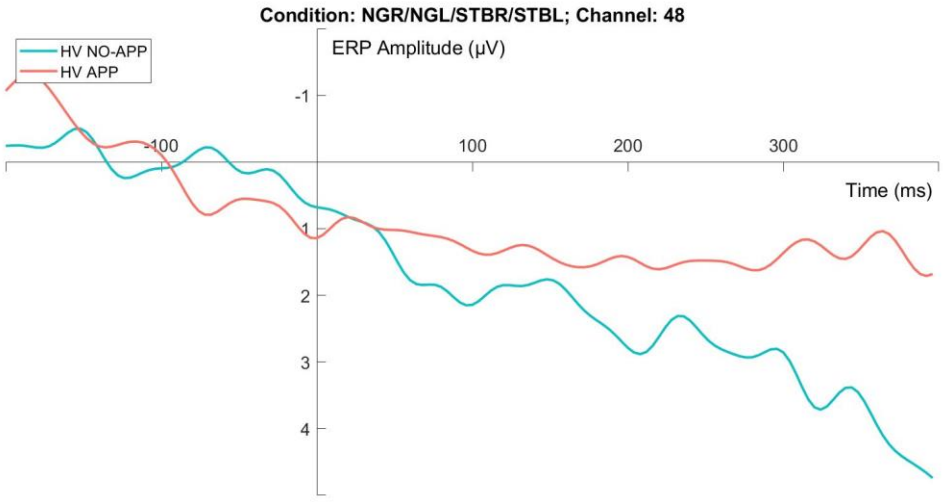


No significant differences were found between APP and NO-APP subjects on ERN amplitudes, with *t*(27)=0.49, p=0.63, d=0.18, two-tailed. Means and standard deviations were M= -1.23(4.48) and M= -2.04(4.4) for APP and NO-APP groups, respectively.

3.2.4.2. Pe

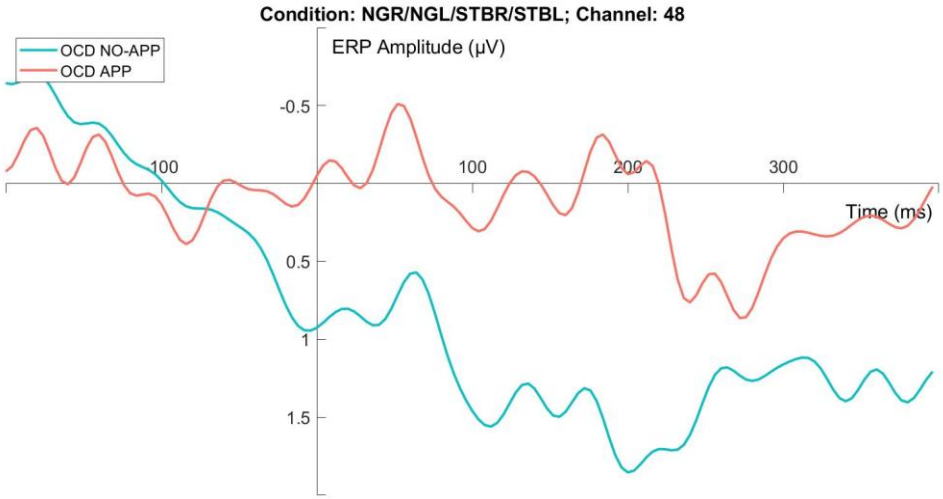
Results of the error positivity can be found in figures 8a (HV) and 8b (OCD).

Figure 8a. *HV post-intervention Pe results*



Independent sample *t* tests did not find differences between groups on Pe amplitudes *t*(28)= -0.48, p=0.63, d= -0.18, two-tailed. Means and standard deviations were M=1.43(3.28) and M=3.27(14.41) for APP and NO-APP participants, respectively.

Figure 8b. *OCD post-intervention Pe results*

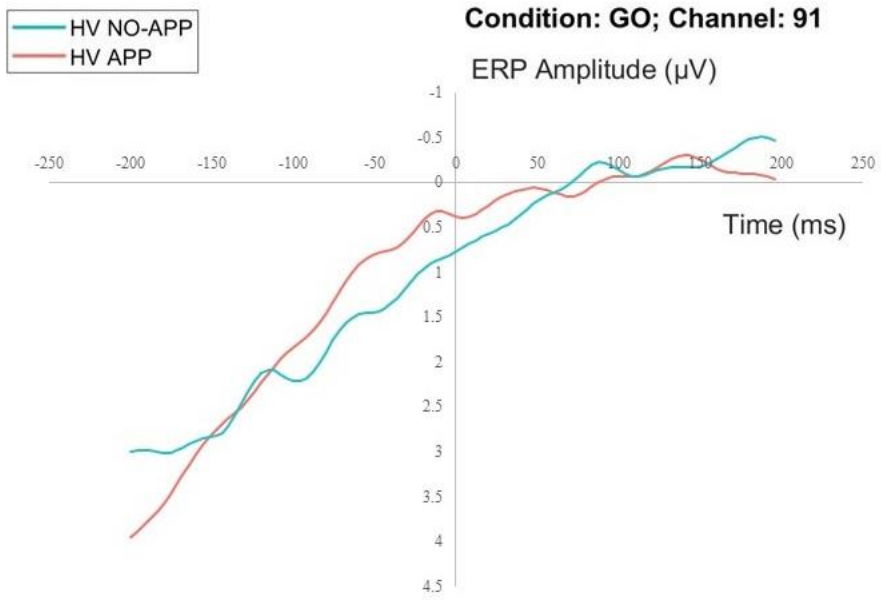


Statistical analyses did not reveal differences between groups on Pe amplitudes *t*(27)= -0.72, p=0.48, d= -0.27, two-tailed. Means and standard deviations were M=0.36(3.8) and M=1.37(3.7) for APP and NO-APP subjects, respectively.

3.2.4.3. RP

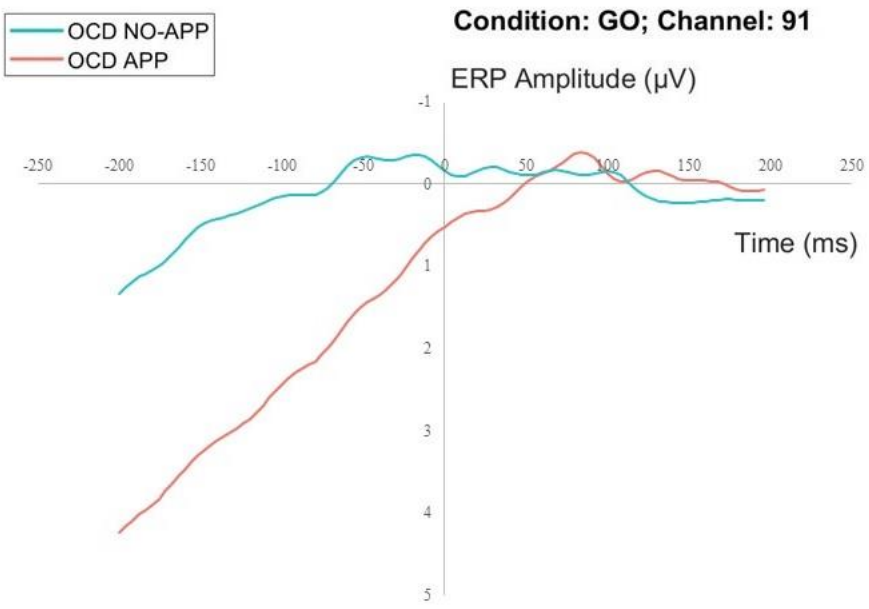
Figures 9a and 9b depict group amplitudes of the readiness potential.

Figure 9a. *HV post-intervention RP results*



Finally, no differences were found on RP amplitudes between APP and NO-APP participants *t*(28)= -0.64, p=0.53, d= -0.23, two-tailed. Means and standard deviations for the APP and NO-APP groups were M=0.93(2.04) and M=1.44(2.32), respectively.

Figure 9b. *OCD post-intervention RP results*



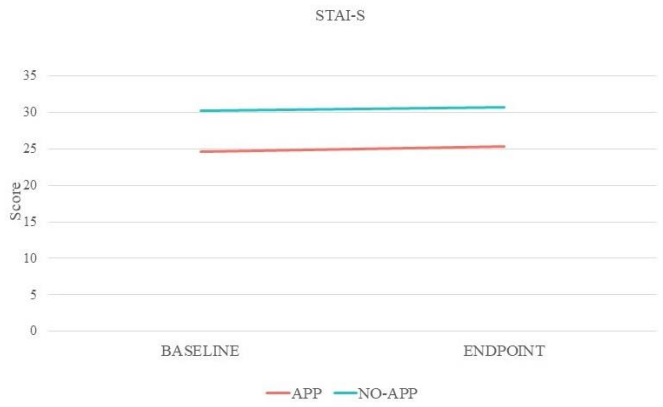
Conversely, a significant difference was found between OCD samples, indicating more positive amplitudes for the APP group $t(27)=2.96$, $p=0.006$, $d=1.09$, two-tailed. Means and standard deviations for APP and NO-APP subjects were M=1.5(1.57) and M= -0.15(1.43), respectively.

3.3. Post-intervention between and within groups comparisons

3.3.1. Clinical measures

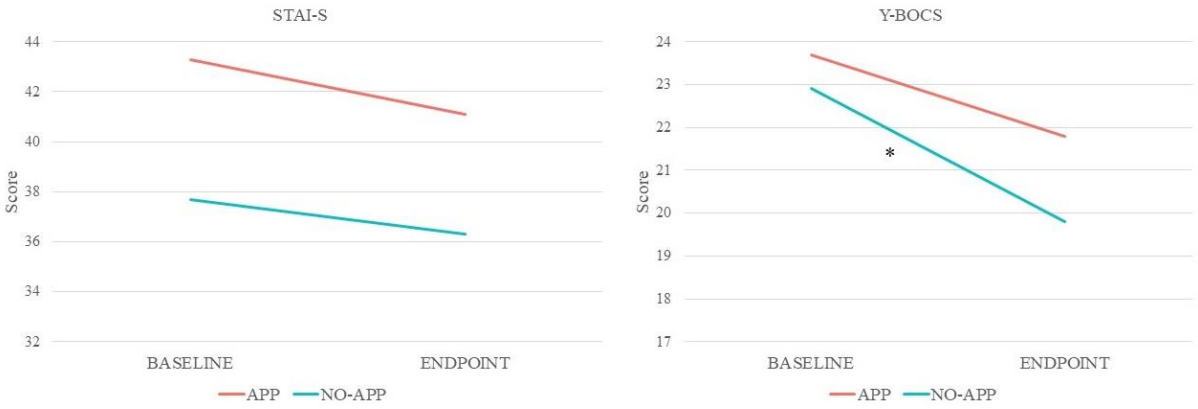
Results from clinical measures are depicted in figures 10a (HV) and 10b (OCD).

Figure 10a. *Baseline vs endpoint comparison for HV-APP and HV-NO-APP participants.*



Paired sample *t* tests did not reveal differences from baseline to endpoint for the APP $t(13)= -0.59$, p=0.57, d= -0.16, two-tailed, or the NO-APP group $t(11)= -0.35$, p=0.73, d= -0.1, two-tailed. Analyses of variance (ANOVAS), conversely, demonstrated a significant between-subjects effect of group $F(1,24)=4.75$, p=0.039, $\eta^2=0.14$. No interactions were found.

Figure 10b. *Baseline vs endpoint comparison for OCD-APP and OCD-NO-APP participants.*



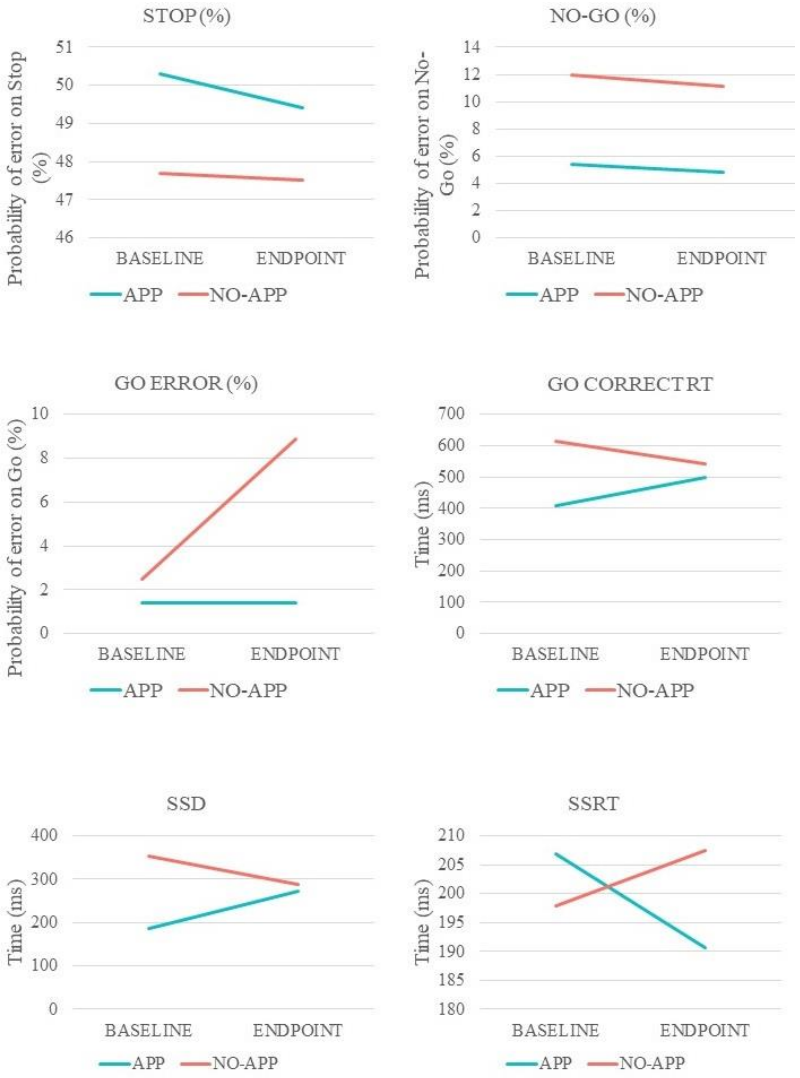
No differences were found between baseline and endpoint STAI-S for the OCD-APP $t(21)=0.77$, p=0.45, d=0.16, two-tailed, or NO-APP group $t(13)=0.8$, p=0.44, d=0.2, two-tailed. An ANOVA confirmed these results and found no effects of time, group, or any interactions $F(1,34)=2$, p=0.17, $\eta^2=0.04$.

Results of the Y-BOCS, alternatively, indicated significant differences between time-points solely for the NO-APP group $t(13)=3.77$, p=0.002, d=1, two-tailed, whilst the APP group did not differ $t(20)=1.75$, p=0.09, d=0.38, two-tailed. Analyses of variance revealed a main effect of time on Y-BOCS scores $F(1,33)=9.52$, p=0.004, $\eta^2=0.04$, with no interactions found.

3.3.2. Stop-Signal Go/No-Go Task results

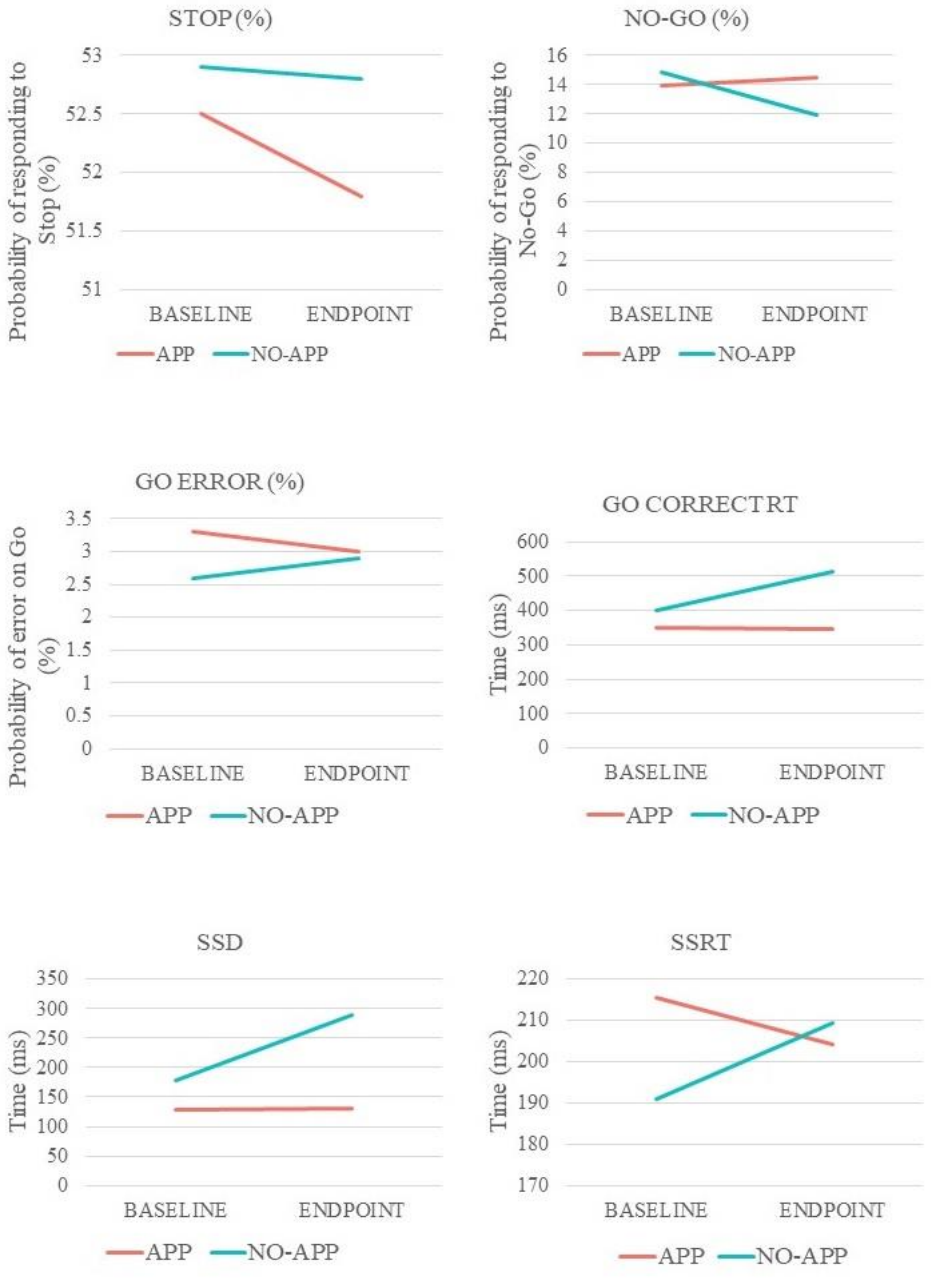
Baseline and endpoint comparisons of performance on the SSGNG for all groups are presented in figures 11a (HV) and 11b (OCD).

Figure 11a. *HV baseline vs endpoint performance on the SSGNG task*



No significant results were found on the paired samples *t* tests in any of the SSGNG measures. Similarly, ANOVAS did not reveal any significant differences.

Figure 11b. *OCD baseline vs endpoint performance on the SSGNG task*

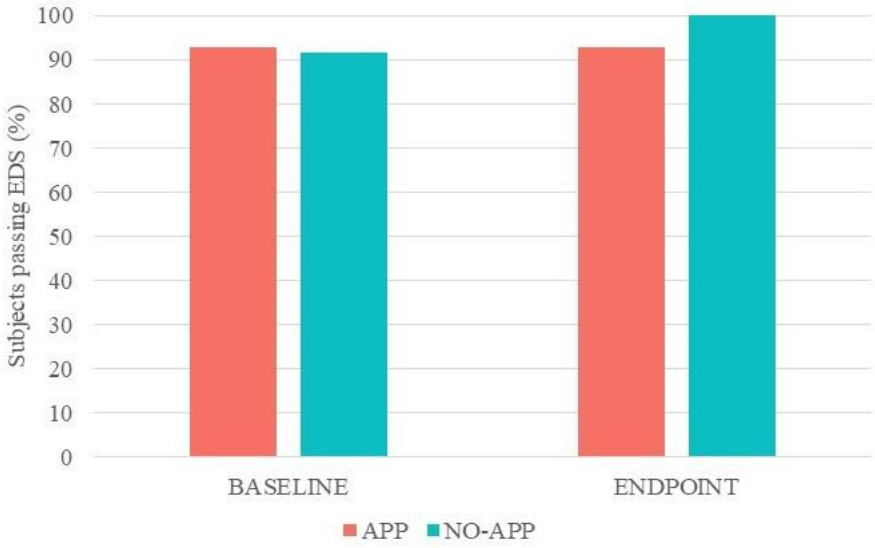


Paired samples *t* tests did not reveal any differences between OCD groups on any of the measures. Analyses of variance, similarly, did not find significant results between groups.

3.3.3. Intra-Extra Dimensional Set-Shifting Task

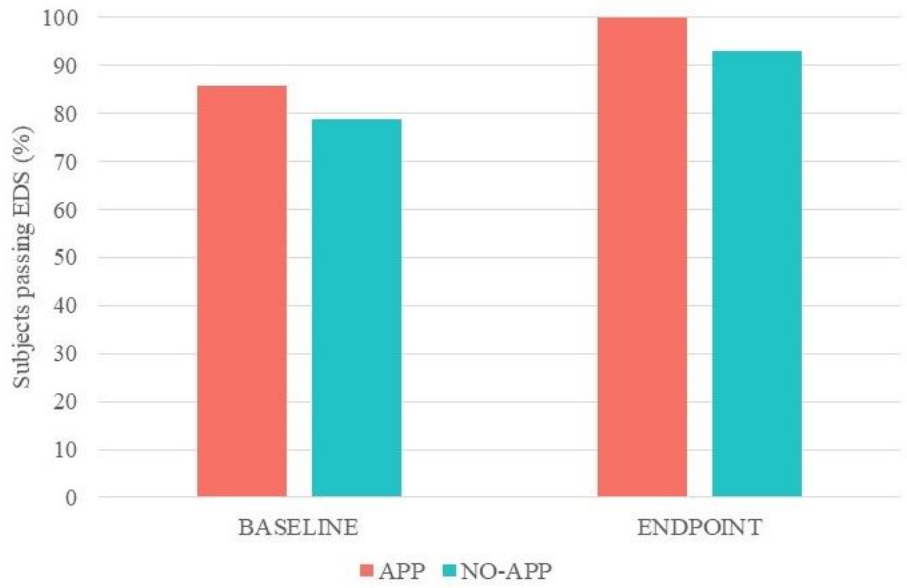
Figures 12a (HV) and 12b (OCD) depict the results of the Extra-Dimensional Shift (EDS) stage of the IED task for both participant samples.

Figure 12a. *Baseline vs endpoint comparison of EDS performance for HV-APP and HV-NO-APP*



The Wilcoxon signed-rank test did not find significant differences between baseline and endpoint for the APP (Z=58.500, p=0.13) or the NO-APP group (Z=29.000, p=0.14). Interestingly, an ANOVA revealed a main effect of time on EDS errors $F(1,23)=5.11$, $p=0.034$, $\eta^2=0.034$.

Figure 12b. *Baseline vs endpoint comparison of EDS performance for OCD-APP and OCD-NO-APP*



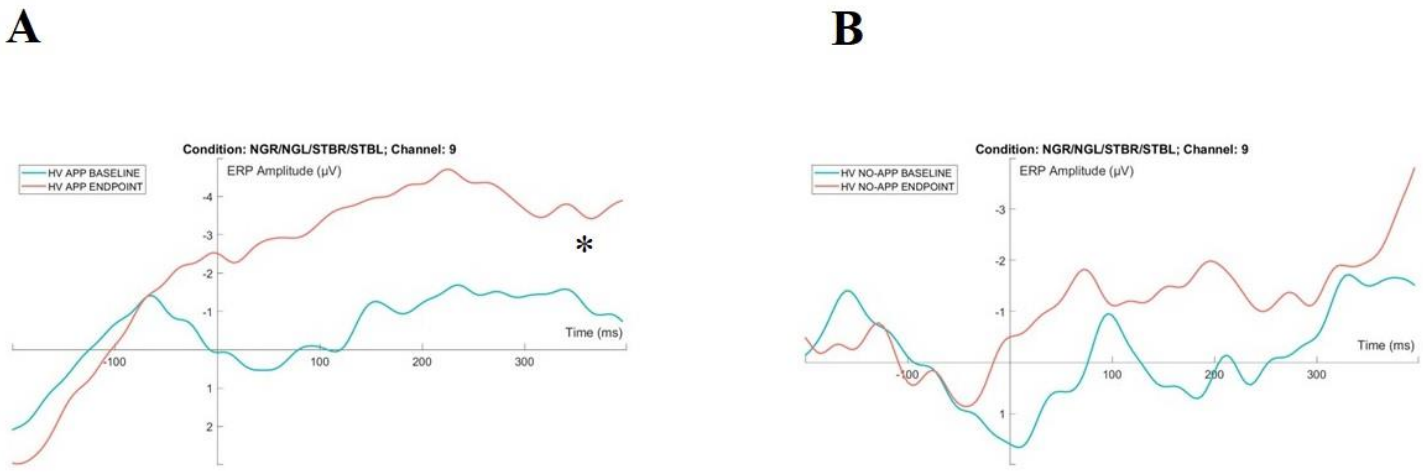
Similarly, the OCD-APP ($Z=116.500$, $p=0.18$) and NO-APP ($Z=47.000$, $p=0.22$) groups did not differ between baseline and endpoint. Analyses of variance also did not find effects of time, group, or interactions $F(1,33)=0.09$, $p=0.77$, $\eta^2=0.001$.

3.3.4. Electroencephalographic results

3.3.4.1. ERN

Figures 13a and 13b depict baseline vs endpoint ERN amplitudes for HV and OCD.

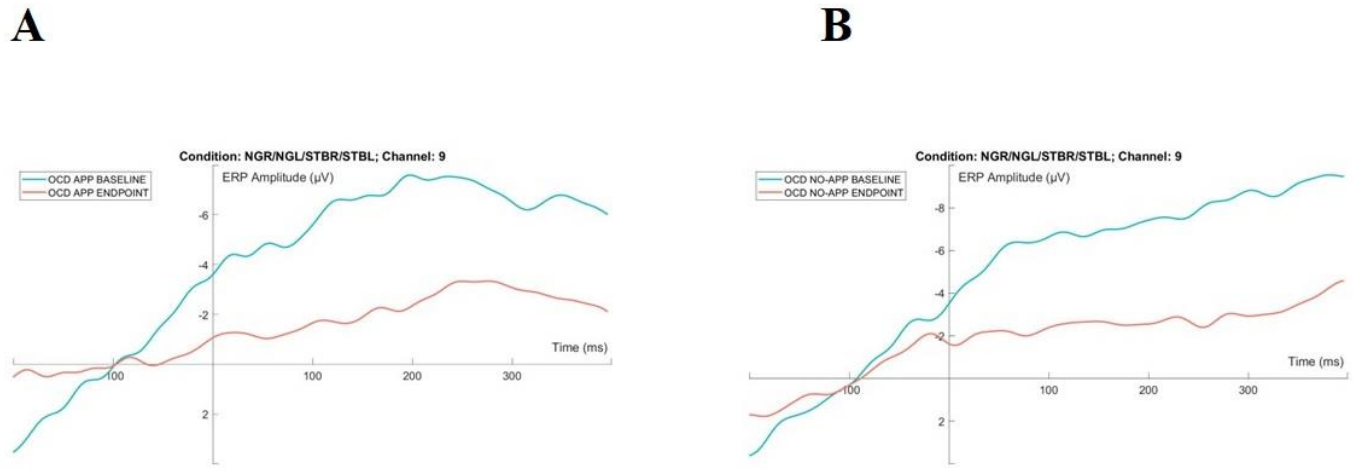
Figure 13a. *Baseline vs midpoint ERN amplitudes for HV-APP and HV-NO-APP participants.*



Paired sample *t* tests indicated significantly more negative ERN amplitudes for the APP group $t(14)=3.03$, $p=0.009$, $d=0.78$, two-tailed. No differences were found for the NO-APP group $t(14)=1.01$, $p=0.33$, $d=0.26$, two-tailed.

An ANOVA revealed a main effect of time on the amplitudes $F(1,28)=5.79$, $p=0.023$, $\eta^2=0.06$. No effects of group or interactions were found.

Figure 13b. *Baseline vs midpoint ERN amplitudes for OCD-APP and OCD-NO-APP participants.*

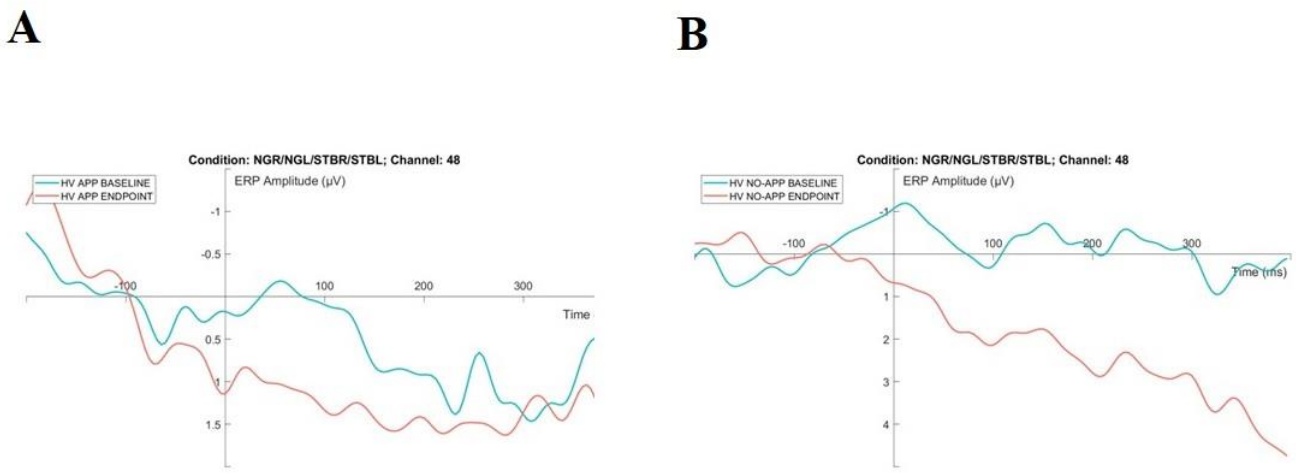


Within-groups comparisons found a borderline difference on ERN amplitudes for the APP group $t(14)= -2.14$, p=0.051, d= -0.55, two-tailed. No differences were found for the NO-APP group $t(13)= -1.85$, p=0.09, d= -0.5, two-tailed. Analyses of variance indicated a main effect of time $F(1,27)=7.9$, p=0.009, $\eta^2=0.08$, with no effects of group or interactions.

3.3.4.2. Pe

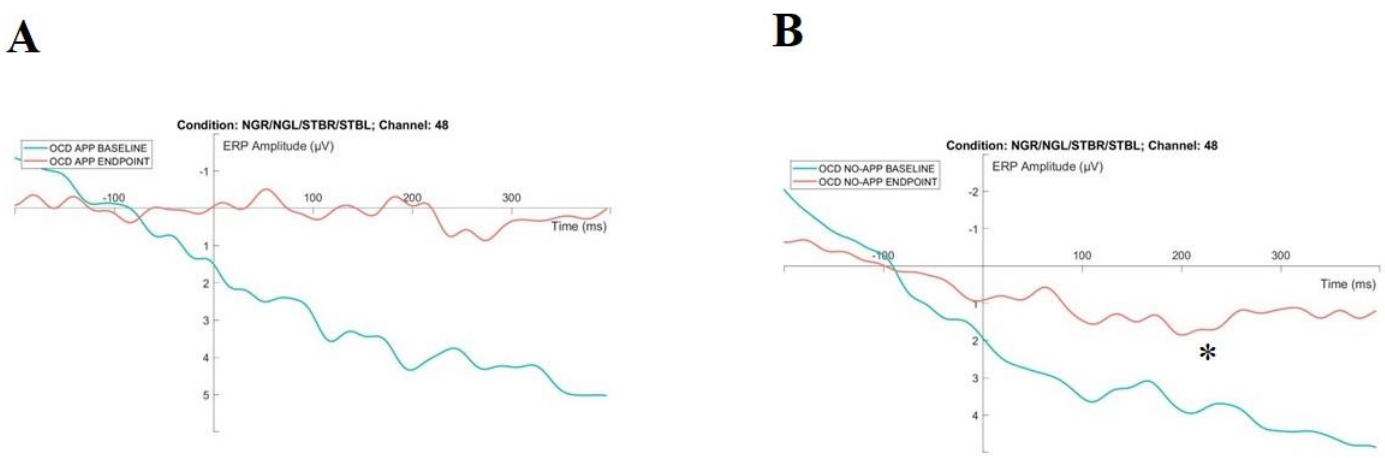
Figures 14a and 14b depict baseline vs endpoint ERN amplitudes for HV and OCD.

Figure 14a. *Baseline vs midpoint Pe amplitudes for HV-APP and HV-NO-APP participants.*



No differences were found between baseline and endpoint amplitudes of the error positivity for APP participants $t(14)= -0.52$, p=0.6, d= -0.13, two-tailed. Similarly, the Wilcoxon signed-rank test did not reveal any differences for the NO-APP group (Z=60.000, p=1.000). An ANOVA corroborated these results and found no effects of time on Pe amplitudes $F(1,28)=0.84$, p=0.37, $\eta^2=0.01$. No effects of group or interactions were found.

Figure 14b. *Baseline vs midpoint Pe amplitudes for OCD-APP and OCD-NO-APP participants.*

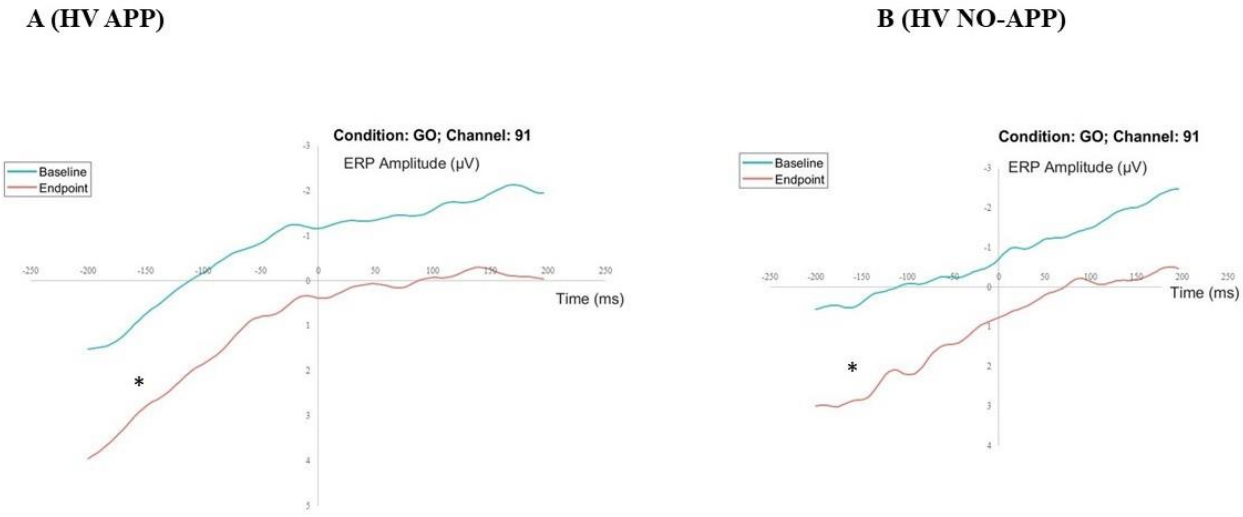


The Wilcoxon signed-rank test did not indicate differences between baseline and endpoint Pe amplitudes for the APP group (Z=79.000, p=0.3). Conversely, significant differences were found for the NO-APP group $t(13)$-2.31, p=0.04, d=0.62, two-tailed. An ANOVA did not reveal any effects of time $F(1,27)=3.2$, p=0.09, $\eta^2=0.05$, group, or interactions.

3.3.4.3. RP

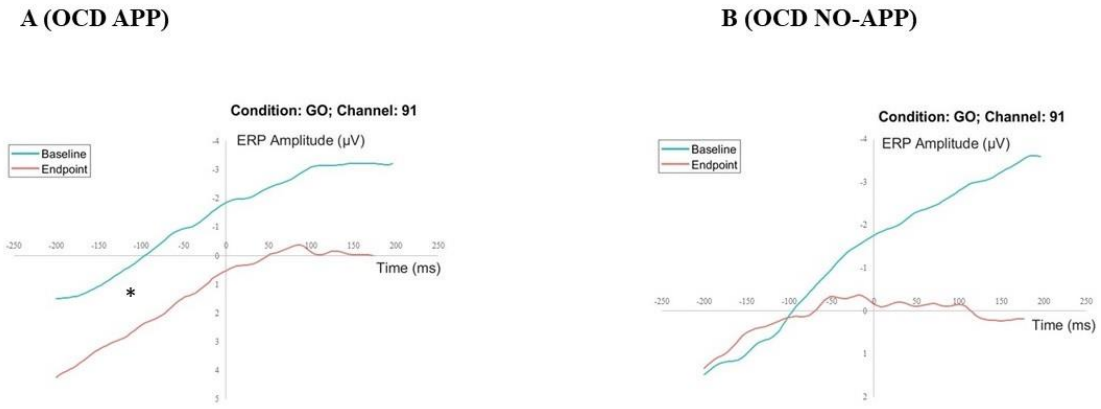
Figures 15a and 15b depict baseline vs endpoint ERN amplitudes for HV and OCD.

Figure 15a. *Baseline vs midpoint RP amplitudes for HV-APP and HV-NO-APP participants.*



Paired sample *t* tests indicated significant differences between baseline and endpoint amplitudes of the readiness potential for the APP $t(14)= -3.14$, p=0.007, d= -0.8, two-tailed, and NO-APP groups $t(14)= -2.83$, p=0.013, d= -0.73, two-tailed. Analyses of variance confirmed these differences and found a main effect of time $F(1,28)=17.6$, $p<0.001$, $\eta^2=0.2$. No other effects or interactions were found.

Figure 15b. *Baseline vs midpoint RP amplitudes for OCD-APP and OCD-NO-APP participants.*

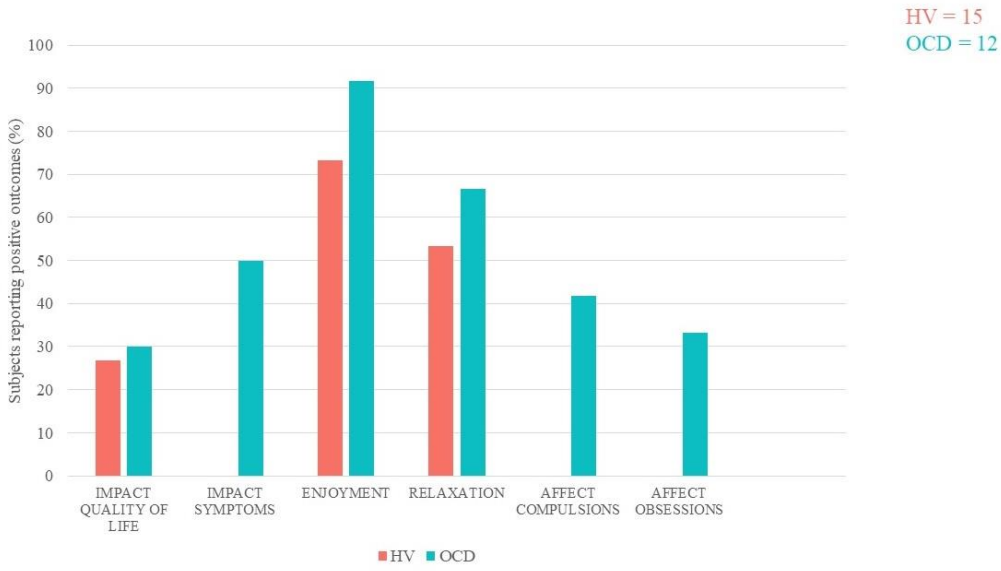


Significant differences were found between baseline and endpoint amplitudes of the RP for the APP group $t(14)= -3.95$, p=0.001, d= -1.02, two-tailed. The NO-APP group, conversely, did not differ between time-points $t(13)= -1.66$, p=0.12, d= -0.44, two-tailed. Analyses of variance revealed main effects of time $F(1,27)=16.9$, $p<0.001$, $\eta^2=0.24$, group $F(1,27)=6.53$, p=0.02, $\eta^2=0.06$, and an interaction between time and group $F(1,27)=4.6$, p=0.04, $\eta^2=0.06$.

3.3.5. Self-report APP results

Subjective reports during the app training month are depicted in figure 16.

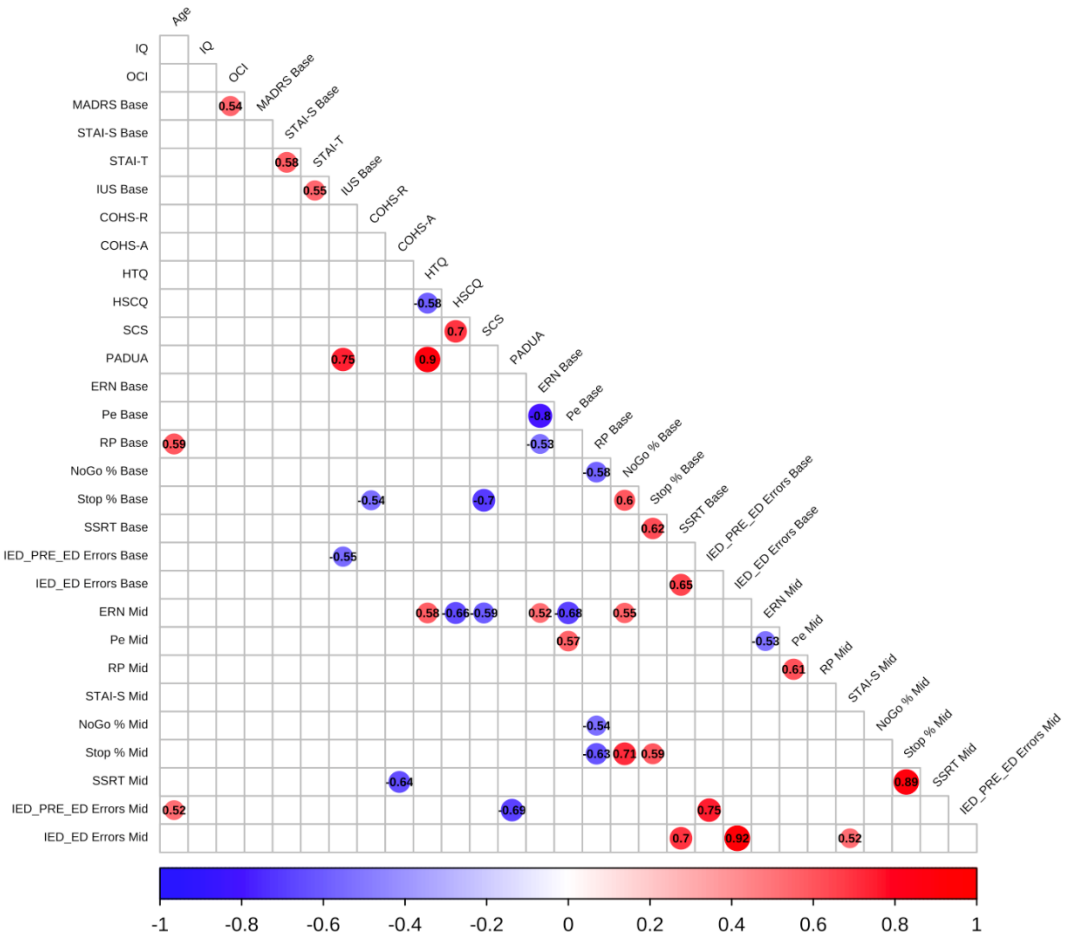
Figure 16. *Qualitative positive reports of app training*



Qualitative analyses show a trend of higher enjoyment and relaxation caused by the app training for the OCD group. Interestingly, participants in this group also reported subjective improvement of symptoms following the intervention.

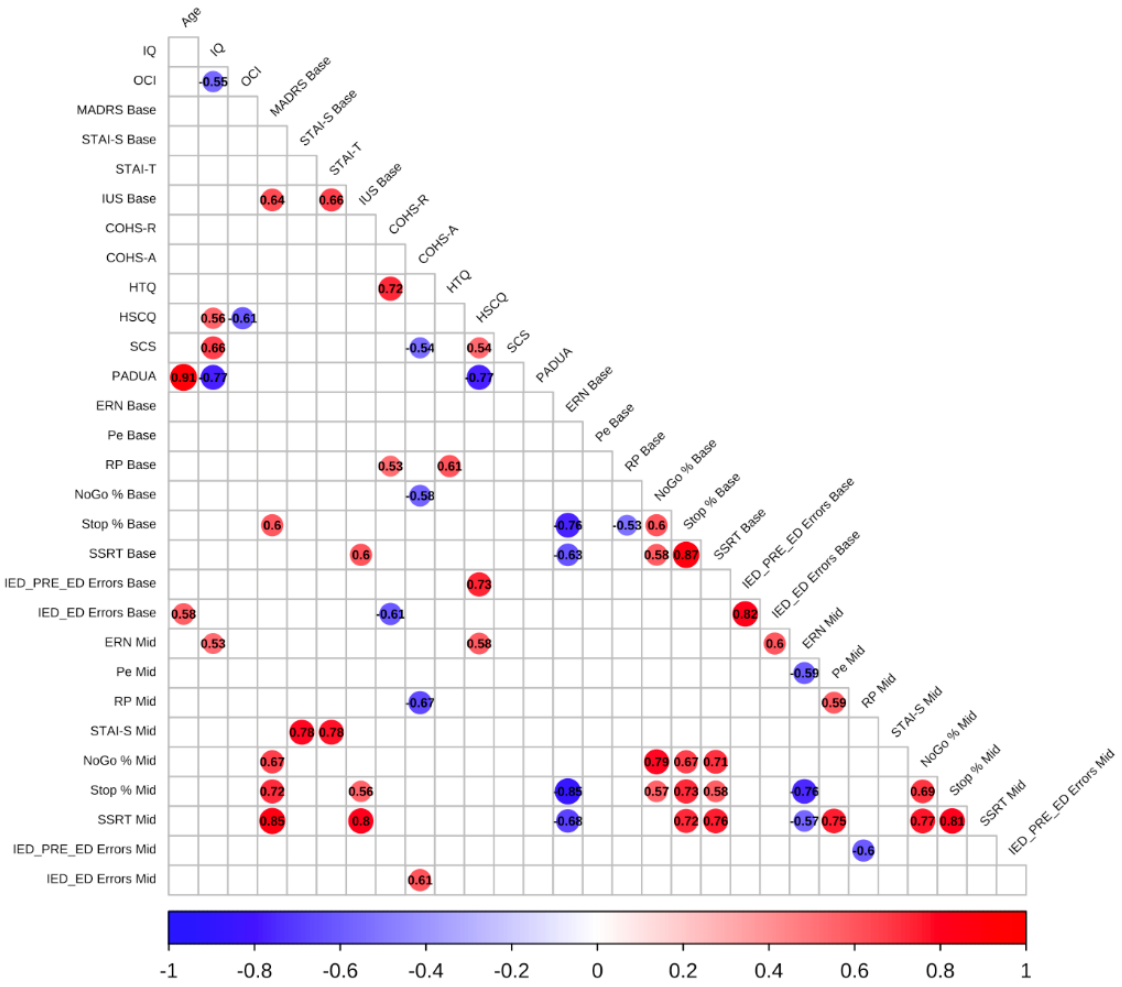
3.3.6. Correlations

3.3.6.1. HV-APP



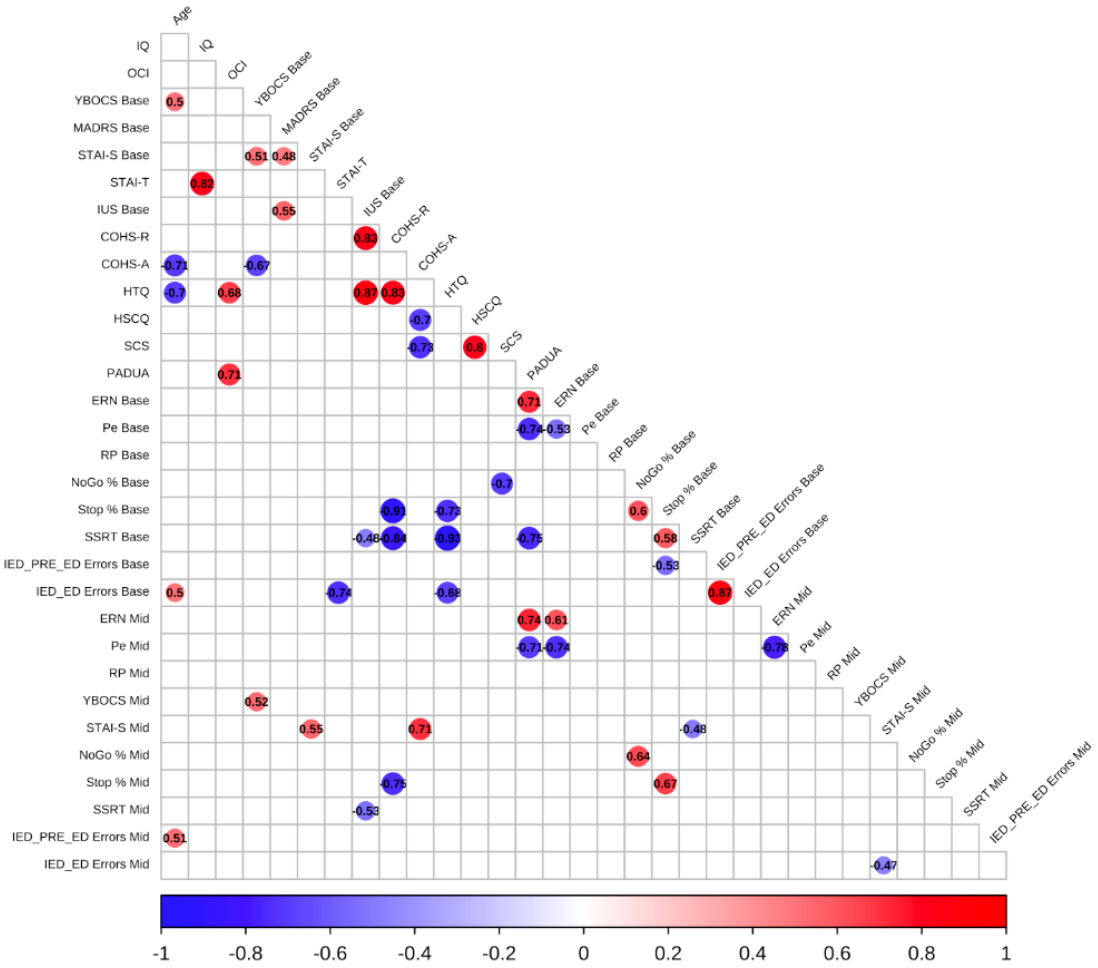
Strong negative correlations were found between RP amplitudes and probability of responding to stop and no-go stimuli, indicating that lower motor control contributes to inhibition deficits. Paradoxically, ERN amplitudes correlated positively with habitual tendencies and negatively with self-control measures, suggesting that more negative ERN amplitudes are associated with higher inhibitory control in the HV-APP group.

3.3.6.2. HV-NO-APP



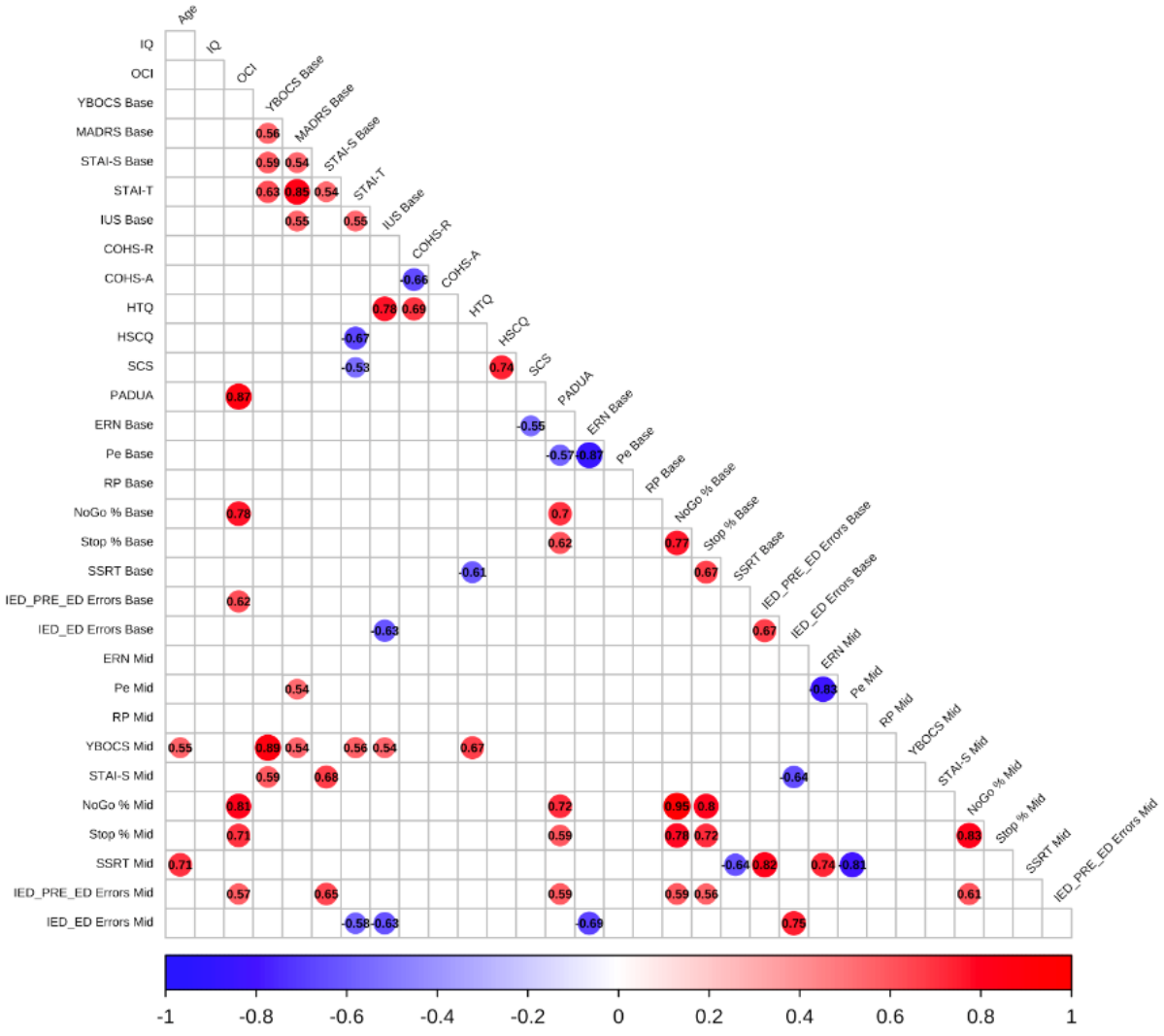
ERN amplitudes correlated negatively with behavioural performance on the SSGNG task, indicating an opposite trend to the one found for APP participants. Additionally, lower motor control was associated with more errors on the IED task. Strong negative associations were found between IQ and OCD symptomatology.

3.3.6.3. OCD-APP



Behavioural performance on the SSGNG task correlated negatively with self-report scores of routine, suggesting better performance for participants with higher routine tendencies. Higher self-reported OCD symptoms as measured by the PADUA, interestingly, correlated with more positive ERN amplitudes.

3.3.6.4. OCD-NO-APP



Higher self-reported OCD symptomatology, as measured by the OCI and the PADUA, was associated to poorer performance on both behavioural tasks. More negative ERN amplitudes were also associated with deficits on the IED task.

3.4. Summary of findings

- Endpoint readiness potential was attenuated for HV-APP, HV-NO-APP, and OCD-APP
- Endpoint error-related negativity (ERN) presented borderline attenuation for OCD-APP
- Endpoint ERN was heightened for HV-APP
- Endpoint error positivity (Pe) was attenuated for OCD-NO-APP
- Endpoint extra-dimensional shift errors were reduced for HV-APP and HV-NO-APP
- Y-BOCS scores were diminished for OCD-NO-APP
- Patients reported subjectively higher enjoyment and relaxation than controls when practising the mobile application
- Patients reported improvement of symptoms following the app practice

4. Discussion

This study aimed at investigating the effects of introducing a novel set of ritualised motor behaviours on patients with OCD and matched healthy volunteers, in comparison to equally matched passive groups, who received no intervention. It was expected that both groups training the ritualised behaviours (HV-APP and OCD-APP) would improve from baseline to endpoint on clinical, behavioural, and electroencephalographic measures, given the known impacts of rituals on goal-directed behaviour and emotional regulation (Hobson et al., 2018). Groups receiving no intervention (HV-NO-APP and OCD-NO-APP) were expected to remain unchanged.

Supporting the original hypothesis, the results demonstrated an attenuation of the amplitudes of the Readiness Potential (RP) on the OCD-APP group, also corroborating the findings presented in chapter 4. As a measure of pre-SMA and SMA activation (Cunnington et al., 2003; Deecke, 1987, 1995; Deecke & Kornhuber, 1978; Kornhuber & Deecke, 2016), areas responsible for motor preparation, initiation, and inhibition (de Wit et al., 2012; Tomiyama et al., 2021; Yazawa et al., 2000), the RP has been reported as increased in OCD by several authors (Dayan-Riva et al., 2021; Johannes et al., 2001; Morand-Beaulieu et al., 2021; Takashima et al., 2019). The attenuation of this ERP component seen in the OCD-APP, but not in the OCD-NO-APP group, provides evidence for the hypothesis that the practice of complex,

voluntary motor skills can impact the RP, requiring less 'effort' from the SMA (Di Russo et al., 2005; Kristeva, 1984; Wright et al., 2012). In addition, it is possible to hypothesise that the ritualised behaviours have attenuated premonitory urges, which would lead to a lower necessity to perform compulsions. Evidence for this comes not only from habit-reversal (Lee et al., 2019; Shephard et al., 2021), and brain stimulation studies (Balzus et al., 2022; van Westen et al., 2015; Vieira et al., 2021), but also from the patients' reports of the impact of the mobile application on their symptoms presented in the results section. Comparing those reports with the ones provided by the HV group, it seems that patients attribute higher rates of enjoyment and relaxation provoked by the execution of the motor acts, which is possibly connected to the predisposition of the disorder in maintaining repetitive actions (Fineberg et al., 2018; Gillan, Robbins, et al., 2016; Robbins et al., 2012). Although the results did not suggest a reduction in anxiety in both APP groups (although a trend was seen for HV-APP participants), a plethora of evidence suggests that engagement in ritualised behaviours is associated with stress, anxiety, and uncertainty, serving a role of promoting relief and controlling an unpredictable environment (Cobos et al., 2022; Hirsh et al., 2012; Hobson et al., 2018; Tonna et al., 2019, 2022). Indeed, both patient samples (OCD-APP and OCD-NO-APP) exhibited strong positive correlations between intolerance of uncertainty and routinely, habitual behaviours, which could explain why the mobile application was subjectively associated with better quality of life and symptom improvement by the OCD-APP group, a finding also reported in chapter 4. Unfortunately, however, uncertainty scores were not measured at both time-points, hindering conclusions concerning whether the app did, in fact, impact this mechanism.

Several studies propose that alleviation of feelings of uncertainty promotes better performance and decrease negative responses to errors, with the ERN being an ideal candidate to test these hypotheses (Brooks et al., 2016; Hobson et al., 2017). Indeed, feelings of uncertainty have been proposed as a core feature of OCD (Pinciotti et al., 2021; Tolin et al., 2003), and as a potential underlying mechanism of the ERN (Jackson et al., 2015, 2016). Nevertheless, growing evidence reports the opposite trend, with uncertainty being unrelated or negatively associated to the ERN (Malbec et al., 2022; White et al., 2018), which explains the lack of association between those constructs in this study. It is plausible to hypothesise, hence, that the positive subjective reports and the improvement of the RP and ERN (although borderline for the latter) are less associated with symbolic environmental control than to a sense of agency and motor control, since the pre-SMA has also been linked to response selection and error processing (Grützmann et al., 2016; Kolling, Wittmann, et al., 2016; Wolpe et al., 2022). In fact, several studies have proposed that the ERN should be considered as a marker of motor

impulsiveness (Ruchsow, Spitzer, et al., 2005; Stahl & Gibbons, 2007; Taylor et al., 2018), which further corroborates findings of lower ERN following reduction of the pre-SMA and SMA activation (Balzus et al., 2022). One study has found that cortical thickness of the pre-SMA was associated with a specific subgroup of patients with OCD, composed predominantly by washers and checkers, in comparison to those with neutralising and hoarding compulsions (Wagner et al., 2019). This seems to suggest that dimensions with higher premonitory urges and overt motor behaviours could be particularly benefited by habit-reversal treatment (Shephard et al., 2021). Unfortunately, no measures of impulsivity were collected as part of this study, rendering it impossible to conclusively address this hypothesis.

Paradoxically, both HV groups exhibited an attenuation of the RP, making results somewhat more difficult to interpret. It is known that ERP components tend to decrease due to habituation and practice (Di Russo et al., 2005; Kononowicz & van Rijn, 2011; Kristeva, 1984; Wright et al., 2012), and that an ERP closely related to the RP, the Contingent Negative Variation (CNV), also generated by the SMA, has been reported to decrease over time (Kononowicz & van Rijn, 2011; Travers et al., 2021). It remains unclear, nonetheless, why this habituation did not occur in the OCD-NO-APP group.

The OCD-NO-APP group exhibited decreased amplitudes of error positivity at endpoint, with the OCD-APP group remaining unchanged. A possible explanation for this can be derived from the continuous feedback provided by the mobile application, which made participants more aware of their errors (de Souza et al., 2018; Hajcak et al., 2006; Holroyd et al., 2006; Holroyd & Coles, 2002; Luu et al., 2003). The lack of the same effect in the HV-NO-APP group, once again, seems to reflect different outcomes of the error monitoring system between controls and patients, as previously reported in chapter 3. This is further corroborated by an increase of ERN amplitudes in the HV-APP group, in opposition to the improvement of this component in the OCD-APP sample. It seems, thus, that whilst the application promotes relief and deactivation of the SMA in OCD, in HV it could be placing greater emphasis on performance and accuracy, a factor known to influence conflict monitoring (Hajcak et al., 2005; Holroyd et al., 2006; Nieuwenhuis, 2004). Nevertheless, this hypothesis awaits further investigation.

Behavioural performance, contrary to the original hypothesis, did not differ between baseline and endpoint for all groups, with the exception of extra-dimensional shift errors for both HV groups. Although difficult to conclusively address this difference, it is possible that controls have learned the task more efficiently than patients, given the exhaustively reported deficits in behavioural flexibility attributed to this sample (Chamberlain et al., 2021). Indeed,

the dorsal Anterior Cingulate Cortex (dACC), a core brain region implicated in OCD symptomatology (Graybiel & Rauch, 2000; Norman et al., 2019; Robbins et al., 2019), has also been linked to behavioural flexibility (Kolling, Wittmann, et al., 2016; Shenhav et al., 2013, 2016).

Finally, OCD severity, as measured by the Y-BOCS (Goodman et al., 1989), was significantly reduced in the NO-APP group, with ANOVAS indicating an effect of time, a contrasting result to the findings presented in chapter 4. It is possible that the heterogeneity of patients with OCD, due to the combination of Cambridge and NHS samples in the APP group, but not in the NO-APP group, have impacted these scores, given that the NHS OCD sample was significantly more severe than the Cambridge one (see Chapter 3). Nevertheless, the effects of the passage of time on Y-BOCS scores should be the subject of future investigation.

Despite its limitations, this study has provided evidence of the impact of introducing novel, ritualised behaviours to patients with OCD and healthy volunteers, compared with matched passive groups, highlighting not only the impact of the intervention, but effects of passage of time. The combination of neural, behavioural, and clinical measures in a longitudinal design adds to the intensive attempts of developing new treatments for OCD and once and for all disentangling the concepts of rituals and compulsions.

CHAPTER 6 – RETRIEVAL-INDUCED FORGETTING IN OCD

I would forget it fain,
But oh, it presses to my memory,
Like damnèd guilty deeds to sinners' minds.

Romeo & Juliet, Act III, Scene 2

William Shakespeare

1. Introduction

"Interruptive, salient, experienced mental events". This definition of intrusions, proposed by Visser and colleagues (2021, p.126)**,** derives from an extensive review of a plethora of circumstances in which intrusive thinking can be considered, both clinical and non-clinical (Visser et al., 2021). From athletes' performances to affect regulation, intrusions are a daily part of individuals' lives (Clark & Purdon, 1995), and can impact functioning both positive and negatively (Monfils & Buss, 2021).

Albeit mostly considered as an unpleasant phenomenon (Clark, 2005)**,** intrusions can, indeed, have a positive connotation, when thoughts of a loved one come into mind, for instance (Gregory et al., 2010). Nevertheless, their interruptive nature can hinder goal-directed behaviour, calling for cognitive and inhibitory control to the same extent as stopping an action does (Apšvalka et al., 2022)**.**

In Obsessive-Compulsive Disorder (OCD), a psychiatric condition marked by deficits in inhibitory control (Mar et al., 2022; Robbins et al., 2019; Ruscio et al., 2010), obsessions and intrusions are conceptualised almost interchangeably as unwanted thoughts, urges, or images, and their presence constitute the first criterion for the diagnosis of the disorder (American Psychiatric Association, 2013). The second one, represented by an attempt to suppress these unwanted thoughts, depicts the very core of the disorder: the feeling of being out of control (Visser et al., 2021).

Paradoxically, the more an individual with OCD attempts to control these intrusions, the stronger and more frequent they get, replicating the famous 'white bear' effect (Wegner, 1989). It is understood that the mere control attempt reinforces the thought by granting it

importance (Magee & Teachman, 2007), for who would bother trying to suppress irrelevant stimuli? Once the brain learns about the relevance of the intrusion, it increases the frequency in which it happens, leading to more attempts of suppression, anxiety due to the failure in controlling the thought, and behaviours aimed at weakening it, completing the OCD cycle (Visser et al., 2021) in what is known as the metacognitive model of OCD (Wells et al., 2017)**.** Thought suppression, therefore, has been extensively studied in a myriad of psychiatric conditions, including depression (Holmes & Mathews, 2010), post-traumatic stress disorder (Visser et al., 2018), attention deficit hyperactivity disorder (Franklin et al., 2017), addiction (Heinz, 2017), schizophrenia (Vosgerau & Voss, 2014), among others (Schlagenhauf et al, 2021).

Given the transdiagnostic nature of intrusive thinking (Pascual-Vera et al., 2017, 2019), researchers have attempted to investigate common underlying mechanisms of this phenomenon (Kalivas & Kalivas, 2016). Interestingly, results suggest the role of corticostriatal circuits (Balleine, 2021), which are at the core of OCD aetiology (Rauch et al., 1994), as a mechanism strongly associated with inhibitory control and the ability to override competitive stimuli in favour of goal-directed responses (Bari & Robbins, 2013; Hampshire et al., 2019).

Inhibitory control, thus, plays a role not only in the suppression of actions, but of thoughts as well (Aron et al., 2004, 2014; Guo et al., 2018). Evidence indicates that broad motor suppression is recruited in the face of intrusions, with one study reporting associations between a motor-evoked potential recruited in participants' hands and unwanted thoughts (Castiglione & Aron, 2021). Additionally, Castiglione and colleagues (2019) were also able to replicate findings of increased right frontal Beta for successful vs failed action and thought stopping (Castiglione et al., 2019). Nevertheless, the challenge remains as to how to best measure this phenomenon in a laboratory setting (Banich, 2021).

One of the paradigms developed to address this issue relates to memory retrieval (Anderson et al., 1994; Anderson & Green, 2001). Contrary to traditional views that forgetting is a passive mechanism, such as those proposed by the trace decay (Brown, 1958; Peterson & Peterson, 1959) or the classic interference (Muller & Pilzecker, 1900) theories, current approaches recognise the role of inhibitory control in thought suppression (Anderson, 2003; Murayama et al., 2014; Storm & Levy, 2012). Indeed, the ability to select and to stop particular thoughts amongst multiple competitors is essential for goal-directed behaviour and an integral part of executive control (Chamberlain et al., 2005), a key deficit in OCD (Chamberlain & Menzies, 2009; Marzuki et al., 2020; Menzies et al., 2007).

Perhaps not surprisingly, research suggests that this is indeed the case when participants with OCD are evaluated with the Retrieval Induced Forgetting (RIF) paradigm, showing no RIF effect (Demeter et al., 2014; Jelinek et al., 2012). Developed in 1994 by Anderson and colleagues (Anderson et al., 1994), the RIF task relies on the assumption that active retrieval of target items leads to inhibition of associated items that compete at retrieval. A classic version of the task involves word pairs pertaining to different semantic categories, such as fruits (fruit – banana; fruit – orange) and metal (metal – copper; metal – bronze), for example. Participants are presented with the category-exemplar pairs at baseline and will then solely practise a subset of the words of a subset of the categories, for instance, only the 'fruit' category and the exemplar 'banana', via category-plus-letter stem cues (i.e. fruit – b-----) (Marsh and Anderson, 2022). Exemplars practised at this stage are termed 'RP+', whereas neglected exemplars of practised categories (in the example above, the word 'orange') comprise the 'RP- ' group of stimuli. Unpractised items from unpractised categories (any metal exemplar, for instance) are known as 'NRP' (no retrieval practice).

A final stage of the task includes all category-exemplar pairs followed by a letter stem cue, with typical results suggesting that recall of the practised items is improved (Anderson et al., 1994). More interestingly, though, is the forgetting phenomenon that occurs with RP- items, which become less accessible than the NRP exemplars from baseline, demonstrating that retrieval recruits inhibition to overcome competing memories (Hellerstedt & Johansson, 2014) and causes forgetting (Anderson et al., 1994). A standard calculation of the RIF effect is, thus, conducted by comparing RP- vs NRP- exemplars, whereas the comparison of RP+ vs NRP+ serves as a measure of facilitation. The RIF effect, therefore constitutes an adaptive process to resolve conflict caused by competitive stimuli (Marsh & Anderson, 2022).

In OCD, research suggests not only that the RIF effect is absent (Demeter et al., 2014; Jelinek et al., 2012), but also that memory deficits in general are more strongly related to checking compulsions (MacDonald et al., 1997; Tolin et al., 2001). Nevertheless, the debate concerning memory abnormalities in OCD is still ongoing, with advocates suggesting both inherent deficits (Savage et al., 2000; Woods et al., 2002) and meta-cognitive ones (Cuttler & Graf, 2009; Harkin & Kessler, 2011).

One theory advanced to explain the relationship between memory and compulsive checking derives from the repetitive nature of the compulsion (Fradkin et al., 2020). Albeit a logical assumption would be that checking is caused by memory deficits, several researchers have shown the opposite, suggesting that checking may be responsible for memory uncertainty (Hansmeier et al., 2015; van den Hout et al., 2019; van den Hout & Kindt, 2004). Analogous

to the RIF paradigm, it is possible to assume that repetition could lead to forgetting or to the feeling of it, since retrieval can cause forgetting of competing items (Anderson et al., 1994; Camp et al., 2007; Racsmány et al., 2010). According to the inhibitory theory proposed to explain the RIF effect (Anderson, 2003; Anderson et al., 1994), competition between associated items and the retrieval target must be resolved through inhibition (Wimber et al., 2009, 2015). In the case of checking, it is plausible to argue that the memory of the action is constantly being updated, creating a loop of retrieval-induced forgetting.

Studies on the effect of checking and repetition have historically employed a paradigm called the 'stovetop task' (van den Hout & Kindt, 2003, 2004). In this task, participants are presented with a virtual stovetop and are asked to turn on and off specific burners that are displayed to them on the computer screen. In a classic version of the task, after each trial participants will indicate through a confidence bar how vivid is their recollection of turning the stove on/off and how confident they are that the burners are indeed off. Different manipulations of the task have been designed, with the possibility of checking or not, however, standard analyses tend to compare the results from the first and last trials, typically finding decreases in memory confidence in the general population (Burns et al., 2020; van den Hout et al., 2019; van den Hout & Kindt, 2003, 2004). Once again, this corroborates the assumption that repetition might be more causal then consequential concerning forgetting (van den Hout et al., 2019).

Given the extensive literature on the role of inhibition in the aetiology of OCD, contributing to both obsessions and compulsions, the present study aimed to investigate the relationship between control of thoughts and actions in OCD by combining the classic paradigms of RIF, stovetop task, and Stop-Signal Task. It was hypothesised that individuals with OCD, compared to control volunteers, would exhibit deficits in the three behavioural measures, underlying a common mechanism driving obsessions and compulsions.

2. Methods

2.1. Participants

Thirty-five individuals with OCD and 41 healthy volunteers took part in the study. Participants were recruited via social media and Prolific or had taken part in previous studies and had consented to be invited for new experiments. Inclusion criteria stipulated that all participants had to be aged between 18 and 65 years and be native English speakers, due to the verbal component of the RIF task. Exclusion criteria comprised the use of recreational drugs,

excessive alcohol intake (higher than 14 units/week), neurological or brain trauma, presence of learning disorders, ADHD, and nicotine consumption less than 4h prior to the experiment, due to the effects of this substance on the RIF task (Edginton & Rusted, 2003; Rusted & Alvares, 2008). Specific exclusion criteria for control participants involved the presence of any psychiatric conditions, as measured by the standard screening of Structured Clinical Interview Research Version (SCID-RV) for DSM-5 (First et al., 2018) and use of psychiatric medication. Participants with OCD, though, could present comorbid disorders (aside from those mentioned as exclusion criteria), providing that OCD was the primary diagnosis. A psychiatrist would assess the participants in case of doubt. Table 1 in the results section depicts demographic information of the sample.

2.2. Materials and Procedure

Upon demonstration of interest in the study, participants would receive the Participant Information Sheet (PIS) which described the study's procedures and would consent to the screening phase. The study followed guidelines proposed by the Declaration of Helsinki (1964) and was approved by the Psychology Research Ethics Committee of the University of Cambridge.

The study was conducted entirely online, via Qualtrics and Inquisit, and contact with participants was achieved through e-mail. At this point, all participants would receive unique identification codes (IDs), to ensure anonymous data storage. The screening phase involved acceptance of the consent form, followed by demographic questions related to age, gender, educational level, native language, and health history. The Beck Depression (BDI-II) (Beck et al., 1996) and the Obsessive-Compulsive (Foa et al., 1998) inventories were also completed at this stage.

Upon completion of the screening, a trained researcher would verify participants' responses and decide upon inclusion or exclusion. All subjects would be informed of the decision, regardless of outcome. Included subjects would then be invited to proceed with the study and receive a Qualtrics link directing them to a new consent form, followed by the remaining of the experiment. A new link containing the self-report questionnaires was sent separately, to avoid burden on participants due to the length of the study, which had an approximate duration of 1h30 minutes. Participants in the OCD group would, additionally, be asked to complete the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989) with a trained researcher (see Chapter 2-Methods, for a description of the Y-BOCS). Subjects were paid £15 Amazon vouchers for their participation.

2.2.1. Behavioural paradigms

2.2.1.1. RIF task

This task was designed on Qualtrics and comprised neutral category-exemplar pairs, with a total of eight categories with six exemplars each, plus two filler categories. Despite being neutral, to maximise the RIF effect, the exemplars chosen varied in strength (strong = high frequency; weak = low frequency in common vocabulary), with strong words placed as RP- items, which increased competition. For instance, a strong word in the category fruit could be 'apple' (high frequency), whereas the word 'fig' would represent a weak (low frequency) one. The task consisted of 3 stages:

Initial encoding phase - An incidental encoding design was used. Participants were presented with each category-exemplar pair for three seconds, and then were asked to indicate how well the exemplar 'fits' the category on a response bar ranging from 0 (not at all) to 5 (perfect fit). To ensure participants were paying attention to the experiment, a few items that did not fit the associated category were displayed, and participants would be excluded if they did not mark '0' in the response bar. Pairs were presented only once, and no learning criterion was stipulated.

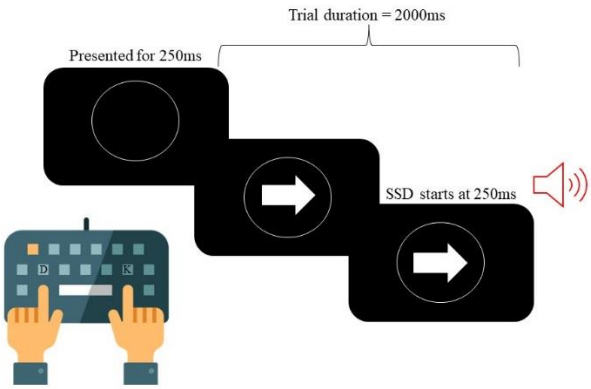
Retrieval practise phase - Participants practised retrieving a subset of exemplars from a subset of categories, in a counterbalanced design. They were presented with the category name and a 2-letter stem of the target exemplar (e.g. Fruit: Fi___?), having to type the correct word in a response box. Each exemplar was presented three times. Once the practice was finished, a distracting task with a duration of approximately 15 minutes, not related to memory (in this case, the Stop-Signal Task), was administered.

Final recall test - The final stage required participants to recall all studied items. Category + single letter stem words were presented one by one, and participants were asked to type the correct word in the test box (E.g. Fruit: F___?). At this stage, RP- exemplars and their baseline (NRP-) are tested first, being followed by practised exemplars (RP+) and NRP+. NRP+ and NRP- are defined based on their serial position during the study phase. This order of the final recall test ensures that the RIF effect can be more reliably attributed to an inhibitory aftereffect, rather than forgetting due to interference from earlier retrieval of practised items on later retrieval of unpractised ones, a phenomenon termed 'blocking' (Marsh & Anderson, 2022). Final RIF scores are obtained through the subtraction of the total number of correctly recalled RP- items from correctly recalled NRP- items (RIF = NRP- minus RP-). Higher scores, hence, indicate higher inhibition (i.e. forgetting).

2.2.1.2. Stop-Signal Task

The Stop-Signal Task was run on Inquisit 6 (2020) and was composed of one practice block (32 trials) plus three blocks of 72 trials (432 active trials) of arrows as stimuli. Trials initiated with a fixation circle on a black screen, followed by a white right or left-pointing arrow inside it. The direction of the arrow was determined at random, however, it was equally divided between right and left (50% of trials each). Participants were asked to press the letter K or the letter D on the keyboard for right and left responses, respectively, unless a beep sound (stop signal) was played after the presentation of the arrow, indicating the need to suppress the motor response. Participants could respond until the next trial started. The distribution of 'go' and 'stop' trials was set at 3:1, resulting in 18 'stop' trials per active block. A tracking algorithm was in place and adjusted the Stop-Signal Delay (SSD) by 50ms (up to 1150ms) up or down, depending on the success of the previous 'stop' trial. The initial SSD was set at 250ms. Stimulus onset asynchrony between the start of each trial (presentation of the fixation circle) was set at 2000ms. The task had an approximate duration of 15 minutes and was developed incorporating the 'best practice' recommendations by Verbruggen and colleagues (Verbruggen et al., 2019). Figure 1 depicts a typical trial of Inquisit's stop-signal task.

Figure 1. *Typical trial of the SST.*

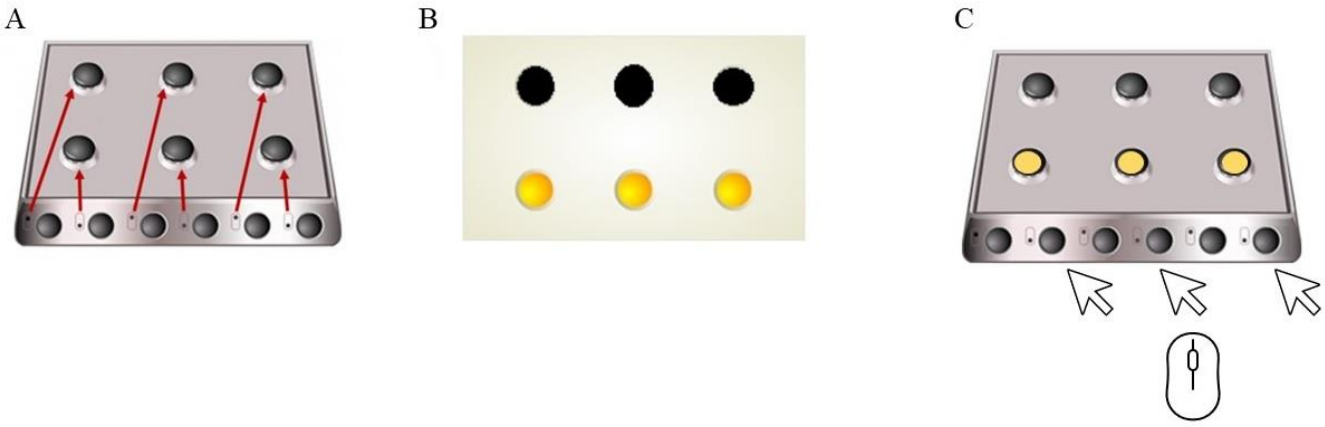


2.2.1.3. Stovetop task

This task was implemented in Qualtrics and developed by Burns and colleagues (Burns et al., 2020). It consisted of a practice trial followed by six active trials in which participants were asked to manipulate a virtual stovetop. Trials initiated with a three second presentation of a schematic diagram consisting of two rows of three circles inside a rectangle, with three

randomly selected circles highlighted in yellow, each representing a burner. They were then shown a more realistic picture of a stovetop and asked to turn on and off (by clicking on the corresponding knobs below the stove) the burners they had been presented with in the previous screen. The knobs turned green once selected. The stovetop was, therefore, presented twice, so that participants could turn burners on and off. After each trial, memory confidence, vividness, and desire to check were measure through a sliding bar ranging from 0 to 100. Importantly, solely after trials one (first) and six (last), memory of the burners manipulated was tested. This was done after participants had turned the burners off, when they were presented with a short distractor task (counting the number of "M″s in a row of 40 uppercase letters) and then asked to select the three burners they had previously turned on/off. Participants were allowed unlimited time and clicks on each stovetop before seeing the next trial. A schematic representation of the task is found below.

Figure 2. *Depiction of the stovetop task.*



Panel **A**. Schematic representation of the virtual burners and corresponding knobs. **B.** Illustration of burners to be turned on/off in the proceeding trial, displayed for 3 seconds. **C**. Virtual stovetop with computer mouse and arrows indicating where participants should click (virtual knobs) to turn on (yellow circles) the burners presented on the previous screen (panel B).

2.2.2. Self-report questionnaires

2.2.2.1. Ruminative Responses Scale (RRS) - (Treynor et al., 2003)

This questionnaire is composed of 22 items that measure thoughts and attitudes people engage on when feeling sad or depressed. Responses are rated on a 4-point Likert scale, ranging from 1 (almost never) to 4 (almost always). Total scores are obtained by the sum of the items,

with higher scores indicating stronger ruminative responses. This questionnaire, however, can also be subdivided in factors, namely depression, brooding, and reflection (Treynor et al., 2003).

2.2.2.2. Thought Control Ability Questionnaire (TCAQ) – (Luciano et al., 2005)

Developed to assess individual differences in the ability to control unwanted thoughts, the TCAQ is a 25-item questionnaire scored on a 5-point Likert scale ranging from 1 (completely disagree) to 5 (completely agree). Items represent statements that some people make when referring to thoughts, images, memories, and urges that intrude in their minds. Total scores are obtained by the sum of the items, with higher scores indicating lower ability to control unwanted intrusions.

2.2.2.3. Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale (UPPS-P) - (Whiteside & Lynam, 2001)

Composed of 59 items, this questionnaire was developed to create consensus on traits measured across different impulsivity scales (Whiteside & Lynam, 2001). Participants are asked to rate agreement on a series of items that describe ways in which people act and think via a 4-point Likert scale ranging from 1 (agree strongly) to 4 (disagree strongly). The scale is subdivided into 5 factors, measuring: i) negative urgency, conceptualised as a tendency to act impetuously under negative emotions; ii) lack of premeditation, described as a proneness to act without thinking; iii) lack of perseverance, reflecting an inability to persist on activities; iv) sensation seeking, representing a tendency to pursue novel and exciting activities; and v) positive urgency, defined as a proneness to act rashly under positive emotions. Higher scores indicate more impulsive behaviour.

2.2.2.4. Memory and Cognitive Confidence Scale (MACCS) - (Nedeljkovic & Kyrios, 2007)

This questionnaire comprises 28 items that assess beliefs about memory and related processes, such as confidence in one's ability to focus, make decisions, and expectations about cognitive performance. Participants are asked to rate the extent to which each item applies to them on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Higher scores suggest lower belief in memory abilities. This scale can also be subdivided in four factors, namely 'general memory', 'decision-making', 'concentration', and 'perfectionism' (Nedeljkovic & Kyrios, 2007).

2.2.2.5. Beck-Depression Inventory II (BDI-II) - (Beck et al., 1996)

This questionnaire comprises 21 items that assess depressive mood in the general population, based on feelings and beliefs concerning the past two weeks of the individuals' lives. Questions are rated through a 4-point scale, with 0 indicating the absence of the depressive mood/belief and 3 indicating the highest severity. Typical cut-off thresholds suggest that scores above 17 fall within the clinical range.

2.2.2.6. Obsessive-Compulsive Inventory (OCI) - *(*Foa et al., 1998)

For a detailed description, see Chapter 2 (Methods).

2.2.2.7. State-Trait Anxiety Inventory (STAI-T) - (Spielberger et al., 1983).

For a detailed description, see Chapter 2 (Methods).

2.2.2.8. Intolerance of Uncertainty Scale (IUS) - (Buhr & Dugas, 2002; Carleton et al., 2007)

For a detailed description, see Chapter 2 (Methods).

2.2.2.9. Creature of Habit Scale (COHS) - (Ersche et al., 2017)

For a detailed description, see Chapter 2 (Methods).

2.2.2.10. Habitual Tendencies Questionnaire (HTQ) - (Ramakrishnan et al., 2022)

For a detailed description, see Chapter 2 (Methods).

2.2.2.11. Self-Control Scale (SCS) - (Tangney et al., 2004)

For a detailed description, see Chapter 2 (Methods).

2.2.2.12. Habitual Self-Control Questionnaire (HSCQ) - (Schroder et al., 2013)

For a detailed description, see Chapter 2 (Methods).

3. Results

3.1. Demographic, clinical, and self-report measures

Given the fact that this study is still ongoing, preliminary results are presented as part of this thesis. Based on a power analysis assuming a medium effect size (≥ 0.3), the final sample is estimated as 84 participants with OCD and 60 healthy volunteers. Table 1 depicts current demographic and clinical data for both groups of participants.

Table 1. *Demographic and clinical characteristics of OCD patients and healthy volunteers*

	HV (n= 41)	OCD (n= 35)	t	df	p	d
Gender ratio (male/female/non-binary)	17/24	7/27/1	$X^2 = 4.9$	2	0.086	-
Age	42.3 (11.9)	33.2 (11.6)	3.37	74	0.001*	0.78
Medication ratio (yes/no)	0/41	21/14	-	-	-	-
YBOCS	0.0	20.9 (6.7)	-	-	-	-
YBOCS Obsessions	0.0	10.7 (3.7)	-	-	-	-
YBOCS Compulsions	0.0	10.2 (3.7)	-	-	-	-
Trait Anxiety (STAI-T)	38.4 (11.2)	55.4 (11.7)	-6.34	71	<0.001*	-1.49
BDI[a]	5.0 (4.8)	11.9 (9.3)	-3.89	46	<0.001*	-0.94
OCI_42[a]	10.0 (14.2)	55.7 (25.9)	-9.32	48	<0.001*	-2.24
OCI_12[a]	3.4 (4.7)	19.0 (8.5)	-9.80	49	<0.001*	-2.3
Washing[a]	0.4 (0.9)	3.9 (4.3)	-4.8	34	<0.001*	-1.15
Checking[a]	1.3 (2.2)	4.3 (3.2)	-4.56	55	<0.001*	-1.11
Ordering[a]	1.0 (1.6)	3.2 (3.1)	-3.90	47	<0.001*	-0.92
Obsessing[a]	0.7 (1.3)	7.6 (3.8)	-10.4	38	<0.001*	-2.57

* $p < 0.05$ level (2-tailed). [a] Levene's test is significant, therefore equal variances were not assumed.

OCD: Obsessive-compulsive disorder; HV: Healthy volunteers; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; STAI: The State-Trait Anxiety Inventory; BDI: Beck Depression Inventory; OCI: Obsessive-Compulsive Inventory.

As can be seen on the table, 2/3 of the OCD sample was taking psychiatric medication, most of them (n=18) Selective Serotonin Reuptake Inhibitors (SSRI), namely: i) Sertraline (n=10); ii) Fluoxetine (n=4); iii) Paroxetine (n=2); iv) Escitalopram (n=1); and v) non-specified SSRI (n=1). Two additional participants were medicated with Tricyclic Antidepressants (Clomipramine (n=1) and Nortriptyline (n=1)). The remaining patient was receiving beta blockers (Propranolol) solely. Finally, two of the patients medicated with SSRI were also taking beta blockers (n=1) or atypical antipsychotic drugs (n=1).

Results of the self-reported questionnaires are presented below. The vast majority of measures were significantly different between groups, with the exception of the Creature of Habit Scale (COHS) and its subscales, the Habitual Self-Control Questionnaire (HSCQ), the Self-Control Scale (SCS), the aversion to novelty subscale of the Habitual Tendencies Questionnaire (HTQ), and the positive and negative urgency and lack of perseverance subscales of the Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale (UPPS-P).

Table 2. *Self-reported questionnaires*

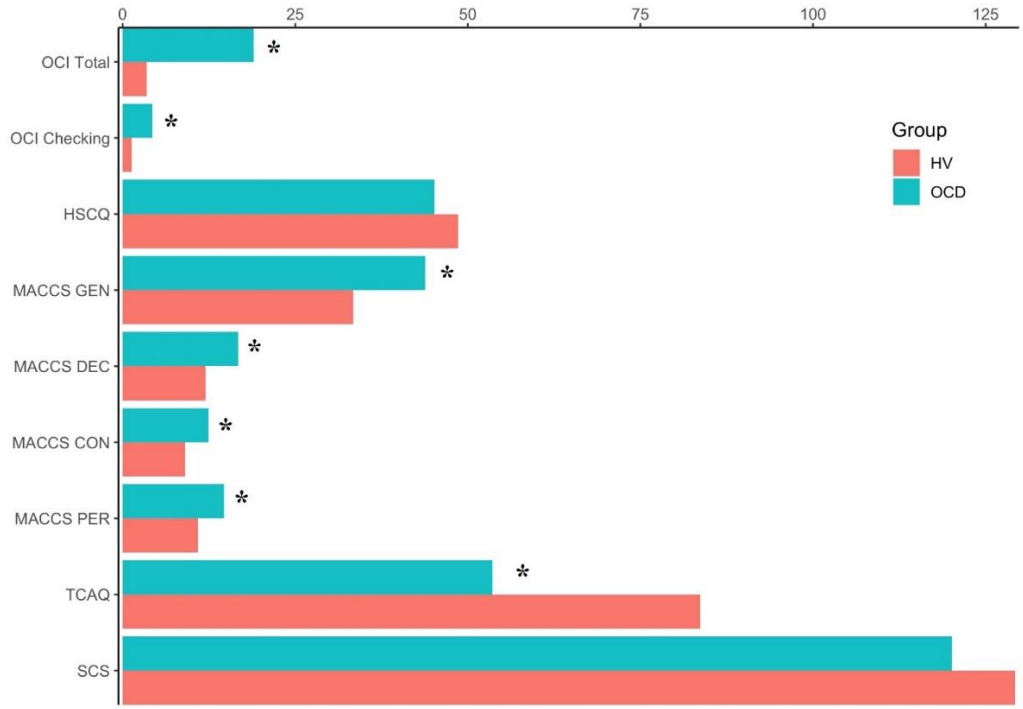
	HV (n= 40)	OCD (n= 33)	t	df	p	d
COHS routine	52.5 (11.0)	56.6 (10.8)	-1.58	71	0.12	-0.37
COHS automaticity[b]	32.1 (11.0)	41.4 (30.3)	U = 633.5	-	0.773	-0.04
HSCQ	48.6 (8.7)	45.2 (10.5)	1.53	71	0.13	0.36
HTQ Total	40.9 (11.0)	55.2 (7.6)	-6.33	71	<0.001*	-1.49
HTQ compulsivity[a]	15.2 (6.6)	23.9 (3.7)	-7.14	63	<0.001*	-1.59
HTQ preference for regularity	17.1 (5.0)	21.0 (3.9)	-3.69	71	<0.001*	-0.87
HTQ aversion to novelty	8.6 (3.1)	10.3 (3.7)	-2.22	71	0.03	-0.52
RRS Total	38.2 (11.7)	53.5 (14.0)	-5.07	71	<0.001*	-1.2
RRS depression	21.3 (6.7)	29.2 (8.6)	-4.43	71	<0.001*	-1.04
RRS brooding	8.5 (2.8)	13.2 (3.5)	-6.34	71	<0.001*	-1.49
RRS reflection	8.5 (3.1)	11.1 (3.4)	-3.38	71	<0.001*	-0.79
MACCS GEN	33.4 (15.8)	43.8 (15.8)	-2.8	71	0.01*	-0.66
MACCS DEC	12.0 (4.9)	16.7 (5.2)	-3.98	71	<0.001*	-0.94
MACCSCON	9.1 (3.4)	12.4 (4.3)	-3.77	71	<0.001*	-0.89
MACCSPER	10.9 (3.3)	14.7 (3.7)	-4.55	71	<0.001*	-1.07
TCAQ	83.6 (16.0)	53.6 (16.7)	7.83	71	<0.001*	1.84
SCS	129.3 (20.8)	120.1 (21.3)	1.85	71	0.07	0.43
IUS Total	56.9 (20.9)	86.9 (22.4)	-5.9	71	<0.001*	-1.39
IUS prospective	29.6 (11.2)	45.8 (13.6)	-5.57	71	<0.001*	-1.31
IUS inhibitory	27.3 (10.6)	41.1 (10.1)	-5.64	71	<0.001*	-1.32
UPPS-P positive urgency	23.9 (9.3)	23.8 (7.9)	0.03	71	0.98	0.007
UPPS-P negative urgency	25.5 (7.8)	28.5 (6.7)	-1.8	71	0.08	-0.42
UPPS-P lack of premeditation	22.2 (4.4)	19.6 (4.8)	2.45	71	0.02*	0.58
UPPS-P lack of perseverance	18.8 (4.4)	19.5 (4.3)	-0.77	71	0.44	-0.2
UPPS-P sensation seeking	31.5 (8.5)	25.8 (6.9)	3.07	71	<0.001*	0.72

* $p < 0.05$ level (2-tailed). [a] Levene's test is significant, therefore equal variances were not assumed. [b]Mann-Whitney and rank biserial correlation tests used.

COHS: Creature of Habit Scale; HSCQ: Habitual Self Control Questionnaire; HTQ: Habitual Tendencies Questionnaire; RRS: Ruminative Responses Scale; MACCS: Memory and Cognitive Confidence Scale; TCAQ: Thought Control Ability Questionnaire; SCS: Self-Control Scale; IUS: Intolerance of Uncertainty Scale; UPPS-P: Impulsive Behavior Scale.

For visualisation purposes, a bar plot of the questionnaires directly related to memory and inhibition is provided below.

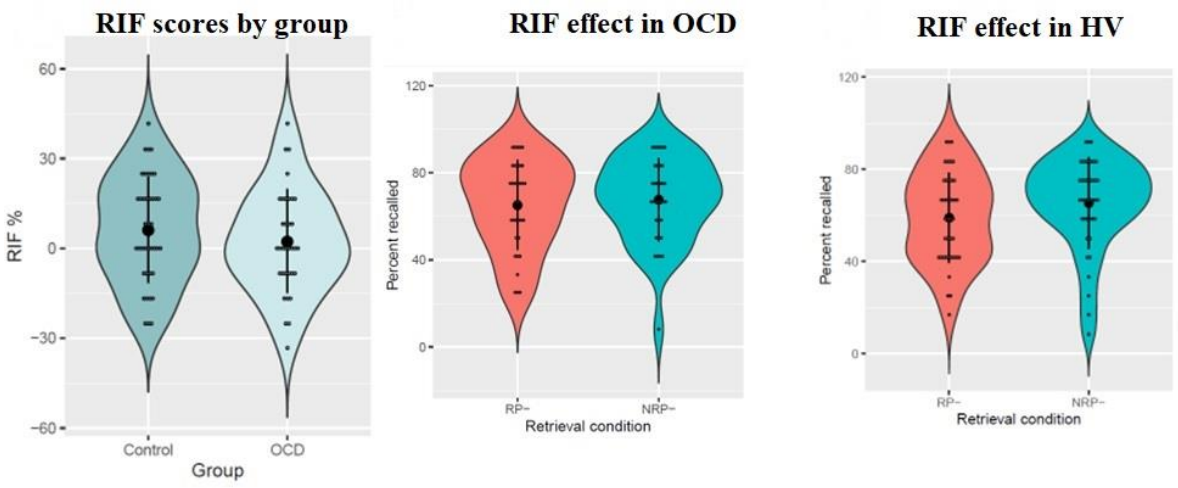
Figure 3. *Bar plot of memory and inhibition questionnaires.*



*p<0.05 (2-tailed). **X** axis. Self-report questionnaires. **Y** axis. Total scores on each questionnaire. OCI: Obsessive-Compulsive Inventory; HSCQ: Habitual Self Control Questionnaire; MACCS: Memory and Cognitive Confidence Scale; TCAQ: Thought Control Ability Questionnaire; SCS: Self-Control Scale.

3.2. Behavioural paradigms

3.2.1. RIF Task



A total of 40 healthy volunteers and 34 patients with OCD contributed to the analyses. Control participants, as predicted, showed a significant RIF effect (RP- = 58.97, SD = 19.64; NRP- = 65.20, SD = 19.78), t (39) = -2.22, p = 0.032, d = 0.351. Nevertheless, no RIF effect was observed in the OCD sample (RP- = 65.2, SD = 20.66; NRP- = 67.65, SD = 19.22), t (33) = 0.83, p = 0.41, d = 0.14. However, RIF scores (HV = 6.25%, SD = 17.78%; OCD = 2.46%, SD = 17.35%) were not significantly different between groups t (72) = 0.926, p = 0.358, d = 0.22.

3.2.2. Stop-Signal Task

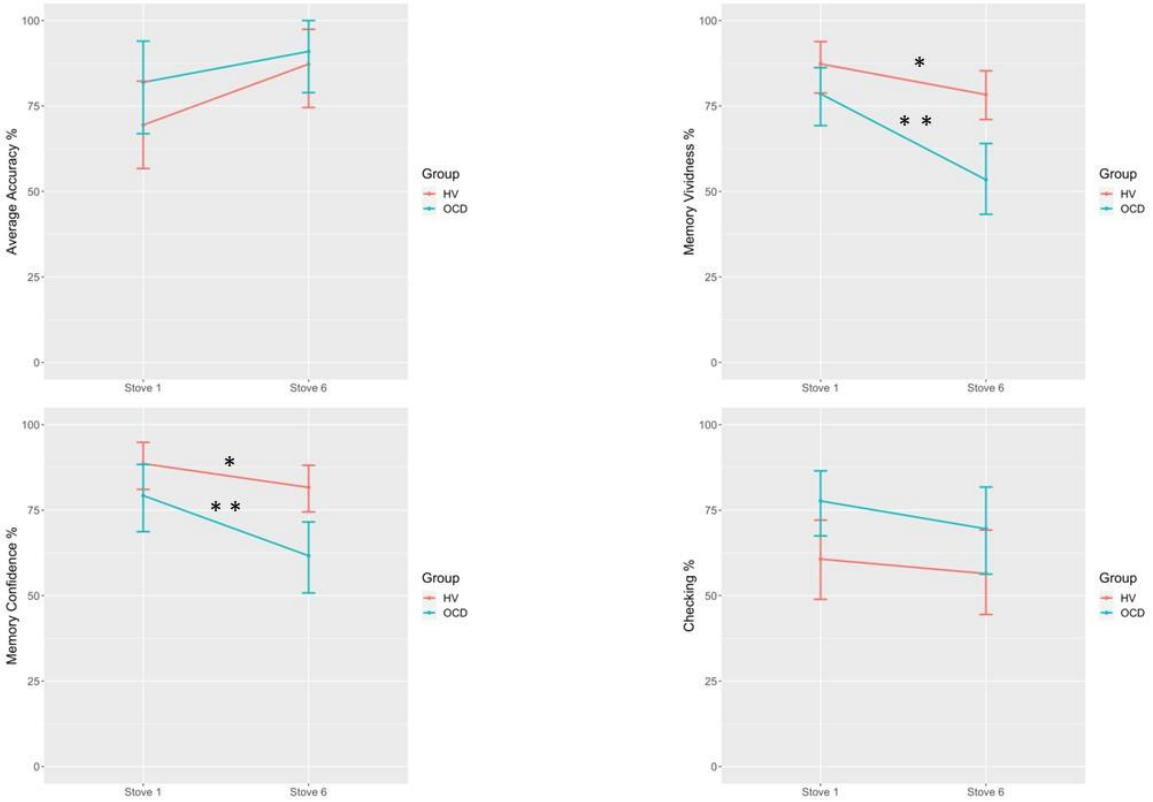
Results of the SST are reported below. Three subjects were excluded from SSRT and 1 from probability analyses due to violations of the race model assumption and of the probability to responding to the stop-signal (Verbruggen et al., 2019).

Table 3. *SST descriptive and between-group statistics.*

	HV (n= 41)	OCD (n= 35)	t	df	p	d
Probability of responding to stop	49.5 (5.1)	51.6 (10.5)	-1.15	71	0.25	-0.27
Go Hits	97.6 (2.9)	97.6 (3.2)	0.04	72	0.96	0.01
SSD	309.7 (172.4)	299.2 (163.3)	0.27	72	0.79	0.06
SSRT	221.3 (82.7)	205.5 (75.4)	0.81	66	0.42	0.2

* $p < 0.05$ level (2-tailed)

3.2.3. Stovetop Task



*p<0.05 (2-tailed). **p<0.001 (2-tailed).

A repeated-measures analysis of covariance (ANCOVA), with age as a covariate, was conducted to assess the differences between groups for stoves 1 and 6 with regards to accuracy, memory confidence, memory vividness, and desire to check. Results for accuracy indicated both a significant within subjects effect of time ($F(1,69) = 4.5$, $p = 0.037$, η^2=0.026), and an interaction between time and age ($F(1,69) = 8.677$, $p = 0.004$, $\eta^2 = 0.049$), with no between subjects effects of group ($F(1,69) = 0.851$, $p = 0.359$, $\eta^2 = 0.006$) or age ($F(1,69) = 0.474$, $p = 0.494$, $\eta^2 = 0.004$) found. Memory confidence was significantly different as a result of time ($F(1,69)$, $= 4.095$, $p = 0.047$, $\eta^2 = 0.010$) and group ($F(1,69) = 8.417$, $p = 0.005$, $\eta^2 = 0.088$), with no interactions or effects of age ($F(1,69) = 1.044$, $p = 0.310$, $\eta^2 = 0.011$). Memory vividness, on the other hand, showed significant effects of time ($F(1,69) = 10.234$, $p = 0.002$, η^2=0.028), group ($F(1,69) = 9.723$, $p = 0.003$, $\eta^2 = 0.094$) and an interaction between time and group ($F(1,69) = 4.610$, $p = 0.035$, $\eta^2 = 0.013$). Results on checking did not suggest an effect of time ($F(1,69) = 0.868$, $p = 0.355$, $\eta^2 = 0.002$), group ($F(1,69) = 2.806$, $p = 0.098$, $\eta^2 = 0.034$) or interactions between time and group ($F(1,69) = 0.212$, $p = 0.646$, $\eta^2 = 0.00037$). Table 4 depicts means and standard deviations for both groups on the task.

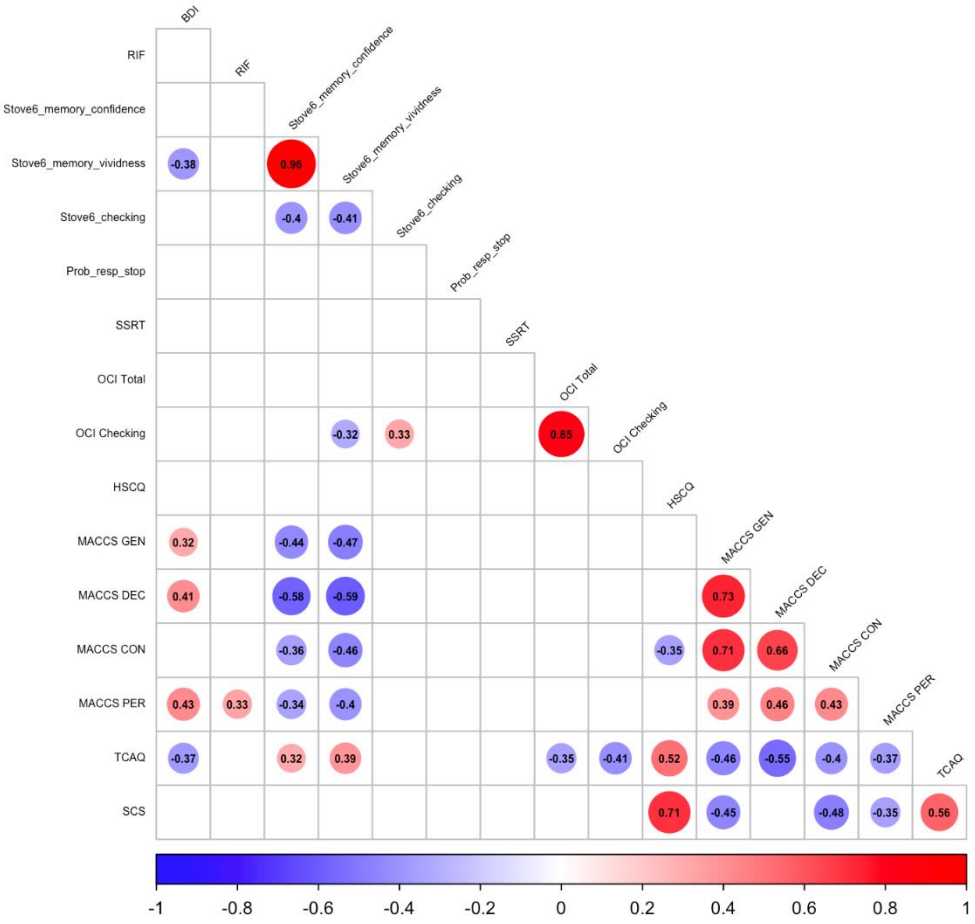
Table 4. *Stovetop task descriptive statistics*

Time	Group	Mean	SD	N
Stove 1 avg accuracy	HV	69.453	46.42	39
	OCD	81.946	38.892	33
Stove 6 avg accuracy	HV	87.279	33.605	39
	OCD	90.963	29.021	33
Stove 1 memory confidence	HV	88.615	22.203	39
	OCD	79.273	27.394	33
Stove 6 memory confidence	HV	81.641	21.741	39
	OCD	61.667	30.03	33
Stove 1 memory vividness	HV	87.333	23.79	39
	OCD	78.576	25.617	33
Stove 6 memory vividness	HV	78.333	22.664	39
	OCD	53.424	31.167	33
Stove 1 checking	HV	60.692	39.183	39
	OCD	77.697	30.028	33
Stove 6 checking	HV	56.436	40.811	39
	OCD	69.545	37.336	33

3.3. Correlations

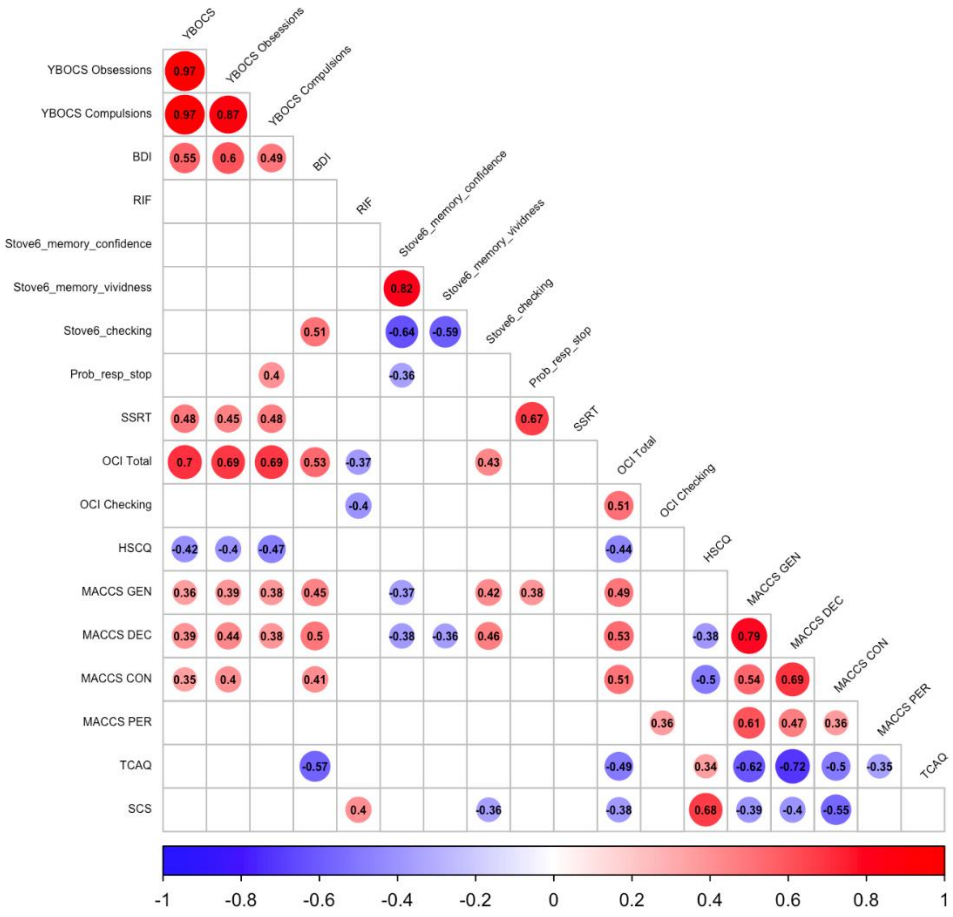
Heat maps divided by group (OCD and HV) are provided below. Given the large number of possible correlations, variables more closely related to memory and inhibitory control were included. Results indicated few correlations in the HV group, demonstrating strong positive associations between confidence and memory vividness on the stovetop task and an appropriate checking response negatively associated to those. In the OCD group, severity of OCD symptomatology, as measured by the Y-BOCS and the OCI, was associated to deficits on all behaviour paradigms, and strong correlations between self-report questionnaires were also found and behaviour deficits could also be seen.

3.3.1. HV



RIF: Retrieval-Induced Forgetting; BDI: Beck Depression Inventory; Prob_resp_Stop: probability of responding to stop; SSRT: Stop-Signal Reaction Time; OCI: Obsessive-Compulsive Inventory; OCI Checking: Checking subscale of the Obsessive-Compulsive Inventory; HSCQ: Habitual Self-Control Questionnaire; SCS: Self-Control Scale; TCAQ: Thought-Control Ability Questionnaire; MACCS GEN, DEC, CON, and PER: General, Decision-Making, Confidence and Perfectionism subscales of the Memory and Cognitive Confidence Scale.

3.3.2. OCD



YBOCS: Yale-Brown Obsessive-Compulsive Scale; RIF: Retrieval-Induced Forgetting; BDI: Beck Depression Inventory; Prob_resp_Stop: probability of responding to stop; SSRT: Stop-Signal Reaction Time; OCI: Obsessive-Compulsive Inventory; OCI Checking: Checking subscale of the Obsessive-Compulsive Inventory; HSCQ: Habitual Self-Control Questionnaire; SCS: Self-Control Scale; TCAQ: Thought-Control Ability Questionnaire; MACCS GEN, DEC, CON, and PER: General, Decision-Making, Confidence and Perfectionism subscales of the Memory and Cognitive Confidence Scale.

3.4. Summary of findings

- Solely the HV group presented a RIF effect
- Memory confidence and vividness decreased for both groups from the first to the last trial of the stovetop task
- The OCD group reported worse memory and ability to control thoughts
- Checking was not impacted by the stovetop task
- SST measures did not differ between groups
- Correlations between the three paradigms suggest a general inhibitory deficit in OCD

4. Discussion

The ability to control thoughts and actions in favour of goal-directed behaviour is essential for an adaptive life (Coutlee & Huettel, 2012; Logan et al., 2014; Logan & Cowan, 1984), and serves a protective role against the development of psychopathologies (Linkovski et al., 2021; Nigg, 2017). Indeed, a myriad of psychiatric conditions are marked by deficits in inhibitory control, such as depression (García-Martín et al., 2021; Li et al., 2021), anxiety (Cardinale et al., 2019; Myles et al., 2020), obsessive-compulsive disorder (Marzuki et al., 2020; Robbins et al., 2019; Vaghi, 2021), among others.

Rather than distinct cognitive abilities, evidence suggests that suppression of thoughts and actions is regulated by the same mechanisms, with corticostriatal brain regions implicated (Apšvalka et al., 2022; Aron et al., 2004; Castiglione & Aron, 2021). Given obsessive-compulsive disorder's characterisation as a condition marked by obsessions (intrusive and uncontrollable thoughts, urges, and images), and compulsions (repetitive behaviours and mental acts that the individual feels driven to perform), accompanied by persistent attempts to suppress those (American Psychiatric Association, 2013), this study aimed to investigate inhibitory control in a sample of patients with OCD and healthy volunteers (HV).

Suppression of thoughts and actions were measured through robust behavioural paradigms, namely the Retrieval-Induced Forgetting (RIF) paradigm (Anderson et al., 1994) and the Stop-Signal Task (Lappin & Eriksen, 1966; Logan & Cowan, 1984). Additionally, metacognitive beliefs about memory were assessed with the classic stovetop task (Burns et al., 2020; van den Hout & Kindt, 2003).

Results of the RIF task corroborated previous literature (Demeter et al., 2014; Jelinek et al., 2012), suggesting no group differences between OCD and HV, albeit demonstrating significant RIF effects in HV and the absence of an effect in patients with OCD. Nevertheless, a trend towards higher inhibition in HV, as represented by higher RIF means, was observed. Interestingly, though, solely in the OCD sample, the RIF effect correlated negatively with total scores on the Obsessive-Compulsive Inventory (OCI) (Foa et al., 1998) and its 'checking' subscale, and positively with self-control as measured by the Self-Control Scale (SCS) (Tangney et al., 2004) . These results add support to the hypothesis that checking compulsions may impact RIF in an analogous way as they interact with memory, sharing repetition as a common mechanism (Hansmeier et al., 2015; Harkin & Kessler, 2011; Radomsky et al., 2006; van den Hout & Kindt, 2003b, 2004). Additionally, higher self-reported checking in the OCD sample correlated positively with metacognitive beliefs of high standards in cognitive performance, which can be defined as perfectionism (Nedeljkovic & Kyrios, 2007). This key feature of OCD symptomatology (Pozza et al., 2019; Wong et al., 2021), hence, is thought to be associated to 'not just right' behaviours (Moretz & McKay, 2009; Tolin et al., 2008), which lead to repetition, checking and memory distrust (Tolin et al., 2001).

The results of the stovetop task support these interpretations. Albeit both patients and controls exhibited significant decreases in memory confidence and vividness, these effects were more pronounced in the OCD sample, who also resorted to checking more strongly. Not surprisingly, memory vividness and confidence in patients with OCD was negatively associated with dysfunctional beliefs on general memory and decision-making - once more illustrating the impact of metacognition in OCD symptomatology (Harkin & Kessler, 2011; van den Hout & Kindt, 2004; Wells et al., 2017).

Contrary to the hypothesis, nevertheless, no differences were found between OCD and HV in the Stop-Signal task, although results indicated a greater probability of patients responding inappropriately more on the 'stop' trials, a clear marker of inability to inhibit actions (Logan et al., 2014; Verbruggen et al., 2019). Corroborating the hypothesis, though, SSRT in the OCD sample was positively correlated with YBOCS score, and greater probability of responding to 'stop' trials was associated with each of (i) YBOCS compulsions, (ii) lower memory confidence in the stovetop task, and (iii) more dysfunctional beliefs about general memory, with no correlations being found in the control sample. Taken together, these results appear to indicate a general inhibitory control deficit in OCD, encompassing thoughts and actions and mediated by dysfunctional metacognitive beliefs (Apšvalka et al., 2022; Castiglione & Aron, 2021; Seow & Gillan, 2020; Wells et al., 2017), with repetition playing a

key role both causally and consequentially in the maintenance of OCD symptomatology (Tolin et al., 2008; Visser et al., 2021; Wong et al., 2021; Woods et al., 2002).

This study, nonetheless, had limitations that should be addressed. Firstly, the incomplete sample size hinders reliable interpretation of results. Secondly, given the online nature of the experiment, it is not possible to assume total concentration of the participants whilst undertaking the tasks, which may affect the results. Albeit attentional checks were in place to minimise these caveats, some participants have reported difficulties with software downloads (i.e. Inquisit) and distractions during the presentation of stimuli in the tasks. Regardless of their exclusion from the final data analyses, it remains a challenge to differentiate those participants from the ones that did not report issues, although being affected by them. Most importantly, delays in the SST would severely impact the RIF final recall phase, since the former served as a distractor for the latter. Finally, the stovetop task designed might have been somewhat arduous, as participants showed a significant increase in accuracy between trials 1 and 6, with a significant effect of age, which was mainly driven by the HV group. These results corroborate evidence that older adults experience higher difficulties with technology (Czaja et al., 2006), with qualitative analyses suggesting strains in attributing knobs to burners by older participants, which seem to have been resolved by practice. These findings, unfortunately, impact the possibility of addressing basic memory deficits in both samples of the study.

However, this study provides some preliminary evidence of general inhibitory control deficits in OCD in three well-established and robust paradigms, suggesting that both basic suppression difficulties and metacognitive beliefs play a role in OCD symptomatology. Future goals of this study involve including a sample of first degree relatives of patients with OCD, given that inhibitory control deficits are thought to be an endophenotype of the disorder (Chamberlain & Menzies, 2009; Marzuki et al., 2020; Vaghi, 2021). This would bring research closer to finally being able to answer the ‘who came first?’ dilemma between inhibition of thoughts and actions.

CHAPTER 7 – GENERAL DISCUSSION

All's Well That Ends Well

William Shakespeare

Regulating and inhibiting behaviours is one of the most crucial abilities individuals must develop to live adaptive and functioning lives (Apšvalka et al., 2022; Riesel, 2019). If one is unable to control the urge to go out or cannot stop irrelevant thoughts from coming to mind whilst studying for an important exam, this will have serious consequences over their performance and will hinder goal-directed behaviour. This example, as elementary as it may seem, underlies a rather complex mental disorder characterised by the inability to control actions and thoughts, which leads to significant distress and quality of life impairment (American Psychiatric Association, 2013).

Obsessive-compulsive disorder (OCD), a condition that affects between 2-3% of the world's population (Ruscio et al., 2010), is marked by the presence of obsessions (unwanted and intrusive thoughts) and compulsions (physical or mental actions that the individual feels compelled to perform in a rigid, stereotypical manner) (American Psychiatric Association, 2013). A plethora of studies has attempted to determine the neurobiology of OCD and its causal origins, which remain unknown (Hauser, 2021). Concerning the former, the vast majority of research concurs that deficits in cortico-striato-thalamo-cortical (CTSC) circuits underlie the aetiology of the disease (Ahmari & Rauch, 2022; Banca, Vestergaard, et al., 2015; Graybiel & Rauch, 2000; Milad & Rauch, 2012; Pauls et al., 2014; Robbins et al., 2019). Albeit much progress has been achieved in isolating pathways and attributing functions to different brain regions, the exact contribution of each in the generation and maintenance of OCD remains unclear (Soriano-Mas, 2021; Veltman, 2021).

This thesis, hence, has attempted to elucidate some of those puzzles by focusing on the core symptoms of the disease, namely obsessions and compulsions. Evidence suggests that both phenomena share common underlying mechanisms (Apšvalka et al., 2022; Castiglione & Aron, 2021; Guo et al., 2018; Leisman et al., 2016; Logan et al., 2014; Matheson & Kenett, 2020), which makes those an ideal starting point. Specifically, inhibitory control was selected as the target function, given that unwanted thoughts and urges are considered a common and

natural occurrence in individuals with and without psychiatric disorders (Dulaney & Fiske, 1994; Muris et al., 1997; Rassin et al., 2007), whereas the inability to suppress those is characteristic of OCD (American Psychiatric Association, 2013).

To do so, clinical, self-report, behavioural, and electroencephalographic measures were collected in four different experimental chapters, each aiming to address unanswered questions from the previous one. Robust neurocognitive endophenotypes of OCD (Marzuki et al., 2020; Menzies et al., 2007; Vaghi, 2021) served as the primary source of impaired mechanisms, with special attention being given to (i) action monitoring; (ii) inhibitory control; and (iii) cognitive flexibility. A fourth endophenotype, termed working memory, was also assessed to some extent in chapter 4 and shall be discussed later.

First and foremost, it is important to consider whether these endophenotypes in fact reflect some common function or neural system. Action monitoring, for instance, refers to the exaggerated observation of one's actions and their expected outcomes (Gehring et al., 2000; Maltby et al., 2005; Ursu et al., 2003; van Veen & Carter, 2006). One of the pioneers in attributing action monitoring as a function responsible for the generation of symptoms in OCD, Pitman (1987) proposed that patients with the disorder would experience high error signals that could not be remediated by behavioural output, giving rise to the feeling that 'something is not right' (Pitman, 1987). Decades later, the 'just not right' dimension of OCD has been extensively reported (Coles et al., 2003; Coles & Ravid, 2016; Fornés-Romero & Belloch, 2017; Moretz & McKay, 2009), and appears to underlie compulsive behaviour and feelings of incompleteness (Fornés-Romero & Belloch, 2017; Summerfeldt, 2004; Szalai, 2019). Albeit still undergoing meticulous scrutiny, the dorsal portion of the anterior cingulate cortex (dACC) has been proposed as the host of this endophenotype (Botvinick et al., 2004; Botvinick, 2007; Carter, 1998; Kolling, Wittmann, et al., 2016; Luu & Pederson, 2004; Shenhav et al., 2016; Wang et al., 2005). Considered the *Rorschach Test* of cognitive neuroscience (Ebitz & Hayden, 2016), the dACC is implicated in a myriad of functions, ranging from conflict monitoring (Botvinick et al., 1999), action evaluation (Ruitenberg et al., 2018), and selection (Kolling, Wittmann, et al., 2016), cognitive control (Shenhav et al., 2016), decision-making (Heilbronner & Hayden, 2016), behavioural flexibility (Sheth et al., 2012), and reinforcement learning (Santesso et al., 2008).

Surprisingly or not, this same region plays a role in a second target mechanism of this thesis: cognitive flexibility (Demanet et al., 2011; Dignath et al., 2015). This executive function concerns the ability to successfully adapt behaviour following negative feedback or when actions become devalued, in order to maintain goal-directed behaviours (Chamberlain et al.,

2007, 2021; Chamberlain, Fineberg, et al., 2006; Vaghi, Vértes, et al., 2017). Typical findings in OCD research, nevertheless, suggest that patients adopt perseverative, habitual responses at the expense of goal-oriented ones, enabling the repetition loop seen in the disorder (Banca, Voon, et al., 2015; de Wit & Dickinson, 2009; Gillan et al., 2011; Gillan, Kosinski, et al., 2016; Gillan & Robbins, 2014; Hardwick et al., 2019).

Finally, inhibitory control is also mediated by ACC activity (Anderson et al., 2016; Le et al., 2020; Luijten et al., 2014; Tissier et al., 2018), making this a region of the utmost importance for OCD (Aouizerate et al., 2004; Barahona-Corrêa et al., 2015; McGovern & Sheth, 2017). Curiously, two other brain regions seem to be implicated in the very same mechanisms previously discussed, albeit being originally associated solely to motor control: the pre-supplementary (pre-SMA) and supplementary motor areas (SMA) (Donoghue & Sanes, 1994). Both areas are equally involved in the monitoring of actions (Bonini et al., 2014; Grützmann et al., 2016), cognitive and behavioural flexibility (Badre & Wagner, 2006; Morris et al., 2016; Müller et al., 2015), and inhibitory control (de Wit et al., 2012; Tomiyama et al., 2021; Wolpe et al., 2022). Given the association between these structures in the generation and maintenance of OCD symptoms, this thesis aimed at evaluating, and possibly altering, the activity of these regions via the robust event-related potentials (ERPs) which may underlie them.

Error-related negativity (ERN) and the readiness potential or *bereitschaftspotential* are two components associated with conflict monitoring and motor preparation, respectively (Deecke, 1987; Weinberg et al., 2012). Several studies have reported both ERPs as enhanced in OCD patients when compared to controls (Dayan et al., 2017; Riesel et al., 2019), but not many have attempted to investigate and manipulate those in the same sample. Furthermore, an integrated functional significance of the ERN and the RP in OCD has not been reported.

This thesis, thus, has attempted to evaluate both components, in addition to error positivity (Pe), which follows the ERN, in a large sample of patients with OCD and matched controls, tested twice over the period of a month. Additionally, clinical, self-reported, qualitative, and behavioural data were collected to enable the formulation of a broader overview of OCD, aiming at identifying shared causal links between obsessions and compulsions.

Possible frameworks integrating obsessions and compulsions, or intrusions and urges, with these cognitive and motor areas can be derived from their functions. For instance, considering that compulsions might precede obsessions, which are formulated *post hoc* in order to rationalise an urge (Gillan & Sahakian, 2015; Robbins et al., 2019), and taking into account

the overactive habitual system of OCD (Banca, Voon, et al., 2015; Gillan, 2021; Gillan, Kosinski, et al., 2016), it is possible to infer that compulsions were originally behaviours devoid of meaning that became reinforced (i.e. checking, for instance). As it happens with habits, those behaviours soon became purposeless (Poldrack, 2021), requiring behavioural and cognitive adaptation, abilities impaired in OCD (Badre & Wagner, 2006; Chamberlain et al., 2021), leading to perseveration (Barahona-Corrêa et al., 2015). In addition, 'breaking habits' is yet more challenging in OCD as a result of the overactivation of the motor areas, responsible for the 'motivation-for-action (see Chapter 4) (Cavanna et al., 2017; Shephard et al., 2021). Given the also overactive error monitoring system (Daw et al., 2011; van Veen & Carter, 2006), this non-adaptive, perseverative behaviours will result in high error signals (Pitman, 1987), which in turn will cause increased behavioural attempts to minimise the 'just not right feeling' (Coles & Ravid, 2016; Fornés-Romero & Belloch, 2017), finally employing superstitious beliefs and magical thinking to alleviate the discomfort caused by the uncertainty (Einstein & Menzies, 2004; Gillan, Morein-Zamir, Durieux, et al., 2014; Reuven-Magril et al., 2008; West & Willner, 2011). The resulting 'illusion of control' (Reuven-Magril et al., 2008) completes the cycle by creating behaviours that are often ego-dystonic (Jacob et al., 2014) and that will become habitual and unable to silence the error signals (Pitman, 1987), strengthening both the activity of the motor areas (urges) (Asemi et al., 2015) and of the monitoring systems (intrusions) (García et al., 2022). Undoubtedly, this is a simplistic approach focusing solely on ACC and cortical motor areas, yet it illustrates the importance of taking both into account in OCD (Szalai, 2019). Importantly, this interpretation must consider Plutarch's ancient causality paradox of the chicken or the egg (O'Brien, 2015), as it cannot be conclusively stated activity of these areas promote the symptoms or the opposite. Nevertheless, endophenotype studies suggest abnormalities in action monitoring, behavioural flexibility, and inhibitory control in healthy first-degree relatives of patients with OCD, which supports the notion that symptoms may appear subsequently (Chamberlain et al., 2007; Grützmann et al., 2022).

Conversely, similar attempts at reducing uncertainty by engaging in ritualised, rigid sequences of actions by individuals without psychiatric disorders seem to work by boosting confidence (Hobson et al., 2017), alleviating anxiety (Brooks et al., 2016), increasing motivation (Hobson et al., 2018), creating physical readiness (Foster et al., 2006), and facilitating goal-directed performance (Kapitány & Nielsen, 2017). See chapter 5 for a more detailed differentiation between compulsions and rituals.

In light of this evidence and differences between patients with OCD and healthy volunteers, this thesis aimed to: (i) differentiate OCD from matched HV in a two-session study

using self-report, clinical, behavioural, and electroencephalographic measures; (ii) investigate the underpinnings of thought and action suppression, and how they correlate with intrusions and urges; (iii) elucidate the reason why rituals are effective in alleviating anxiety in certain circumstances (e.g. for athletes), but not in OCD; (iv) test the impact of a novel ritualised behaviour in OCD and HV in a two-session study, comparing clinical, self-report, behavioural, ad electroencephalographic measures; and (v) assess the feasibility and efficacy of habit-reversal treatment in OCD, when compared to cognitive-behavioural therapy and exposure-response prevention therapy.

A summary table of each chapter's main measures, hypotheses, and findings can be found below.

Table 1. *Overview of chapters, hypotheses, and findings.*

CHAPTER	MEASURES	HYPOTHESES	FINDINGS
3 – Baseline (OCD vs HV)	- SSGNG - IED - ERN, Pe, RP - Y-BOCS, MADRS - Self-report	- OCD would present impaired ability in stopping actions - OCD would commit more extra-dimensional errors - OCD would present increased amplitudes of ERN, Pe, and RP - OCD would differ significantly from HV on self-report measures	- OCD responded significantly more on stop trials - OCD and HV did not differ significantly on extra-dimensional shift errors - OCD presented increased ERN and RP amplitudes - OCD and HV did not differ on Pe amplitudes - OCD reported significantly more symptoms than HV - Greater amplitude ERN was associated with lower symptomatology and better behavioural performance
4 – HRT in OCD (measured twice)	- SSGNG - IED - ERN, Pe, RP - Y-BOCS, MADRS - Self-report	- SSGNG would improve for the HRT group - IED would improve for the HRT group - ERN and RP amplitudes would be attenuated for the HRT group - Y-BOCS and MADRS would improve for the TAU group	- No differences were found for SSGNG - No differences were found for IED - No differences were found for ERN and Pe amplitudes - Both groups showed attenuated RP amplitudes - Both groups improved Y-BOCS - TAU improved MADRS - HRT improved quality of life

Table 1. *Overview of chapters, hypotheses, and findings. (cont.)*

CHAPTER	MEASURES	HYPOTHESES	FINDINGS
5 – Rituals in OCD and HV (measured twice)	- SSGNG - IED - ERN, Pe, RP - Y-BOCS, MADRS - Self-report	- APP participants would improve SSGNG - APP participants would improve IED - APP participants would attenuate ERN, Pe, and RP amplitudes - OCD-APP would improve on Y-BOCS	- No differences were found for SSGNG - Both HV groups improved IED but OCD groups did not - Borderline improvement was found for ERN amplitudes on OCD-APP - OCD-APP attenuated RP amplitudes - No differences were found for Pe amplitudes - OCD-NO-APP attenuated Pe - OCD-NO-APP improved Y-BOCS - HV-APP increased ERN amplitudes
6 – Suppression of thoughts and actions in OCD and HV	- SST - Stovetop Task - RIF - Y-BOCS, BDI - Self-report	- OCD would present impaired ability in stopping actions - OCD and HV would decrease memory vividness and confidence on the last trial of the stovetop task - OCD would not present a RIF effect	-No significant differences were found on the SST - Both groups decreased memory vividness and confidence (OCD more significantly) - OCD did not exhibit a RIF effect

OCD: Obsessive-Compulsive Disorder; HV: Healthy Volunteers; SSGNG: Stop-signal Go/No-Go task; SST: Stop-Signal Task; IED: Intra-Extra Dimensional Set-Shifting Task; ERN: Error-Related Negativity; Pe: Error Positivity; RP: Readiness Potential; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; MADRS: Montgomery–Åsberg Depression Rating Scale; BDI: Beck Depression Inventory; RIF: Retrieval-Induced Forgetting

As can be seen in table 1, original hypotheses were partially supported, especially in corroborating neurocognitive endophenotypes of OCD (Vaghi, 2021). Increased action monitoring, as represented by the ERN, was found in both chapters 3 and 5, aligning with previous literature that postulates the ERN as an endophenotype of OCD (Perera et al., 2019;

Riesel et al., 2019). Similarly, results of the stop-signal task on chapter 3 corroborated previous literature and indicated higher inability to inhibit actions, as demonstrated by an increased probability to respond to stop trials (Chamberlain, Fineberg, et al., 2006; Mar et al., 2022; Menzies et al., 2007; Verbruggen et al., 2019). Further supporting inhibitory control deficits of actions and thoughts in OCD, results of chapter 6 revealed a lack of RIF effect in this population, highlighting their strains in suppressing memories (Apšvalka et al., 2022; Demeter et al., 2014; Guo et al., 2018; Storm & Levy, 2012).

Importantly, chapter 6 addressed another ongoing debate in OCD, especially related to checking behaviours, namely memory deficits. Although working memory impairment is considered a neurocognitive endophenotype of OCD (Marzuki et al., 2020; Menzies et al., 2007), the extent to which it is causal to checking is still unknown (Burns et al., 2020; MacDonald et al., 1997; Savage et al., 2000; Tolin et al., 2001). Indeed, it appears that the relationship is inverted in this case, with behavioural repetition in the stovetop task leading to memory impairment (Hansmeier et al., 2015; Radomsky et al., 2006; M. A. van den Hout et al., 2019; M. van den Hout & Kindt, 2003b). This adds further support to general domain hypotheses of inhibitory control of actions and thoughts (Apšvalka et al., 2022; Aron et al., 2004; Guo et al., 2018; Logan et al., 2014), given that the inability to suppress behaviours (in this case, checking) leads to lack of confidence in memory veracity that will ultimately cause uncertainty and obsessions (Strauss et al., 2020; M. van den Hout & Kindt, 2004).

Paradoxically, though, neither chapter 6 nor chapter 5 were able to replicate the motor inhibition deficits seen in chapter 3, although behavioural performance in the Stop-Signal Task (SST) did correlate with RIF scores. A possible explanation for this finding relates to the sample size. Whilst chapter 3 included 67 patients with OCD, chapters 5 and 6 comprised 36 and 35 patients, respectively, nearly half of the sample from chapter 3. Numerical scores indicated higher difficulty in suppressing actions by the OCD sample when compared to HV, but it is plausible that statistical analyses were underpowered.

Similarly, the absence of IED performance differences in all chapters has contradicted the original hypotheses. Albeit not possible to address this issue conclusively, it is possible that patients did not present sufficiently severe symptomatology to yield behavioural differences, as symptom severity seems to be associated with flexibility deficits (Wetterneck et al., 2011). Indeed, Marzuki et al (2021) was unable to demonstrate deficits on the Wisconsin Card Sorting Task (WCST) in adolescents with OCD, and Gotteswald and colleagues (2018) found no impairments in extra-dimensional shift in this population as well (Gottwald et al., 2018; Marzuki et al., 2021). It is possible to infer that cognitive rigidity is a consequence of

symptoms, rather than the opposite. Unfortunately, the vast majority of severe OCD cases were reported in chapter 4, a study that did not comprise a control group, hindering final conclusions difficult. Once again, nevertheless, numerical scores suggested higher inflexibility in OCD in all chapters.

The training of novel behavioural sequences through the mobile application provided interesting results. Supporting the original hypotheses, both chapters 4 and 5 demonstrated that performing these sequences was able to increase quality of life and diminish Y-BOCS scores (significantly on chapter 4 and numerically on chapter 5). In addition, an attenuation of the RP amplitudes of patients training the motor sequence in both chapters suggests that rituals may engage the same circuitry responsible by the formation of urges. Evidence for this can be found in motor imagery studies. It is proposed that not only the physical performance of an action, but its visualisation or imagination activates the same motor areas responsible for its execution (Holmes & Mathews, 2010; Mulder, 2007; O'Shea & Moran, 2019). Indeed, a recent study has found that watching oneself performing a compulsion (in this case, handwashing) was able to reduce compulsive behaviours and compulsivity scores in participants with high OC symptomatology (Jalal et al., 2018).

Furthermore, research has shown that the dACC and the anterior mid-cingulate cortex (aMCC), a region implicated in error-related processing (Debener et al., 2005), are crucially involved in the preparation for action, modulating SMA activity (Asemi et al., 2015; Nguyen et al., 2014). Nguyen and colleagues (2014) propose that the aMCC and the SMA regulate each other's self-feedback connection, maintaining activity of the network and enabling voluntary action to be performed (Haggard, 2008). This is particularly relevant when one compares compulsions and rituals. Rituals, which are *voluntary* behaviours (Hobson et al., 2018), are subjected to intentional binding (see chapter 4 for details), promoting the feeling that the action has been executed (Haggard, 2017; Jo et al., 2014; Kühn et al., 2013), the very feeling that is absent in OCD due to interference and loss of confidence caused by the repetitive nature of the disorder (i.e. findings from the stovetop task) (Morand-Beaulieu et al., 2021; Szalai, 2019). In addition, the 'Reinvestment theory' proposes that consciously performing automated movements disrupts the motor system (Hobson et al., 2017; Masters & Maxwell, 2008), which may lead to less urges. Thus, it is possible that the training of voluntary rituals helps patients regain a sense of control, which results in attenuated RPs.

Although rituals did not improve behavioural performance, as originally expected, similar reports can be found in the literature. Hobson and colleagues (2017), for instance, have employed a similar paradigm and tested participants (healthy) twice, at baseline and after

training a random sequence of rigid and repetitive movements, mimicking a ritual. Their results suggested that error-monitoring signals, as measured by the ERN, were attenuated, but behavioural performance was not improved. In fact, the authors propose that by diminishing the activity of the monitoring system, also known for its role in recruiting cognitive control to maintain optimal performance (Botvinick et al., 2001; García et al., 2022), the latter could actually be impacted, highlighting the role of the ERN in optimising behaviour (Hobson et al., 2014, 2017). Indeed, a similar finding was reported in chapter 3, in which patients with higher ERN amplitudes were also more clinically and behaviourally preserved.

Paradoxically, rituals do not seem to have aided healthy volunteers, who exhibited *larger* ERN amplitudes following the intervention (chapter 5). It is thus possible to infer that the ritualised behaviours had opposing impacts in OCD and HV, given the predisposition of the former in adopting those associated to a bias towards habit formation (Ferreira et al., 2017; Fineberg et al., 2018; Snorrason et al., 2016; Voon, Derbyshire, et al., 2015). It is plausible that, whilst the ritual regulated the disrupted motor areas in OCD, in HV they in fact disrupted the system (Masters & Maxwell, 2008), given that effective rituals are supposed to prevent against 'reinvestment' (Hobson et al., 2017). Moreover, the training of a repetitive response sequence as a model of ritualised behaviour is likely to have engaged cognitive control, depleting its reserve and yielding a larger ERN signalling the need for top-down control activity (García et al., 2022). It is possible, thus, that the 'ritual' training manipulation was not perceived by the HV as presenting a symbolic meaning, a key element of a ritual (Legare et al., 2015; Watson-Jones et al., 2014), but was rather interpreted in the light of the ‘instrumental stance’ theory, which poses that purposeful meaning can be derived from certain behaviours that may appear random (Kapitány & Nielsen, 2015, 2017). Future studies should investigate in which circumstances ritualised behaviours are understood as instrumental or not.

Undoubtedly, this thesis presents limitations that warrant consideration. Firstly, as a caveat of most clinical papers, the effects of medication on clinical, cognitive, behavioural, and electroencephalographic measures were challenging to account for. Despite reports that chronic medication does not impact ERN amplitudes (Stern et al., 2010), it is known that other drugs impact the activity of the brain areas studied (Murray et al., 2017; Westphal, 2003; Ye et al., 2016). Ideally, patients in HRT and TAU, and APP and NO-APP groups would have been matched by medication, eliminating possible confounding effects.

Another important limitation refers to the lack of data on duration and age of onset of OCD. Studies show that patients who have experienced the disorder for longer tend to present worse symptoms, higher rigidity, poorer cognitive ability, lower response to treatment, and

higher comorbidities (Dell'Osso et al., 2013; Diniz et al., 2004; Mathis et al., 2008; Nakao et al., 2009). In addition, early onset has been associated with greater levels of superstitious belief (Millet et al., 2004), which would impact patients' approach towards the app.

Moreover, the lack of specific analyses subdividing Y-BOCS scores by obsessions and compulsions presents a caveat in the investigation of shared and specific factors of inhibitory control over thoughts and actions and their contribution to deficits seen in the disorder. Analogously, the separation of patients by OCD dimension (i.e. checking, ordering, aggressive, somatic, sexual, neutralising) hindered the possibility of uncovering the extent of their contribution to the overall symptomatology and how they present behaviourally and electroencephalographically. Nevertheless, this thesis was underpowered to perform such analyses.

In spite of these limitations, this thesis has provided some novel contributions to the literature. Firstly, it represents a comprehensive study with a large sample of patients with OCD and matched controls, obtaining demographic, clinical, self-report, behavioural, and electroencephalographic measures. The OCD sample size, indeed, is one of the largest reported in the literature tested with EEG, with the largest only comprising five more patients (Riesel et al., 2014). Furthermore, different ERPs and behavioural paradigms enabled the investigation of diverse research questions, yielding an integrative framework.

Secondly, this is one of the first studies to have employed robust behavioural paradigms of inhibitory control of both actions and thoughts in patients and controls, further demonstrating the link between motor and cognitive domains in OCD, alongside established clinical and self-report measures.

Thirdly, the presence of two OCD groups (see chapter 3), with distinct clinical and electroencephalographic profiles has shed light on the relationship between the ERN and cognitive control, contributing to the heated debate concerning the function of the dACC (Behrens et al., 2007; Botvinick, 2007; Kennerley et al., 2006; Kolling, Behrens, et al., 2016). Furthermore, novel hypotheses have been created to address the relationship between the RP and the ERN and their links with OCD symptomatology.

This thesis has also been able to pilot and provide preliminary evidence of the feasibility and efficacy of habit-reversal treatment in OCD in a large NHS facility, with severe patients and experienced professionals. This is a pioneer study evaluating HRT versus CBT+ERP with clinical, self-report, behavioural, and electroencephalographic measures, and has been able to support the clinical application of HRT for OCD.

Finally, the distinction between rituals and compulsions achieved by the results of the studies contributes to the vast literature that poses the former as adaptive (Brooks et al., 2016; Hobson et al., 2018; Norton & Gino, 2014; Schippers & Van Lange, 2006) and the latter as distressful (Muris et al., 1997; Robbins et al., 2012), and provides one of the first studies to train novel repetitive ('ritualised') motor sequences in patients with OCD. The findings that voluntary, stereotypical action sequences, as opposed to involuntary ones, aid patients with OCD serves as a potential novel treatment for the disorder. Moreover, my findings demonstrated that rituals not only attenuated neuromarkers, symptomatology, and quality of life by replacing compulsions, as proposed by the habit-reversal approach (Lee et al., 2019; Sulkowski et al., 2013; Toffolo & Saxena, 2019), but rather work independently by engaging motor circuitry and regaining a sense of control.

Albeit much is still unclear about the pathophysiology, neurobiology, and treatment of OCD, this thesis has attempted to clarify the mechanisms underlying the origins and maintenance of urges and intrusions in OCD. Future studies should take into account both cognitive and motor components of OCD (Gentsch et al., 2012; Morand-Beaulieu et al., 2021; Szalai, 2019; Tonna et al., 2022), potentially associating those to the proven well-tolerated mobile application interventions, to develop efficient and ecological treatments. A Research Domain Criteria (RDoC) approach (Cuthbert & Insel, 2013; Gillan et al., 2017; Insel et al., 2010; Insel, 2014; Sanislow et al., 2010) could inspire transdiagnostic mechanisms as an ideal starting point for developing treatments for disorders characterised by lack of control.

Our wills and fates do so contrary run

Hamlet, Act III, Scene 2
William Shakespeare

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What's past is prologue.

The Tempest, Act II, Scene 1.

William Shakespeare