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CONTINUOUS THETA BURST STIMULATION: EFFECTS OF DORSOLATERAL PREFRONTAL CORTEX STIMULATION ON EMOTIONAL PROCESSING

DOCTOR OF PHILOSOPHY DISSERTATION

KATERINA KONIKKOU

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CONTINUOUS THETA BURST STIMULATION: EFFECTS OF DORSOLATERAL PREFRONTAL CORTEX STIMULATION ON EMOTIONAL PROCESSING

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The present doctoral dissertation was submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy of the University of Cyprus. It is a product of original work of my own, unless otherwise mentioned through references, notes, or any other statements.

Katerina Konikkou

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ΠΕΡΙΛΗΨΗ

Εισαγωγή: Ο προμετωπιαίος φλοιός (DLPFC) παίζει βασικό ρόλο στον έλεγχο της επεξεργασίας συναισθηματικών ερεθισμάτων και αντιδράσεων. Ωστόσο, ο λειτουργικός ρόλος του PFC στη ρύθμιση νεύρο-φυσιολογικών μηχανισμών και μηχανισμών της προσοχής που αποτελούν βασικές λειτουργίες για την κωδικοποίηση των συναισθημάτων παραμένει σε μεγάλο βαθμό ασαφής. Ένας τρόπος για να διερευνήσουμε περισσότερο την εμπλοκή του PFC στη συναισθηματική επεξεργασία αποτελεί η καινοτόμα μέθοδος της Διακρανικής Μαγνητικής Διέγερσης (ΔΜΔ). Χρησιμοποιώντας ένα σχεδιασμό έρευνας που περιλάμβανε πραγματική αλλά και εικονική μαγνητική διέγερση (sham stimulation), οι ακόλουθες μελέτες διερεύνησαν την αποτελεσματικότητα της ανασταλτικής συνεχής διέγερσης έκρηξης θήτα (cTBS) στο να επηρεάσει τρεις μηχανισμούς που σχετίζονται με την συναισθηματική επεξεργασία σε υγιείς συμμετέχοντες. Οι τρεις μηχανισμοί που επιδιώξαμε να δούμε αν συνδέονται με την δραστηριότητα του PFC μέσα από την χρήση cTBS και με απώτερο στόχο την μελλοντική συμβολή αυτής της μεθόδου σε θεραπευτικά προγράμματα είναι: Α) Νευρο-φυσιολογική δραστηριότητα κατά την παρουσίαση συναισθηματικών εικόνων, Β) Διαδικασίες προσοχής που σχετίζονται με τη συναισθηματική επεξεργασία και, Γ) Αναγνώριση συναισθηματικών εκφράσεων σε άτομα με χαμηλά και ψηλά επίπεδα αντικοινωνικής συμπεριφοράς.

Μέθοδος: Για την πρώτη μελέτη συγκεντρώσαμε 40 συμμετέχοντες από πανεπιστημιακό δείγμα. Στη συνέχεια καταγράψαμε τις φυσιολογικές τους αντιδράσεις (καρδιακούς παλμούς και εφίδρωση) και την δραστηριότητα του μετωπιαίο φλοιού (PFC) χρησιμοποιώντας εγγύς υπέρυθρη φασματοσκοπία (fNIRS) κατά την διάρκειά παρουσίασης συναισθηματικών εικόνων και μετά από cTBS ενεργοποίηση στον δεξί προμετωπιαίο λοβό (DLPFC). Για τη δεύτερη μελέτη συγκεντρώσαμε 91 υγιείς συμμετέχοντες στους οποίους χορηγήθηκε μια δοκιμασία που εξέταζε την ταχύτητα προσοχής σε συναισθηματικά ερεθίσματα αμέσως μετά την ενεργοποίηση (cTBS) στα δεξιά ή στα αριστερά του DLPFC. Τέλος, για το σκοπό της τρίτης μας μελέτης συγκεντρώθηκαν 93 υγιείς συμμετέχοντες. Μετά από την ενεργοποίηση (cTBS) δεξιά ή αριστερά στον DLPFC οι συμμετέχοντες έλαβαν μέρος σε μια δοκιμασία που περιλάμβανε την αναγνώριση συναισθηματικών εκφράσεων (φόβος, ευτυχία, θλίψη και πόνος) χρησιμοποιώντας τυποποιημένα δυναμικά ερεθίσματα από το Montréal Pain and Affective Face Clips (MPAFC). Παράλληλα χρησιμοποιήθηκε ερωτηματολόγιο για την καταμέτρηση συμπτωμάτων της αντικοινωνικής διαταραχής της προσωπικότητας (Adult Self-Report Inventory-4).

Αποτελέσματα: Η πρώτη μας μελέτη έδειξε σημαντική μείωση της αιμοσφαιρίνης στον PFC κατά τη διάρκεια των αρνητικών και θετικών εικόνων στην ομάδα που έλαβε cTBS. Δεν διαπιστώθηκαν στατιστικά σημαντικές επιδράσεις του cTBS όσο αφορά τις ψυχοφυσιολογικές μετρήσεις. Η δεύτερη μελέτη έδειξε ότι όσοι έλαβαν cTBS διέγερση (αριστερά και δεξιά) εμφάνισαν σημαντικά ταχύτερες αντιδράσεις στα συναισθηματικά ερεθίσματα σε σύγκριση με τις ουδέτερες εικόνες και αυξημένη διευκόλυνση της προσοχής προς τις δυσάρεστες και ευχάριστες εικόνες σε σύγκριση με την ομάδα που έλαβε sham. Τέλος, τα αποτελέσματά στην τρίτη μελέτη έδειξαν ότι τόσο η αριστερή όσο και η δεξιά διέγερση του DLPFC ακολουθήθηκαν από λιγότερα σφάλματα στην αναγνώριση προσώπων που απεικόνιζαν πόνο και χαρά σε σύγκριση με την sham ομάδα. Οι συμμετέχοντες που έλαβαν αριστερή διέγερση cTBS παρουσίασαν επίσης υψηλότερα ποσοστά ακρίβειας σε πρόσωπα που απεικόνιζαν λύπη. Είναι σημαντικό ότι τα αποτελέσματα της ανάλυσης αλληλεπίδρασης έδειξαν ότι αυτές οι διαφορές στα ψηλότερα ποσοστά ακρίβειας παρέμειναν στατιστικά σημαντικές μόνο για την ομάδα με τα ψηλότερα επίπεδα αντικοινωνικής συμπεριφοράς που έλαβε cTBS.

Συζήτηση: Τα αποτελέσματα της παρούσας μελέτης έχουν σημαντικές πρακτικές εφαρμογές, αφού τα ευρήματα συμβάλλουν στην κατανόηση του ρόλου του αριστερού και δεξιού DLPFC στην συναισθηματική επεξεργασία. Επιπρόσθετα, τα ευρήματα μπορούν να βελτιώσουν και να κατευθύνουν τα μελλοντικά ερευνητικά βήματα της ομάδας μας για εντοπισμό νέων θεραπευτικών παρεμβάσεων για την αντικοινωνική συμπεριφορά.

ABSTRACT

Introduction: The prefrontal cortex (PFC) plays a key role in the modulation of affective processing. However, its specific role in the regulation of neuro-physiological and attention processes underlying emotion processing has remained largely unclear. One way to learn about this circuit and design novel interventions is to probe DLPFC using transcranial magnetic stimulation (TMS). Using a sham-controlled design, the following studies investigated the effects of inhibitory continuous theta-burst stimulation (cTBS) which is a technique worthy of further investigation on three underlying processes associated with affective processing in healthy participants. The three mechanisms we aimed to investigate by which cTBS may contribute to symptom improvement are: A) Neuro-physiological activity during the presentation of emotional pictures, B) Attention processes associated with emotional processing and, C) Recognition of emotional facial expressions in individuals with various symptoms of antisocial behaviour.

Methods: For the first study we collected 40 participants from a college sample. Next, we recorded their physiological responses (heart rate and skin conductance) and prefrontal activity using functional Near Infrared Resonance (fNIRS) during the presentation of emotional pictures taken from the International Affective Picture System (IAPS) and after cTBS over the right dorsolateral prefrontal cortex (DLPFC). For the second study we recruited 91 healthy participants and used an emotional dot-probe task with images from IAPS dataset to measure their attention facilitation indices and response times (RTs) after participants received cTBS on the right or left DLPFC. Finally, for the purpose of our third study we recruited 93 healthy participants. A dynamic version of an emotion recognition task was created using standardized stimuli of expressions from the Montréal Pain and Affective Face Clips (MPAFC) to measure emotion recognition responses (fear, happiness, sadness, and pain) after cTBS over the left or the right DLPFC. The Adult Self-Report Inventory-4 was used to assess antisocial personality disorder (ASPD) symptoms.

Results: Our first study indicated a significant PFC decrease of haemoglobin levels during distressing and positive pictures in the cTBS group compared to sham. No significant effects of cTBS were identified on physiological activity. The second study showed that those receiving real stimulation (both left and right), but not sham, showed significantly faster RTs to emotional compared to neutral images and increased attention facilitation in response to distressing and pleasant images compared to sham groups. Our results in the third study showed that both left and right DLPFC stimulation was followed by lower errors for happy and painful

emotions compared to the sham groups. Participants receiving left stimulation also showed higher accuracy rates in response to sad expressions. Importantly, interaction effects suggested that these differences in accuracy rates remained significant only for the high ASPD group.

Discussion: Findings confirm the role of both left and right DLPFC in affective processing and provide evidence for the clinical potential of fast theta burst protocols. These results can inform and improve our future work on identifying novel interventions for improving attentional and emotional processing in individuals with antisocial behaviour.

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‘’ The character of our nation isn't reflected on how we treat the rich and the privileged, but how we treat the poor, the disfavoured, and condemned.’’

-Bryan Stevenson

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DEDICATION

To one of the truest of humans. To my amazing strong mother and to all the mothers that show the feeling of unconditional love to their children and believe with open eyes in their dreams.

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INTRODUCTION

Repetitive Transcranial Magnetic Stimulation (rTMS) has shown great promise in the literature, and it is becoming an increasingly popular tool because it allows for the direct manipulation of neural networks. It is a non-invasive procedure that uses magnetic fields to stimulate nerve cells. Currently, it is one example of novel methods that has provided over two decades of data in non-invasive brain stimulation based on electromagnetic principles (Valero et al., 2017). Its minimal risk, excellent tolerability and ability to modify neurophysiology and brain plasticity make it a promising therapeutic tool for various mental conditions that do not respond to traditional psychotherapy techniques. For example, for antisocial-related disorders where although good treatments, such us medication, psychotherapy and parent training exist their effects are only moderated and not effective for everyone (Baker et al., 2017; Geynes et al., 2017; Gurnani et al., 2016). Importantly, rTMS is currently available as an FDA approved treatment for depression and Obsessive Compulsive disorder in psychiatry and has allowed the translation of neuroimaging findings about the circuitry in the brain underlying these conditions into targeted circuit based treatments that are complementary to other treatment modalities. In the question of what could be an innovative and complementary treatment for targeting impaired emotional processing, rTMS applications were examined for the first time in order to contribute to the limited body of literature on non-invasive brain stimulation and emotional processing.

Prefrontal cortex (PFC) plays an important role in emotional processing and therefore is one of the most frequently targeted regions examined for the application of non-invasive stimulation treatment in emotional disorders. Numerous studies have provided evidence that PFC plays a critical role in emotion processing and exerts cortical control over lower brain circuits important for emotional processing including the amygdala (Grimshaw and Carmel, 2014; Prete et al., 2015; Dixon et al., 2017; Urry et al., 2006). Additionally, explanations of emotional processing deficits often refer to impairments in self-regulation, the capacity to understand or feel what another person is experiencing or the ability to implement control over ones emotions and behaviours (Fanti, 2018; Gillespie et al., 2018). Based on this rationale we chose to examine for the first time the effects of PFC as a potential stimulation target of brain circuits mediating emotional processing and attention to emotional stimuli.

At this preliminary step we aimed to begin by investigating the effects of a novel theta burst neurostimulation protocol over the PFC in a college sample. We chose the PFC because previous studies indicate that this region may be important for emotional processing and top-

down regulation. Additionally, we chose to use continuous theta burst stimulation (cTBS) because it is a highly efficient variant of rTMS that features several advantages regarding applicability, treatment duration and neuroplastic effects (Schwippel et al., 2019). This novel protocol that recently gained its FDA approval in 2018 for the treatment of depression (Blumberger et al., 2018), allows a treatment session to last less than 15 minutes compared to standard treatment sessions that last about 40-50 minutes. In depression, evidence for the effectiveness of TBS and non-inferiority to conventional rTMS exists but remain weak in other mental disorders (Chen et al., 2019). Nevertheless, TBS remains a promising instrument to target maladaptive brain networks because it is a more convenient intervention for patients and it is certainly a technique more affordable to treat a larger number of people in clinical use.

As the PFC represent a key component of human emotion regulation, we investigated how right and left prefrontally applied cTBS affects emotional responsiveness. Particularly the three major questions which we aimed to address in the current studies are: 1) Can the impact of cTBS on emotion processing be captured on physiological and PFC activity, and is this impact inhibitory or excitatory?, 2) Given the interaction of emotion and attention systems (Öhman et al., 2001; Levenston, et al., 2000), does the cTBS have an impact on attention processes associated with emotional processing and is this effect different in the two hemispheres?, 3) Is there an effect of cTBS on emotion facial recognition and is this effect different in the two hemispheres and between healthy subjects with various symptoms of antisocial behaviour?. The answer to these questions will help elucidate the PFC neural mechanisms by which cTBS may contribute to symptom improvement in emotional processing.

In the following sections I first provide a coherent review of rTMS mechanisms of action and basic protocols. Next, I discuss the rationale behind considering neurostimulation and existing findings regarding the role of PFC in emotional processing and emotional attention and I finally discuss the scientific objectives of the current pilot studies. To date there are only a handful of studies that investigated the cTBS effects on both left and right PFC activity related to emotional processing. Building on these preliminary findings, the aim of the current project was to assess the effects of a novel neurostimulation protocol on emotional mechanisms that may be useful targets in future investigations for building novel interventions for treating emotional processing deficits.

rTMS mechanisms of action and basic protocols

Any rTMS device consists of capacitors capable of producing high discharge currents and an electromagnetic stimulating coil to apply magnetic pulses. The high and rapidly changing currents are discharged into the coil, thereby creating a pulse. This pulse can reach its peak in a few hundred microseconds and induce an electric field in the neuronal tissue underneath the coil. Due to the electrical conductivity of the living tissue, the induced electric field results in an electrical current in the cortex and depolarization of the underlying neurons. Briefly, based on the principle of electromagnetic induction, introduction of focused magnetic fields generates regional cortical electrical fields which, when of sufficient magnitude and density, can change neuronal excitability (Lefaucheur, 2009). Measureable outputs are produced, typically a motor evoked potential (MEP) measured by electromyography in a muscle controlled by the region of motor cortex being stimulated (usually finger movement). TMS can be applied in a single pulse method with one stimulus occurring at a time or paired-pulse methods where a test stimulus is preceded by a conditioning stimulus. When applied repetitively, TMS can also modulate cortical excitability and is called repetitive TMS (rTMS). Effects can be an increase or decrease in excitability depending on the parameters of stimulation; low frequency (e.g. 1 Hz) being inhibitory repetitive rTMS while high frequency (>5 Hz) is excitatory (Lefaucheur et al., 2014).

In general tolerability of rTMS is well-established. Common rTMS adverse effects include headaches, scalp discomfort at the site of stimulation, facial/jaw twitches that occur in-time with stimulation, dizziness, light-headedness, and tiredness following stimulation sessions (Loo et al., 2008). These are usually mild in severity, self-resolving and, as in the case of headaches, resolve with simple analgesia. There is no evidence that rTMS causes long-term adverse effects on cellular, neurological, cognitive, hearing or motor functioning (Machii et al., 2006). The two potentially serious, but rare (0.4%), adverse effects associated with rTMS are seizure induction and treatment-related affective switching (Dobek et al., 2015).

In clinical practice, rTMS is applied over the left or right dorsolateral prefrontal cortex (DLPFC). Numerous studies have provided evidence that PFC plays important role in emotional processing and therefore in one of the most frequently targeted regions for rTMS in clinical trials, especially in the treatment of emotional disorders A standard treatment course involves 20–30 daily stimulation sessions applied over 4–6 weeks. This can be followed by a course of tapering sessions over subsequent weeks or months (Perrera et a., 2016) or a clustered

maintenance rTMS regime (Pridmore et al., 2017), to prevent relapse. Each rTMS session is typically under 45-min duration, depending on the parameters prescribed, with stimulation intensity set at 120% of the patient's resting motor threshold (RMT). Whilst high-frequency 10 Hz rTMS applied to the left DLPFC remains the most studied rTMS protocol with most evidence supporting its efficacy, therapeutic equivalence have been established with low-frequency 1 Hz rTMS applied to the right DLPFC (Chen et al., 2013) and sequential bilateral rTMS, where 1 Hz right-followed by 10 Hz left-sided DLPFC stimulation are applied (Fitzgerald et al., 2013). Detailed review of TMS neurophysiological principles and methodology is available by Rossini and colleagues, 2015.

A promising more recent form of rTMS is theta-burst stimulation (TBS), which applies 50 Hz rTMS repeated with a rate in the theta range of five times per second (Di Lazzaro 2009; Huang et al., 2005). TBS is a novel pattern of applying rTMS shown to induce significant and long-lasting neuronal conditioning responses in motor cortical studies, while electrophysiological effects in the prefrontal cortex have also been observed (Grossheinrich et al, 2009). Given the current evidence base, TBS can reasonably be offered as a clinical alternative to traditional rTMS. TBS is a novel patterned rTMS protocol which is not supported by the same weight of evidence as standard rTMS treatment. Intermittent train of TBS (iTBS) induces cortical facilitation, whereas continuous train of TBS (cTBS) decreases cortical excitability (Huang et al., 2005). The first human experiments of TBS investigated its effects on the motor cortex. In 2004, Huang and colleagues reported 5 or 15 rTMS pulses at 50 Hz, repeated at 5 Hz intervals, resulted in greater and longer-lasting motor cortical excitability compared with single pulse TMS applied at the same intensity (Huang & Rothwell, 2004).

Compared to studies investigating TBS's motor cortical conditioning effects, there is a relative paucity of studies investigating its effects on other brain regions such as the prefrontal regions which is an aim of the current studies. More studies are needed to elucidate the mechanisms of TBS applied to this brain region and what, if any, the clinical significance of these effects may be. Neural oscillations in the gamma frequency range (30–150 Hz) are typically found in higher cognitive and sensory processing regions of the brain and has been linked with attention and memory (Jensen, Kaiser, & Lachaux., 2007). Theta activity has been reported to modulate gamma activity in the human neocortex and this coupling is thought to play a role in cognitive processing and certain behavioural tasks (Canolty et al., 2006). The exact mechanisms of interplay between various oscillatory patterns and their biological and clinical significance remain unclear and an area of active research. Recent reviews of TBS safety suggest it is relatively safe (Rachid, 2017), although reports of seizures (Oberman et al.,

2011) occurring with cTBS warrant caution in patient selection and choice of stimulation sites. Preliminary TBS trials in depression show promise while a recent large-scale non-inferiority study demonstrated therapeutic equivalence between iTBS and rTMS (Blumberger et al., 2018) that leaded to its FDA approval. The main obvious advantage of TBS over rTMS relates to its efficiency of delivery, which enables stimulation of multiple cortical targets within a relatively short space of time (Wischnewski & Schutter., 2015).

Prefrontal cortex (PFC) role in emotional processing and influence on neurophysiological activity

PFC impairments have been associated with socio-emotional processing deficits and behavioural problems (Adolphs 2002; Coccaro et al. 2007; Shamay-Tsoory et al. 2003). Evidence from neuropsychological research shows that PFC structures interact with emotional neural circuits that underlie behavioural problems and affect the ability to recognize emotions by inhibiting or modulating their activation (Ocshner et al., 2004). The involvement of the PFC in cognitive processing of emotions has been evident in head-injury and lesion studies, with findings documenting abnormal social-emotional functioning and impaired control of behaviour (Fellows & Farah., 2005). Importantly, to interpret and contextualize emotional information requires correspondence with brain systems involved in generating emotional experience (Barlett et al., 2007). The PFC has a general role in emotion processing and is consistently activated across emotions associated with empathic responses (Decety et al., 2014; Kim & Hamann, 2007). Further, previous evidence demonstrated that PFC activity is correlated with sympathetic system activity (Critchley et al., 2000). The PFC has been directly implicated in the generation of physiological arousal changes in the body that influence affective and cognitive processes (Brooke & Harrison., 2016). Investigating the synergetic action between brain (specifically frontal areas) and its effects on emotional processing and physiological changes can enhance the understanding of how we could use non-invasive neurostimulation techniques therapeutically.

PFC impairments in functional imaging research have been reported in various featured tasks involving social and/or emotional processing, such as fear conditioning (Birbaumer et al., 2005), viewing facial expressions of emotion (Deeley et al., 2006; Gordon et al., 2004) moral decision-making (Glenn, Raine, & Schug,. 2009), recollection of emotionally salient words and viewing emotionally salient scenes (Kiehl et all., 2001). Looking at pictures with emotional content has been found to be a powerful method to activate brain structures involved in emotion

processing (Davidson & Irwin, 1999). In neurophysiological studies, emotionally charged pictures have been proven to successfully evoke a spectrum of measurable emotional reactions (Bauer 1998; Lang et al., 1998). With regard to neural abnormalities adults with behaviour problems have shown decreased activity in the anterior temporal cortex and PFC (especially ventromedial PFC) during emotional picture viewing (Harenski et al., 2010). In their study Muller and colleagues (2003) found that adults exhibiting behavioural and antisocial problems compared to control subjects, showed increased activation in PFC regions, anterior cingulate, and amygdala during negative emotions. Moll and colleagues (2002) also reported increased activation in the orbitofrontal cortex (OFC) during the viewing of scenes with physical assaults, war, and abandoned children. Extending this work, Hirono et al. (2000) showed that violent patients with dementia showed reduced regional cerebral blood flow in bilateral PFC compared with non-violent dementia patients. Soderstrom et al. (2000) also revealed reduced blood flow in the frontal cortex, temporal cortex (the hippocampus in particular), and left angular gyrus in violent perpetrators compared with controls. Furthermore, antisocial behaviour has also been associated with PFC abnormalities during tasks involving social-affective processing, such as moral decision-making (Glenn et al., 2009) and recognition of facial expressions of emotion (Gordon et al., 2004).

Dynamic changes in bodily physiology such as heartbeats impact cognitive and affective processes (Poppa & Bechara, 2018). The sympathetic skin conductance response (SC) and heart rate (HR) are two indices of autonomic arousal. The precise functional neuroanatomy underlying generation of SC and HR during motivational behaviour and emotional information is undetermined, although it is impaired by discrete brain lesions to ventromedial PFC, anterior cingulate, and parietal lobe (Tranel & Damasio, 1994). The somatic marker hypothesis (Damasio, 1996) is one of the most influential neurocognitive theories of emotion and somatic interplay. Emotions, as defined by Damasio, are changes in both body and brain states in response to stimuli (Damasio, 2004). A key aspect of the somatic marker hypothesis is the 'body-loop', which is the claim that emotive events that are expressed in the body can influence behaviour via afferent feedback to the brain. The idea for this came from the realization that patients with PFC lesions especially when the damage was in the medial area indicated weakened ability to express emotion and to experience feelings in situations in which emotions would normally have been expected (Damasio, 1996). The body-loop has often been the subject of debate. However, evidence for the neural and peripheral mechanisms that support interactions between bodily states and affective functions has consistently emerged (Critchley, & Garfinkel, 2018; Poppa & Bechara, 2018). Since, physiological changes (such as HR and

SC) are transferred from the body to the brain (or the reverse) where they are transformed into an emotion we aimed to assess this brain-somatic association through PFC neurostimulation. Following this evidence, the current PhD dissertation assessed the impact of cTBS over the Dorsolateral Prefrontal Cortex (DLPFC) on SC, HR and PFC activity responsiveness during viewing emotional images.

Attention, emotion and PFC

Attention can be considered the process by which stimuli are selected for further processing and control over behaviour. Stimulus selection is biased by bottom-up sensory driven mechanisms (e.g., visual salience), and top-down influences generated outside of sensory cortices (e.g., task demands), (Desimone & Duncan). Previous functional imaging studies have shown that the executive attentional neural network involve PFC regions activation. Particularly, right frontal regions has been associated with alerting and vigilance attention tasks (Fan et al., 2005; Fossella et al., 2002) and dorsomedial and lateral PFC regions has been associated with attention mechanisms for monitoring and resolving conflict among thought, feelings and responses (Ochsner et al., 2002; Ochsner & Gross, 2005; Posner & Rothbart, 2007). In primates, damage to the lateral PFC causes a loss of inhibitory control in attention tasks (Dias et al, 1996; Stefanacci and Amaral, 2002), whereas damage to orbital frontal cortex (OFC) causes a loss of inhibitory control in 'affective' processing and increased aggression (Izquierdo et al, 2005). It has also been suggested that lateral PFC is recruited during emotion regulation cognitive processes such as reappraisal that enables individuals to successfully regulate emotion by reformulating the meaning of a situation (Goldin et al., 2008).

Emotional events rapidly capture attention by activating subcortical neural structures and has been shown to influence behaviour automatically (Blair & Mitchell., 2009; Ohman, 2005). The above means that if an emotional stimulus is a distracter to a stimulus determining task performance, then representational interference will be greater than if this distracter stimulus was neutral. Additionally, if an emotional stimulus is relevant to task performance, then there will be facilitation of performance. Indeed, a variety of studies have shown that emotional stimuli cause greater interference and facilitation on performance than neutral stimuli (Blair & Mitchell, 2009; Mitchell et al., 2006; Vuilleumier et al., 2001). However, with regard to the interaction of emotion and attention, there are unsolved and controversial issues. For example, to what extent PFC affect emotional stimulus processing or attentional control? Previous studies have shown conflicting results, probably due to several

factors, including limitations of computerized tasks to capture this complicated dynamic interaction. Some studies have demonstrated that emotional expressions (especially fearful) evoke automatic brain responses regardless attention processes and PFC engagement, suggesting that some types of emotional perception occur outside of top-down directed attention (Vuilleumier et al., 2001). Alternative claims suggest that the perception of emotional items requires attention. This was demonstrated with attentional manipulations that were designed to utilize a high level of processing resources meaning volunteers did not show an increase in amygdala response to threat under high perceptual load, contrary to evidence to a strong automaticity account of amygdala function (Bishop et al., 2007). In our recent study, we identified variant amygdala functioning patterns during threat conditioning in individuals with various antisocial symptoms (Fanti et al., 2019). We found that stratifying the sample based on various symptoms such as antisocial traits, anxiety and history of abuse revealed different amygdala functioning patterns that furthered our understanding of emotion-based deficits. If PFC controls and inhibits the amygdala and other limbic structures (Rosenkranz & Grace, 2002; Larson et al., 2013) then we could hypothetically use brain stimulation to induce excitability changes in fronto-amygdala circuity and normalise amygdala functioning patterns during attention and emotional processing.

Therefore, the functional interaction of emotional and attentional systems remains to be fully explored, but it might play an important role in psychopathological conditions, such as antisocial behaviour. With the current dissertation we designed a pilot study to further examine this interaction through non-invasive brain stimulation. Since there is some evidence that higher-order cognitive processes, like attention moderate amygdala-mediated responses to emotional cues we examined whether right or left PFC inhibition affected performance in an attention dot-probe task. To date, this is the first study that examined the effects of both right and left lateral PFC stimulation using an attention dot-probe task and aimed to guide our novel forthcoming funded project for combining rTMS with attention modification therapy.

The rationale behind considering neurostimulation for enhancing emotional processing on individuals with Antisocial Behaviour

A possible mechanism hampering favourable treatment outcome in individuals with symptoms of antisocial, angry or violent behaviour concerns their emotional dysregulation and altered brain activity during processing of emotional stimuli (Roberton et al., 2012). Van Goozen and his colleges (2007), suggest that an adequate reaction of the physiological system

followed by a flexible brain system of emotional regulation is necessary to correctly interpret social and emotional information. Arousal levels during emotional stimuli are regulated by the Autonomous Nervous System (ANS) which controls the internal environment of the body and bodily functions translated to emotions. Many regions in the brain, particularly amygdala, the hypothalamus and PFC affect ANS (Bishop et al., 2007; Larson et al., 2013). Specifically, the PFC is thought to intelligently regulate our actions and emotions through extensive connections with deeper limbic brain areas (Anderson & Kiehl, 2012). Reduced emotional attention related with antisocial behaviour is seen at both reduced interference by emotional distracters (Mitchell et al., 2006) and reduced facilitation of emotional targets (Lorenz and Newman, 2002). Although several treatments, such us medication, psychotherapy and parent training exist their effects on antisocial-related behaviours are only moderate (Baker et al., 2017; Geynes et al., 2017; Gurnani et al., 2016). In the question of what could be an innovative treatment for emotional or attentional systems in the future, rTMS applications in the development of interventions for antisocial behaviour is investigated in the third study of the current work.

We can identify neurobiological factors associated with antisocial behaviour as early as childhood (Van Goozen et al., 2007) and these factors are not immutable as they can be amplified or attenuated as a result of brain plasticity (Hummel & Cohen, 2005). Brain plasticity is the ability of the brain to restructure itself. This adaptive potential of the nervous system allows the brain to reduce the effects of neurobiological deficits due to pathologies such as antisocial behaviour. rTMS can be used clinically for turning a specific brain area "on or off" as a method for recovering the function of specific brain circuits in humans. It is to be hoped that improvements in brain circuits using rTMS might be translated into more efficacious treatment for antisocial behaviour or used to emanate faster therapeutic results on existing treatments.

Theta Burst Stimulation (TBS) to enhance emotion processing and attention

In order to suggest rTMS treatment protocols I focused on the application of novel stimulation protocols suggested by neurostimulation review of the literature. More recent protocols have been less systematically tested especially on regions such as the PFC. Therefore, their therapeutic efficacy and clinical relevance have not been optimized. TBS protocols have been proposed as a more effective variant of rTMS (Grossheinrich et al., 2009). Whereas cTBS was found to suppress cortical excitability, iTBS produced a facilitating effect on motor cortex

excitability (Huang et al., 2005). TBS is a newer patterned form of rTMS which can be used to produce the same or greater physiological effects compared to standard rTMS but in a markedly reduced period of time of 3 min compared to around 40 min for a standard session (Chung et al., 2015). Recent research shows that TBS applied on a daily basis may be as effective as standard daily rTMS in patients with depression applied to the left DLPFC (Blumberger et al., 2018). Therefore, TBS would appear to be an ideal intervention to use in an intensive/accelerated format where multiple daily sessions could be applied but still in a reduced amount of time. To date only limited research has explored the potential application of accelerated forms of TBS over the DLPFC and this was a main goal of the current research.

Current results in nonclinical samples indicate that decreasing right DLPFC activation enhance attention bias for threat and alter emotion-related cognitive processes (Notzon et al., 2018). In addition decreasing right DLPFC cortex activation has been found to improve inhibitory control of emotion during decision making (Zwanzger, et al., 2014). Another study have indicated that high-anxiety subjects benefited in greater measure from frontal left stimulation with a reduced negative bias (increased accuracy and reduced response time for the positive stimuli) and a significant increased performance for semantically related distractors (Balconi & Ferrari, 2013). Adding to these findings, low frequency stimulation was used to inhibit right DLPFC activity and results demonstrated significant treatment effects in improving emotion regulation (Diefenback et al., 2016). Thus, strategies to enhance top-down attentional control using DLPFC stimulation may be particularly relevant for enhancing emotional processing to people with antisocial behaviour. The proposed study will be the first to investigate the effect of theta burst neuromodulation in emotion processing and attention using neuro-physiological measures. Since one of the most idiosyncratic dysfunction of antisocial behaviour is their lack of empathy an enhancement of attention to emotional stimuli through TBS which is the fastest stimulation protocol so far will provide promising and potentially useful knowledge for novel methods.

Current Studies

The current research work is structured along three pilot studies for filling a gap in knowledge regarding the potential hemispheric effects of cTBS protocol over the PFC on both emotional and attentional processing. Particularly, the following studies were design to provide evidence for: 1) The impact of cTBS over the right PFC on physiological and PFC activity during emotion pictures viewing, 2) The hemispheric PFC impact after cTBS on attention processes associated with emotional processing and, 3) The effect of cTBS on emotion facial recognition in healthy subjects with various symptoms of antisocial behaviour and if this effect is different in the two PFC hemispheres.

The first study specific objective was the identification of the effects of continuous TBS on Heart Rate (HR), Skin Conductance (SC) and PFC activity during viewing of emotional pictures. Studies investigating cTBS and interrelations with neurophysiological effects in order to better understand the brain-somatic interplay mechanisms are lacking. As a result, the main objective of the first study was to provide evidence of how cTBS over the right DLPFC relates to neurophysiological changes during emotional processing. Through these findings we aimed to increase knowledge about the interaction of cTBS with brain and autonomic activity. These associations are important because a number of psychological problems including antisocial behaviours have been related with impaired neuro-physiological reactions to emotional stimuli.

The second study objective was to identify the effects of cTBS on the right and left DLPFC in attention to emotional stimuli. Accurately processing emotions is critical in social interactions, and paying attention to emotional cues enables the viewer to infer the thoughts, emotions and intentions of others. The aim of this study was to investigate if neuromodulation of DLPFC (right and left) by cTBS would have an effect on attention towards distressing and positive stimuli. Thus, we used an emotional dot-probe task and presented pleasant, distressing and neutral images to test for shifts on attentional facilitation indices and RTs. Such a finding would provide evidence for the etiological mechanisms that might lead to changes in emotional processing after stimulation.

The third study objective was to investigate the impact of inhibitory cTBS over the right and left DLPFC on facial emotion processing in a sample with differentiated symptoms of Antisocial Personality Disorder (ASPD). Evidence from neuropsychological research shows that PFC structures interact with emotional neural circuits that underlie behavioural problems and affect the ability to recognize emotions by inhibiting or modulating their activation. Thus, to examine this hypothesis participants performed a dynamic face recognition task depicting fearful, happy, sad, and painful expressions immediately after receiving inhibitory cTBS. This

is the first test of associations between DLPFC stimulation among individual differentiated on ASPD symptoms, pointing to possible benefits in emotion recognition after cTBS for populations with impaired emotional processing.

Finally, it should be mentioned that the answer to these questions will facilitate the implementation of our teams' next research project regarding the treatment benefits of combining attention modification treatment with rTMS in antisocial individuals that has been funded by the Cyprus Research Promotion Foundation in 2020. With the current pilot studies we needed to assess the applicability of this type of stimulation (cTBS) with duration of only 40 seconds for the purpose of our intervention program. Also, we aimed to assess whether stimulating the left or the right PFC hemisphere would have different effects on emotional and attentional processing since we could not find intelligible answers in the existing neurostimulation literature.

STUDY 1

The effects of continuous Theta Burst Stimulation on neurophysiological activity over the right Dorsolateral Prefrontal Cortex during emotional processing

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a recently developed non-invasive brain stimulation method for the treatment of psychiatric and neurological disorders. Although, its exact mechanism of action is still not clear, current evidence points toward its role in long-term inhibition and excitation of neurons across accessible cortical areas such as the prefrontal cortex (PFC) regions (Lazzaro & Ziemann, 2013). In order to develop standardized protocols for rTMS administration we need to begin from the basics and better understand the brain-somatic interplay in normal individuals as well as in those with various psychiatric disorders. Newer approaches suggest the use of rapid Theta Burst Stimulation (TBS) protocols which are considered just as safe and effective as standard rTMS, but this type of stimulation requires sessions of just 3-6 minutes rather than 20-40 minutes. Studies investigating TBS and interrelations with neurophysiological effects are lacking. As a result, the current study was designed to provide evidence of how TBS relates to neurophysiological changes, by measuring heart rate (HR), skin conductance (SC), and Prefrontal Cortex (PFC) activity after stimulation. Through these findings we aim to increase knowledge about the interaction of neuromodulation techniques with brain and autonomic activity. These associations are important because a number of psychological problems have been related with impaired neuro-physiological reactions to emotional stimuli.

Repetitive TMS has been most promising in the treatment of depression and migraines and has recently received Food and Drug Administration (FDA) approval for Obsessive Compulsive Disorder. TBS is an alternative option of rTMS that mimics endogenous neuronal firing patterns associated with learning and memory (Huang et al., 2009). Typically, TBS in humans involves the application of 3 pulses at 50 Hz at low-frequency interval (5 Hz) using a total of 600 pulses at 70–80% of motor threshold (Huang et al., 2005). When applied continuously (cTBS) for 40 s, TBS has shown to decrease cortical excitability measured via motor-evoked potentials for up to 60 min. When applied intermittently (iTBS) for 192 s, its effects can increase cortical excitability up to 30 min (Huang et al., 2005). Some studies have explored the physiology of TBS using neuroimaging, such as functional magnetic resonance imaging (fMRI); however, the underlying physiological mechanisms are less explored. The optimization of TBS by examining its effects on brain activity and physiological measures would have potential clinical importance, as TBS is increasingly being investigated as an alternative to conventional rTMS in various clinical populations due to its short application time and low intensity requirement (Desmyter et al., 2016; Prasser et al., 2015). The variability in behavioural findings after TBS application and the lack of studies exploring the

physiological effects of TBS present therapeutic limitations, an obstacle that needs to be addressed. In particular, research should address this issue by examining treatment relevant areas such as the prefrontal cortex and underlying neurophysiological activity associated with this type of non-invasive stimulation.

Physiological activity

One of the two main divisions of the autonomic nervous system is the sympathetic system. The sympathetic system is supporting the stress (‘‘fight or flight’’) response to threatening events and is a central component of emotional experience and, by extension, cognition and behaviour (Jansen et al.,1995; Porcelli & Delgado, 2017). Measurements of SC and HR reflect sympathetic tone and are frequently used as an indirect measure of emotional arousal. SC and HR are typical biomarkers of arousal with well-known psychophysiological functioning. An example is when somebody observes a threatening stimulus (for instance a snake) that could generate an autonomic increased in HR or sweating. Insights into the neuronal basis of autonomic reactivity have come from brain lesion and functional imaging studies. Impaired SC for instance, is reported in patients with discrete brain lesions of the right hemisphere (Oscar-Berman and Gade, 1979; Zoccolotti et al., 1982) and of bilateral medial PFC, bilateral anterior cingulate gyrus, right inferior parietal lobe (Tranel and Damasio, 1994), and amygdala (Bechara et al., 1995, 1999).

Brain mechanisms underlying generation of somatic responses such as SC and HR are integrated with those involved in emotional processing (Buchel et al., 1998). In a series of studies, Critchley and colleagues (Critchley et al., 2000; Critchley, Mathias, & Dolan, 2001; Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002) examined the relationship between physiological activity and whole human brain function via fMRI and suggested that the role of PFC areas is of central importance in the understanding of the connection of autonomic changes with emotions. Of critical importance is their finding that there is activity following the generation of autonomic responses predominantly lateralized to the right hemisphere (Critchley et al., 2000). Additional findings have demonstrated that right dorsal and especially lateral PFC is involved in the selection and/or inhibition of various kinds of emotional responses and involved in attention engagement to emotional stimuli (Aron, Robbins & Poldrack, 2004; Konishi et al., 1999; Poppa et al., 2020). Right PFC activity is also found in combination with amygdala deactivation during cognitive emotional processing (Banks et al., 2007). Based on

these findings, inhibition over right PFC regions by cTBS is likely to enhance emotional and autonomic reactions through disinhibition on limbic activity.

Prefrontal cortex

Certain brain regions of the PFC are involved in emotion regulation and autonomic control and simultaneously are accessible to TMS coils (Philips et al., 2003). For example, brain regions such as the DLPFC have been associated with both bottom-up and top-down processes, including the maintenance of attention on emotional stimuli and the ability to inhibit our responses (Hampshire et al., 2010). These processes of emotion regulation depend upon functional and structural interactions between prefrontal and cingulate control systems and cortical and subcortical emotion-generative systems (Banks et al., 2007; Davidson, 2000). One study that have examined the physiological arousal alterations after 1Hz rTMS (inhibitory) over the right PFC, indicated that HR during the presentation of pictures with negative and neutral valence was significantly increased compared to the presentation of positive pictures (Berger et al., 2017). In contrast, the modulatory effect of picture valence and arousal on HR response was absent after excitatory stimulation.

These results suggest that PFC inhibition indirectly activates autonomic response via inhibition of the right PFC activity, likely by enhancing the sensory processing or attention to aversive and neutral stimuli. Based on these initial findings we aim to explore for the first time the effects of inhibitory cTBS over the right PFC in relation to physiological responses and PFC activity. The lateralization of emotion has received a great deal of attention over the last few decades, resulting in two main theories. The Right Hemisphere Theory states that the right hemisphere is primarily responsible for emotional processes and is based on lesion studies (Anaki et al., 1998), while the Valence Theory (Baijal & Srinivasan, 2011; Davidson et al., 1987) suggests that the right hemisphere regulates negative emotion and the left hemisphere regulates positive emotion. Despite the important implications of these theories for the evolution of emotion processes, few studies have attempted to assess the lateralization of emotion using non-invasive stimulation techniques and especially novel TBS protocols. Furthermore, no previous study has examined the brain-physiological interrelations using cTBS, and our study might provide evidence of how right DLPFC neuromodulation (and especially cTBS protocol) may act on autonomic and PFC activity during emotional processing.

Current study

In the current study, we used cTBS (inhibition) over the right PFC to assess physiological responses and PFC activity after stimulation during the passive view of emotional stimuli. SC and HR reactivity reflecting peripheral (bodily) signals associated with emotional responses in previous studies (Critchley et al., 2000; Cristopoulos et al., 2016; Philips et al., 2003) were assessed. Changes in PFC oxygenation were measured during emotional pictures by means of functional multi-channel near-infrared spectroscopy (fNIRS) after stimulation. Results from emotional task-related fMRI studies have employed a range of stimulus and response paradigms to test hypotheses regarding particular patterns of brain activation and their relation to physiological response. Looking at pictures with emotional content has been found to be a powerful method to activate brain structures involved in emotion processing (Davidson & Irwin, 1999) and has been previously employed in rTMS paradigms (e.g. Berger et al., 2017). Emotional stimuli retrieved from the International Affective Picture System (IAPS; Lang et al., 1997) were used, previously found to activate amygdala-frontal coupling during emotion regulation tasks (Banks et al., 2007). Furthermore, we focus on PFC activity that has been implicated in emotion regulation neural networks and autonomic peripheral reactions to emotionally arousing pictures (Cabrerizo et al., 2014; Oschner et al., 2004).

In the present study, we evaluated the after-effects of cTBS to the right PFC cortex on HR, SC and PFC activity during emotional stimuli presentation. Similar to Berger and colleagues (2017) findings that used standard 1Hz inhibitory stimulation compared to sham stimulation, we expect cTBS will significantly increase physiological reactivity during the presentation of emotional pictures. Furthermore, based on previous findings by Tupac et al., 2013, we hypothesized that decreased prefrontal oxygenation will follow inhibitory cTBS of the right DLPFC perhaps more intensively to negative emotional images, as suggested by the Valence theory. By examining the effects of right DLPFC stimulation on autonomic reactions and PFC activity during affective pictures viewing we aim to extend existing literature on future applications of TBS protocols in emotion regulation for psychiatric and cognitive disorders.

Methods

Participants. Forty (8 males, mean age: *M*=21.30, *SD*=1.64, range 18-26 and 32 females, *M*=20.42, *SD*=1.45, range 18-23) were recruited for the purpose of the current study and completed the behavioural task. Exclusion criteria included history of psychiatric/neurological disorders including epilepsy, head trauma and migraine. Participants

were also screened for depression using the Beck Depression Inventory-short form (BDI) with an exclusion criterion of a score of >10 and State-Trait Anxiety Inventory (STAI) with an exclusion criterion of a score of >37.

Recruitment. Participants were recruited at the University of Cyprus via advertisement and word-of-mouth and received course credits. All participants were healthy Greek-Cypriots, medication-free, right-handed and had normal vision (for computer tasks). No participant had any established risk factor related to rTMS based on a screening Transcranial Magnetic Stimulation Safety Questionnaire (e.g., cardiac pacemakers, epilepsy, and use of drugs; see Rossi et al., 2012). All participants provided written informed consent for their participation in the experiment and rTMS procedures.

Experimental procedure. Upon arrival at the lab participants were greeted, briefed about the procedure and written consent was obtained. This study was a double-blinded, randomized, sham-controlled study, where participants were randomly assigned to one of two different stimulation conditions (right cTBS and right sham cTBS). Participants that met preliminary inclusion criteria began with an overview of the study and written informed consent by a blinded to the stimulation condition research assistant. The procedure was driven by the research assistant so that half of the participants were assigned to the 'blue', or 'orange' group (unknown stimulation condition to the participant). Male and female participants were pseudo-randomly assigned to a colour-group according to the order of arrival at the lab. Participants were told that they belong to the colour-group indicated by the card they had chosen and that they will be presented with various emotional images.

Participants were tested individually in one session. They were seated approximately 50 cm from the computer screen (47 cm X 24.5 cm). For the physiological measures, participants were fitted with the physiological monitors and the fNIRS headband and were instructed to relax in order to check the accuracy of recordings. Baseline measures were first collected for a minute while participants were looking at an empty computer screen. Once the physiological task was completed all electrodes and the headband were removed. Following the completion of the task participants were debriefed about the purposes of the study.

cTBS Protocol - Real and Sham cTBS. Coil position was determined using standardized coordinates from the EEG (Steinmetz et al. 1989) International 10–20 system (with F4 corresponding to the right DLPFC). The location and orientation of each participant's coil placement was indicated on a nylon cap that participants wore throughout the single stimulation session. A figure-of-eight focal coil (70 mm diameter) was used. The

coil was held in a fixed position by a mechanical arm and oriented so that the induced electric current flowed in a posterior–anterior direction. Stimulus intensities were set at 70% of active motor threshold (AMT). Previous experiments that used cTBS found significant inhibitory effects using as stimulation intensity 80% (e.g.,Huang et al., 2005) or 70% (Goldsworthy et al., 2013). We chose to use 70% intensity to prevent intense facial muscle twitching during stimulation. Each stimulation session TBS burst consisted of 3 pulses at 50 Hz, with each train being repeated every 200 ms (5 Hz) for 40 seconds (600 pulses). It has been shown that this stimulation paradigm suppresses cortical excitability. The number of pulses per participant used in the present study is consistent with the prototype protocol (see Huang et al. 2005).

Self-report measures. Although a single-session of rTMS is usually not found to acutely affect mood in healthy volunteers (Baeken et al., 2006) it has been reported that state anxiety prior to stimulation (perhaps related to expectations concerning the rTMS procedures) affects both cognitive-affective and cortisol responses to rTMS (Baeken et al., 2011; Vanderhasselt et al., 2011). Therefore, for screening purposes participants completed the Becks Depression Inventory (BDI-II; Beck, Steer, & Brown., 1996) and the State-Trait Anxiety Inventory (STAI) for Adults (Spielberger, 1983) prior to the conditioning session. The BDI-II is a 21-item self-report measure created to assess the severity or intensity of depressive symptoms (Beck & Steer, 1993, Beck et al., 1996). Responses to each item are rated at 0-3 points and according to the manual for the BDI-II, scores ranging from 0 to 13 are considered not depressed. The STAI consists of self-assessment scales that measure state and trait anxiety in terms of negative affect (Grös et al., 2007). Scores on the state scale reflect current anxiety levels, while trait anxiety scores reflect are long-term predisposition for anxiety (Spielberger, 1983).

Experimental tasks and assessments:

*IAPS Pictures***.** The emotional task included images taken from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1997). The IAPS is a widely used stimulus set and presents one of the most reliable and valid systems for the experimental investigation of emotional processing. The pictures were carefully selected to tap distress (e.g. crying child), threat (e.g. a snake in position to attack), positive (e.g. puppies) and neutral emotional content (e.g. book), following prior work (Kimonis et al., 2016; Kimonis et al., 2006; Loney, 2003). Pictures were selected according to normative ratings in the dimensions of valence and arousal reported in the IAPS manual (Lang et al. 2005), to differ in valence and were matched on arousal. Neutral pictures were selected to represent the midpoint between pleasant and unpleasant valence. Ten pictures were represented in one of the four potential

emotions: neutral, distressing, threatening and positive. Each picture appeared for 5-s followed by a fixation asterisk in the center of the screen for 4-s while HR, SC and PFC activity were measured. The emotional picture task, consisted of 40 pictures presented in pseudo-randomized order to avoid sequential repetition of identical emotion type. E-Prime 2.0 scripts were used for the presentation of the pictures. The overall duration of the task was 8 minutes consisting a baseline period of a 60-s and giving instructions about the task.

Functional Near Infrared Resonance (fNIRS) data acquisition and pre-processing analysis: The fNIRS device used in this experimental procedure was composed by a headband, which contains light sources and light detectors, and a control box for data acquisition. For the collection of the fNIRS data, the BIOPAC MP150 system running under Window 10 was used in combination with COBI studio and the Acq4.0 data acquisition (Biopac Systems Inc, Santa Barbara, CA). The flexible fNIRS sensor system, which consists of four light sources and ten photodetectors, was placed on the participants' forehead. The MP150 system consists of eight optodes sensors (four on top, four on the bottom), and COBI studio software automatically converts recorded data into oxygenated (HbO2) and deoxygenated (HhB) hemoglobin measures according to the modified Beer-Lambert Law. For our study, and based on prior work, we focused solely on the oxygenated hemoglobin measure (HbO2), since HbO2 has a higher signal amplitude, is more consistent and more sensitive than HhB hemoglobin (e.g., Monden et al., 2012; Strangman, Boas, & Sutton, 2002). Coverage and data quality across the middle six sensors was good across all participants. However, due to hair obscuring full contact of the sensors at the far left and far right, data quality was not good, and thus we excluded data from these sensors from all subsequent analyses.

The pre-processing of the BOLD signals and the data preparation for statistical analysis were performed with COBI studio software and prefrontal activation during images presentation was calculated for each optode. Specifically, a linear phase low pass filter (0.2 Hz cut-off) was applied to attenuated high-frequency components and noise of the signal. During the pre-processing procedure, optodes or time periods that were influenced by motion artifact or noise were removed via the Sliding-window Motion Artifact Rejection (SMAR) algorithm (Ayaz et al., 2010). Similar to other fNIRS data analysis (Tak & Ye, 2014), in order to remove any signal drift global trends, the linear detrending algorithm was used (for more information about the algorithm see Ayaz et al., 2010).

Additionally, the COBI studio software calculated the changes of HbO_2 concentration by abstracting the reflected light intensity in the baseline condition that happened prior to the experiment, from the light intensity during the presentation of the stimuli. Consequently,

negative values represented lower prefrontal activation compared to the baseline measurement, whereas positive values represented higher prefrontal activation again compared with the baseline measurement. Those changes in HbO_2 concentration expressed the term "prefrontal activation" used in the current study (Fanti et al., 2016). For each participant, the values of increase or decrease in prefrontal activation were determined by comparing the sign of significant changes for each condition and each optode. Further, in order to examine only the prefrontal activation during the viewing of various images, markers were used to make blocks of each image (5-s). In that way, 40 blocks with the average prefrontal activation were calculated for each optode and exported for statistical analysis.

Skin conductance (SC): SC is used as a tonic measure of sympathetic nervous system activity indicating physiological arousal. In most individuals, SC increases following the presentation of novel or significant stimuli (increasing in both pleasant and unpleasant arousing stimuli compared to low arousal neutral stimuli), (Patrick et al, 1993). Elecrodermal activity (EDA) for determining SC responses were measured using two 11mm disposable pre-gelled electrodes placed on the palm of the non-dominant hand. SC is used as a tonic measure of sympathetic nervous system activity indicating physiological arousal. The SC signal was filtered by a Biopac ECG100C bioamplifier and was scored in microsiemens (μS). All pictures presentation lasted 5 s each and SC was averaged for each picture and then for each affective category (positive, threatening, distressing and neutral). SC reactivity was computed by subtracting the mean neutral SC from the mean SC during neutral pictures following prior work (Fanti et al., 2018).

Heart Rate: HR data were acquired using the electrocardiogram (ECG) module of the Biopac system. ECG was recorded using two11-mm disposable Ag/AgCl pregelled electrodes placed on the right and left inner forearms of the participant. The ECG signal was amplified with a gain of 500, filtered using a BiopacECG100C bioamplifier, and sampled online at 1,000 Hz, then converted offline to beats per minute values. HR was measured during a baseline period consisting of a 60-s interval preceding experiment onset (i.e., baseline HR) and during the presentation of affective pictures. All pictures presentation lasted 5 s each and HR was averaged for each picture and then for each affective category (positive, threatening, distressing and neutral). HR reactivity was computed by subtracting the mean neutral HR from the mean HR during neutral pictures.

Results

*Plan of analysis***:** Prior to the main analysis, data was screened for outliers. Initially, we conducted repeated measures Analysis of Variance (ANOVA) with SC, HR and PFC activity

as the dependent variables and emotion type as the within-factor (i.e., neutral, distress, threatening and pleasant). These analyses were used to investigate the effectiveness of the picture-type manipulation before proceeding with the main analysis. Second, we conducted repeated measures Analysis of Variance (ANOVA) with PFC oxygenated haemoglobin (HbO2) as the dependent variable and stimulation type as the independent variable during Distressing, Positive, Neutral and Threatening images. These analyses were used to investigate the effects of right cTBS stimulation on PFC HbO^2 during viewing various image types. Second using repeated measures ANOVA, we examined participants' physiological responses with HR and SC reactivity as the dependent variables, stimulation group was the between subject variable and different types of images the within subject variable (distress, positive and threatening). These analyses were used to investigate how right PFC inhibition using the cTBS protocol might be affecting physiological responses in a free viewing of emotional images context. Partial eta squares (η^2 = .01-.06 small effect size, η^2 = .06-.14 medium effect size, η^2 > .14 large effect size; Cohen, 1988) are reported in the text. Interaction effects are depicted in figures along with 95% confidence intervals.

Descriptive statistics. In order to test for potential individual differences, as well as for screening purposes depressive and anxiety symptoms were measured. *Table 1* presents descriptive statistics among self-report measures of current symptoms of anxiety and depression that have been measured at the beginning of the experiment. The two stimulation groups did not show significant differences based on age, depression or anxiety. Furthermore, post hoc statistical analysis confirmed that men and women did not show different HR levels $F(1, 39)= 0.42$, $p=.52$, $\eta^2=.009$, SC levels $F(1, 39)= 0.41$, $p=.52$, $\eta^2=.009$ or PFC activity $F(1, 39)= 1.47$, $p=.23$, $\eta^2=.03$ in response to cTBS.

Manipulation check of emotion induction using IAPS images: Before proceeding with the main analysis, the effectiveness of emotional images was first verified. Repeated measures ANOVA were conducted with PFC, SC and HR activity as the dependent variables and images type as the independent variables. For PFC activity, results showed that differences in amplitude were not significant between image types, $F(2, 39)= 0.87$, $p=.96$, $\eta^2=.06$. Previous findings on HbO^2 activity has been found to be biased toward positively valent materials during a video affective task (Fanti et al., 2015), but at the present study we were not able to replicate these findings using affective pictures. Differences on SC activity, showed significant within-group differences between various image types, $F(2, 38)= 3.64$, $p=.00$, $\eta^2=.29$. Post-hoc comparisons indicated that SC activity was lower during positive (M=10,47, SE=.92) compared to threatening (M=11,58, SE=1.17; p<.001) and distressing images (M=12.82, SE=1.36;

p<.004). These differences were also significant for HR activity $F(2, 38)= 2.43$, p=.04, η^2=.09, with post-hoc comparisons suggesting that distressing images (M=83.7, SE=1.45; p <.04) resulted in significantly higher HR activity compared to positive images (M=81.15, SE=1.58.). These findings corroborate with previous findings that SC and HR activity is higher during distressing emotional stimuli compared to positive and neutral (Fanti et al., 2015).

PFC activity: The repeated measures analysis comparing the effects of real versus sham stimulation to HbO^2 suggested a between group effect, $F(2, 38) = 9.04$, $p < .00$, $\eta^2 = .17$, $\varepsilon = .98$. Real cTBS resulted in significantly lower HbO^2 activity for two types of emotional images compared to the sham condition (control group). As illustrated in Figure 4, the group receiving real stimulation had lower HbO^2 levels during distressing (M=-,005, SE=,010) and positive images (M=-,024, SE=,010) compared to the sham stimulation group during distressing (M=,005, SE=,008) and positive images (M=,020, SE=,009). No interactive effects between emotion condition and stimulation type were identified.

Skin Conductance: The repeated measures analysis comparing stimulation groups (real right vs sham right) on SC reactivity suggested no significant effects of stimulation, $F(2, 38) = .715$, p =.40, $\eta^2 = .02$. As depicted in *Figure 3* no main or interactive effects, $F(2, 38) = 1.64$, $p = .21$, $\eta^2 = .08$, were identified for stimulation type on SC reactivity.

Heart Rate: Using a 4 (Emotion condition: Distressing, Positive, Neutral and Threatening) x 2 (cTBS vs sham) repeated measures ANOVA, we tested the effects of right DLPFC stimulation on HR reactivity. This analysis revealed no significant main effects, of right cTBS stimulation on HR reactivity levels, $F(2, 38) = 2.26$, $p = .14$, $\eta^2 = .05$ or interactive effects, $F(2, 38) =.146$, $p = .86$, $\eta^2 = .01$ (see *Figure 4)*.

Discussion

To date no previous study have examined the effects of inhibitory cTBS over the right DLPFC on autonomic and PFC activity responses simultaneously and during emotional processing. This randomized, sham-controlled study, examined differential effects between cTBS application and sham-stimulation over the right DLPFC on autonomic (HR and SC) and brain oxygenation (HbO^2) measures. Participants were shown various types of emotional pictures (threatening, distressing, positive and neutral) in a passive viewing condition immediately after a single cTBS session of 40 seconds (Huang et al., 2005). Initially, to verify the effectiveness of emotional pictures (IAPS dataset) to affect physiological reactivity, SC and HR activity were assessed independently of stimulation type. During the presentation of distressing and threatening pictures participants showed increased SC reactivity compared to positive and neutral pictures, as well as increased HR activity during distressing pictures

compared to positive pictures, pointing to a stimulus-directed attention effect (Bradley, 2009). For PFC activity, we showed that there were no significant differences in HbO^2 amplitude between the different image types. As regards to the main results, the current investigation increases understanding of cTBS effects on emotion processing by providing two main findings: First, our findings did not point out cTBS-autonomic reactivity significant interactions. We were not able to provide evidence that a single session of cTBS over the right DLPFC could modulate HR and SC activity responses to emotional pictures in healthy participants. Second, we identified a significant cTBS-effect on the right DLPFC activity as suggested by the decreased HbO^2 levels on distressing and positive pictures compared to sham stimulation group. In this way, we provide novel evidence regarding brain activity of the right DLPFC during viewing of emotional stimuli after cTBS.

The lack of inhibitory stimulation effects on physiological reactivity do not correspond with recent findings reporting that right DLPFC stimulation modulates physiological reactivity. We identified three more studies that checked on autonomic responses after right prefrontal stimulation during emotional tasks of which only one applied cTBS (Poppa et al., 2020). Of the studies that used standard repetitive stimulation protocols both studies were randomized, double-blind and sham-controlled (Berger et al., 2017; Balderton et al., 2019). One study applied high-frequency (10 Hz) rTMS over the right DLPFC in healthy subjects and found an increase in anxiety-potentiated startle reflex. The second study used low-frequency (1 Hz) rTMS over right DLPFC and demonstrated phasic cardiac responses accelerations during the presentation of negative (IAPS) compared to positive pictures (Berger et al., 2017). No effects however were identified on SC responses during emotional pictures passive viewing. The only identified study that used cTBS to the right frontotemporal cortex measured its effects on spontaneous and slow (0.1 Hz) breathing. This study showed increased heart rate variability (increased pulse transit time latency) across breathing rates and suggested that right-lateralized cTBS appears capable of modulating neural cardiovascular processing (Poppa et al., 2020). Possible causes of lack of cTBS effects on autonomic responses on our study could be the use of a single stimulation design. Previous studies that achieved significant therapeutic effects have applied 10-20 sessions of standard rTMS course and standard treatment protocols consists of at least 30 stimulation sessions (Lefaucheur et al., 2014). Therefore, it is likely that a greater number of sessions could result in stronger findings on modulating autonomic reactivity responses.

Our finding that right DLPFC activity was significantly lower during positive and distressing pictures is counter with the frontal valence asymmetry hypothesis suggesting that the left hemisphere is dominant for positive and the right for negative emotions (Heller et al., 1995; Davidson, 2004). According to this hypothesis right DLPFC activity is related with negative valence and increased arousal, while left DLPFC excitation is likely to be related with positive affect. Based on this hypothesis and neurostimulation capability of increasing left DLPFC activity, rTMS have been broadly used during the last decade as a new and effective treatment for depression (Herrington et al., 2010). However, studies following this model application of rTMS targeting the right DLPFC have demonstrated mixed findings in treating anxiety disorders linked with bias towards threat (Cirillo et al., 2019). For example, two studies indicated that 1Hz inhibitory stimulation over the right DLPFC favours treatment in generalized anxiety disorder (Bystritsky et al., 2008; Diefenbachet al., 2017). However another study that used (Dilkov et al., 2017) excitatory stimulation (20 Hz) on the right side demonstrated the best highest effect size in reducing anxiety suggesting that there are contradicting results. Our current results were not consistent with the frontal asymmetry hypothesis, since right DLPFC inhibition was associated with both positive and negative affect. However, it should also be mentioned that during the pictures manipulation check for right DLPFC activity, results showed no differences in oxygenation (HbO^2) between image types. Thus, future work is needed to test the effects of cTBS by the presentation of highly arousing emotional stimuli and perhaps interactive versus passive viewing tasks (Coan et al., 2006).

In regard to the underlying neural mechanisms our results suggest that right DLPFC oxygenation can be impaired following cTBS but autonomic responses were not affected. The lateral PFC, a region with both structural and functional connectivity to the amygdala, has been consistently implicated in the downregulation of subcortical-generated emotional responses (top-down regulation). The coactivation of PFC regions with amygdala reactivity to emotional stimuli is well supported by prior neuroimaging studies that connect these areas with active and voluntary affective reactions (Banks et al., 2007; Phan et al., 2005; Oschner & Gross, 2005). In line with these findings and previous evidence that right DLPFC inhibition increases heart rate during affective picture viewing (Berger et al., 2017), we expected elevated SC and HR activity following cTBS to verify the implication of this brain area in top-down regulation processes. Counter with our hypothesis we were not able to identify significant increases of physiological responses (HR and SC). However, as previously mentioned this might be due to the one session used in the current study.

Recent studies highlight the great potential of newly established theta burst stimulation to modulate GABAergic and glutamatergic transmission with complex effects on intra-cortical and corticolimbic interactions (Gratton et al., 2013; Iwabuchi et al., 2017). However, for the DLPFC, it is unclear whether TBS has similar effects compared to application over motor areas which highlights the significance of the current investigation. In a recent study, cTBS was applied to either the left or right DLPFC in a sample of healthy participants and results showed bilaterally decreased DLPFC oxygenation following inhibitory stimulation but no behavioural effect on an emotional stroop task (Tupak et al., 2013). The results of the current study are in line with these earlier findings and additionally demonstrate that DLPFC oxygenation can be impaired by cTBS with no effects on autonomic activity.

Future studies should aim to examine more closely the effects of TBS protocols using multiple and bilateral stimulation sessions able to therapeutically exploit neuronal plasticity and alter different functional neural abnormalities in psychiatric and other populations. Studies employing imaging techniques and physiological measures examining more closely functional relationships between neural regions and automatic responses are important for emotion processing, and will help to clarify further neuromodulation applications. The potential for cTBS to modulate the cortical-autonomic network may be relevant to various diagnosis such as aggressive behaviour and stress-related psychiatric disorders which are associated with impaired physiological reactivity to emotional stimuli (Chail et al., 2018; Fanti., 2016). This study is one of the first investigations towards providing evidence about brain and physiological reactivity following cTBS associated with emotional processing.

A limitation of the current work is that the stimulation operator had to remain unblinded to the cTBS condition in order to set the coil to active or sham. However, the operator had minimal contact with the participants during their stimulation sessions and the consent with information about the study were given by a blinded to condition research assistant. Another limitation of the current work is that we used the 10-20 system methodology to determine the location of stimulation. More objective methods using fMRI-based localization could strengthen the reliability of cTBS effects. The last limitation points concerns the lack of diversity in sites of stimulation and also the limited time that the autonomic responses were measured during images presentation (5-s). It is possible that the lack of effects of cTBS over autonomic activity do not reflect an actual lack of effect, but shows a lack of engagement with the task. For instance, in healthy participants, passive exposure to film clips have been found to elicit sadness, anger or happiness in healthy participants, associated with HR and SC reactivity likely suggesting a more efficient method to trigger autonomic responses (Bradley

& Lang, 2000; Fanti et al., 2016). This last point warrants careful attention since it is important for future studies to use stimuli that sufficiently influence emotional arousal.

Conclusions

Overall the current investigation provides new findings in support of the idea that the PFC region shows reduced oxygenation levels after cTBS over the right DLPFC during positive and distressing images. Further, we provide evidence that a single cTBS session compared to sham stimulation did not modify SC and HR activity during passive viewing of emotional pictures. The direction of these effects may depend on stimulation parameters such as the stimulation site or the single stimulation paradigm, the sample size and degree of participants' engagement with the task. The broader goals for this line of research are to identify mechanisms underlying neural activity and autonomic responses and provide evidence of how cTBS may affect neural activity and physiological responses such as heart rate HR and SC reactivity. By uncovering a link between cTBS over the right DLPF and brain activity during emotional processing, the current work represents a first step in this process. Since a number of psychological problems have been related to impaired neural and physiological activity these findings might contribute to increase knowledge for future implementation of cTBS in clinical research.

STUDY 2

Effects of Continuous Theta Burst Stimulation to the dorsolateral prefrontal cortex in attention to emotional stimuli

Introduction

Attention to emotional stimuli is fundamental enabling individuals to bring important information into focus and to successfully adapt to the environment. Impaired attention to emotional experiences is considered an important risk factor that may lead to diverse mental health problems associated with emotional dysregulation such as anxiety and antisocial disorders (Thompson et al., 2011; Garofalo et al., 2016; Groeneworld et al., 2013; Kimonis et al., 2006; Murhy et al., 1999). Contemporary models of emotion regulation suggest that brain systems involve bottom-up inputs by subcortical circuits including amygdala as well as top-down influences from frontal control regions such as the dorsolateral prefrontal cortex (DLPFC) and the dorsomedial prefrontal cortex (Ochsber & Gross, 2007; Sarter et al., 2001). These frontal areas are part of complex cortical and subcortical circuits implicated in attentional responses to affective information and consequently in abnormalities to emotional responses (Fenske and Eastwood, 2003; Tipples, 2006; Hopfinger, Buonocore & Mangun., 2000). Considering the important role of frontal control areas in cognitive processing of emotional stimuli, repetitive transcranial magnetic stimulation (rTMS) has been recently proposed as a promising research tool to modulate cortical excitability and develop novel therapeutic interventions. However, further investigation is warranted to clarify the type of rTMS treatment (including laterality and stimulation protocol) that may be utilized for deficits in attention systems and further improvements *in* emotion regulation.

Emotional stimuli are strong competitors for dynamic attention processing resources because of their high behavioural relevance (Vogt et al., 2008; Yiend, 2010). Attention to fearful and threatening stimuli, for example, should be elicited faster than attention to neutral due to the association of negative emotions to escape behaviour and efficient avoidance of dangerous situations (Wentura, Rothermund., & Bak, 2000). Attention is also allocated more rapidly to a location containing pleasant emotional stimuli than to a location containing neutral stimuli to elicit approach behaviour to desirable situations (Lang, Bradley & Cuthbert, 1998). This line of reasoning is supported by the finding that different emotions are accompanied by different attention predisposition tendencies (Rooijen et al., 2017). For instance, studies investigating attention towards pleasant stimuli (e.g. baby faces) reported broaden attention span (Rowe, Hirsh, & Anderson., 2007) and more rapid detection response times than neutral stimuli. Enhanced detection of unpleasant stimuli such as snakes and spiders has been also found in visual search tasks (Eastwood, Smilek, & Merikle, 2001; Öhman, Lundqvist, & Esteves, 2001). Such effects generally indicate a privileged access to awareness for emotionally significant stimuli. Importantly, neuroimaging studies have converged on the conclusion that

this type of preferential control over attention involves prefrontal regions neural activation (Vuilleumier, 2005). Several prefrontal brain regions, such as the DLPFC, have been associated with attentional control processes (both bottom-up and top-down), including the maintenance of attention on a task, the release of inhibitory control and selection of stimuli relevant to a specific task (Hampshire et al., 2010). Given that prefrontal brain activity has been associated with attention control processes its modulatory role by non-invasive neurostimulation techniques remains to be tested for potential therapeutic developments.

During the decade, rTMS has been established as an advantageous research tool, which is capable to selectively modulate neural activity with minimum side effects. It is widely used in therapeutic studies of various neuropsychiatric disorders and has been largely successful in the treatment of depression (McClintock et al., 2018). Previous studies have also indicated that standard rTMS over DLPFC regions may modulate attentional engagement to emotional information in healthy individuals (De et al., 2010). For instance, a recent review reported that rTMS over the DLPFC indirectly affects connected areas that are related to attention and emotion (see Guse et al., 2010). Excitatory 10-Hz rTMS of the right DLPFC was found to strengthen top-down control of aversive stimuli in healthy control subjects (Notzon et al., 2018) and facilitate attention towards threatening information, especially among individuals who have high anxiety (Vanderhasselt et al., 2011). These findings highlight the recruitment of DLPFC during emotion processing which has been continuously associated in neuroimaging research with a functionally interactive network of cortico-limbic pathways and top-down cognitive regulation of emotions (Banks et al., 2007).

Although several findings point to positive effects of rTMS on attentional control there is lack of studies assessing the effects of newer Theta Burst Stimulation (TBS) protocols on the attentional processing of emotion. New developments with regards to the stimulation protocols of rTMS suggest the use of rapid TBS to further improve the efficacy and shorten the required stimulation time. TBS lasts from 20 to190 seconds, whereas conventional rTMS procedures may last up to 37 minutes per session (Blumberger et al., 2018; Mendlowitz et al., 2019). Two main TBS modalities show opposite effects on cortical excitability: the intermittent TBS (iTBS) and continuous TBS (cTBS) generate excitatory and inhibitory effects, respectively. (Huang et al., 2005). Compared to studies investigating the effects of TBS's on motor cortical cortex, there is a relative paucity of studies investigating its effects on prefrontal regions. So far, a small number of clinical sham-control trials support the antidepressant effect of TBS over the DLPFC and demonstrate that it is not inferior relative to traditional rTMS (Chen et al., 2019). More studies are needed to elucidate the effects of TBS applied to DLPFC since several

unanswered questions remain relating to its optimal parameters for future clinical applications (Hakamata et al., 2010).

Initial evidence for the potential effects of TBS protocols on emotional attention facilitation comes from a study applying cTBS (inhibitory) over the right DLPFC (Cao et al., 2018). In this work, the influences of cTBS were investigated during an emotional recognition Go/NoGo task that consisted of happy and fearful faces, while electroencephalogram (EEG) oscillations were recorded (Cao et al., 2018). Participants receiving real versus sham cTBS over right DLPFC showed decreased alpha power oscillations, which is an indication of increased activity (Coan & Allen, 2004) at the cortical level to happy stimuli. In an additional study, the authors demonstrated that cTBS over the right DLPFC enhanced occipital-parietal brain activity in response to negative images (Keuper et al., 2018). These results are counter to the Asymmetric Inhibition Model and the frontal Asymmetry hypothesis that propose that asymmetries on DLPFC activity modulate the executive control mechanisms for positive and negative stimuli separately (Grimshaw & Carmel., 2014; Herrington et al., 2005). According to these models, mechanisms in left DLPFC inhibit negative distractors and may be generally associated with positive affect and right DLPFC inhibit positive distractors and may be associated with negative affect (Grimshaw & Carmel., 2014; Herrington et al., 2005). To the best of our knowledge, lateralization effects of cTBS (inhibition) have not been explored on attention processes to emotional stimuli and more research work is needed to test the laterality of DLPFC function.

The above initial studies demonstrate the potential of employing cTBS to investigate the effects of DLPFC modulation on emotion and attention processing. Although there are mixed findings in the existing studies concerning inhibitory and excitatory rTMS effects on emotional attention processing, a recent study that compared standard excitatory-and-inhibitory rTMS on the DLPFC showed that inhibitory stimulation affected the physiological reactivity in response to emotional stimuli (Berger et al., 2017). Moreover, inhibitory cTBS to the right DLPFC has been associated with accelerated startle reflex during affective picture viewing (Vennewald et al., 2016). Based on these findings, we chose inhibitory left and right cTBS in an attempt to elucidate DLPFC lateralized functioning on attention processing. These findings can provide initial evidence for cTBS effects over the DLPFC that may translate to clinical applications.

Current study

The main purpose of the current study is to examine whether cTBS (inhibition) over the left and the right DLPFC modulate attention facilitation to emotional stimuli. The current study focused on attention to both distressing and pleasant stimuli because understanding the modulation effects of DLPFC on both negative and positive emotions is significant for future therapeutic suggestions (Crawford and Cacioppo, 2002; Smith et al., 2003). The dot-probe task has been used to measure attention facilitation, which has been employed in several studies during the past three decades to investigate attention to emotional stimuli in typical individuals and in clinical samples (see Bar-Haim et al., 2007 for a review). Given that emotional pictures typically facilitate allocation of attention and that rTMS has been found to enhance physiological reactivity and brain activity in response to emotional stimuli (Berger et al., 2017; Keuper et al., 2018; Vennewald et al., 2016), participants were generally expected to respond more quickly to probes replacing positive images after inhibitory cTBS over the right and to probes replacing distressing images after inhibition of left DLPFC compared to sham groups. No previous study have examined the inhibitory lateralization effects of cTBS on attention control toward affective stimuli which may result, at least at a pre-clinical level, in new insights about cTBS mechanisms of action. Furthermore, these findings will show stimulation parameters that influence cTBS effects such as the site of stimulation.

Methods

Participants: Ninety-one participants (32 males, mean age: *M*=21.60, *SD*=1.60, range 18-26 and 59 females, *M*=20, 82, *SD*=1.45, range 18-23) were recruited for the purpose of the current study and completed the behavioural task. Participants were recruited at the University of Cyprus via advertisement and word-of-mouth and received course credits. All participants were healthy Greek-Cypriots, medication-free, right-handed and had normal vision (for computer tasks). No participant had any established risk factor related to rTMS based on a screening Transcranial Magnetic Stimulation Safety Questionnaire (e.g., cardiac pacemakers, epilepsy, and use of drugs; see Rossi et al., 2012). Further exclusion criteria were history of psychiatric/neurological disorders including epilepsy, head trauma and migraine. All participants provided written informed consent for their participation in the experiment and rTMS procedures. Participants were assigned one of four stimulation protocols (right DLPFC vs Sham control and left DLPFC vs Sham control). There were twenty-four participants assigned in the real left group (*F*=17 and *M*=7) and twenty-two in the sham control group (*F*=13

and *M*=9). The real right group included twenty-three participants (*F*=16 and *M*=7) and twenty-two participants were assigned in the right sham group (*F*=13, *M*=9). Post hoc statistical analysis further confirmed that the four experimental groups were comparable regarding age, depression and anxiety scores (table 1).

Experimental Procedure. This study was a double-blind, randomized, sham-controlled study. Participants were randomly assigned to one of four different stimulation conditions (left/right cTBS and left/right sham cTBS). Participants that met preliminary inclusion criteria began with an overview of the study and written informed consent. The procedure was driven by the experimenter so that a quarter of the participants were assigned to the 'blue', 'green', 'yellow' and 'orange' group (unknown stimulation condition to the participant). Male and female participants were pseudo-randomly assigned to a colour-group according to the order of arrival at the lab. Participants were told that they belong to the colour-group indicated by the card they had chosen and that they will be presented with an attention computerized task after receiving a short rTMS stimulation session (40 sec). Immediately after stimulation, participants were comfortably seated in front of a 19' computer screen (1024x768) at an approximate distance of 80 cm. Participants first completed a training phase (12 pairs) of the task, to allow themselves to familiarize with the overall procedure. Images were presented in random order and the E-Prime 2.0 software (Psychology Software Tools, Pittsburg, PA) was used for stimulate presentation and data collection.

Screening Questionnaires. Although a single-session of rTMS is usually not found to acutely affect mood in healthy volunteers (Baeken et al., 2006) it has been reported that state anxiety prior to stimulation (perhaps related to expectations concerning the rTMS procedures) affects both cognitive-affective and cortisol responses to rTMS (Baeken et al., 2011; Vanderhasselt et al., 2011). Therefore, for screening purposes participants completed the Becks Depression Inventory (BDI-II; Beck, Steer, & Brown., 1996) and the State-Trait Anxiety Inventory (STAI) for Adults (Spielberger, 1983) prior to the conditioning session. The BDI-II is a 21-item self-report measure created to assess the severity or intensity of depressive symptoms (Beck & Steer, 1993, Beck et al., 1996). Responses to each item are rated at 0-3points and according to the manual for the BDI-II, scores ranging from 0 to 13 are considered not depressed. The STAI consists of self-assessment scales that measure state and trait anxiety in terms of negative affect (Grös et al., 2007). Scores on the state scale reflect current anxiety levels, while trait anxiety scores reflect are long-term predisposition for anxiety (Spielberger, 1983). The sample was characterized by a mean of Beck Depression Inventory-short form (BDI-II) of 3.68 (SD=2.40) and by a mean of Spielberger State-Trait Anxiety Inventory (STAI-

T; Spielberger, 1983) score of 38.12 (SD=8.96), which both indicate minimal to moderate depression and anxiety levels. There were no participants scoring above the clinical cut-off score of anxiety (>37) or depressive symptoms (>10) included in the study sample.

cTBS Protocol - Real and Sham cTBS. Coil position was determined using standardized coordinates from the EEG (Steinmetz et al., 1989) International 10-20 system (with F4 corresponding to the right DLPFC stimulation target and F3 corresponding to the left DLPFC). The location and orientation of each participant's coil placement was indicated on a nylon cap that participants wore throughout the single stimulation session. A figure-of-eight focal coil (70 mm diameter) was used. The coil was held in a fixed position by a mechanical arm and oriented so that the induced electric current flowed in a posterior–anterior direction. Stimulus intensities were set at 70% of active motor threshold (AMT). Previous experiments that used cTBS found significant inhibitory effects using as stimulation intensity 80% (e.g., Huang et al., 2005) or 70% (Goldsworthy et al., 2013). We chose to use 70% intensity to prevent intense facial muscle twitching during stimulation. Each stimulation session TBS burst consisted of 3 pulses at 50 Hz, with each train being repeated every 200 ms (5 Hz) for 40 seconds (600 pulses). It has been shown that this stimulation paradigm decrease cortical excitability on prefrontal function (Lowe et al., 2018), therefore, this protocol seems suitable to alter DLPFC excitability. The number of pulses per participant used in the present study is consistent with the prototype protocol (see Huang et al., 2005). Safety guidelines based on recent available safety studies on rTMS were followed (Oberman et al., 2011)

Emotion Dot-Probe Task. The dot-probe task is a common laboratory paradigm used to index attentional bias for emotional stimuli at early stages of information processing (MacLeod et al. 1986). It provides a quick, convenient, and inexpensive index of emotional responsiveness. The task is typically modified in terms of specific emotional content based on the focus of a given investigation, in this case the relationship between emotional processing of distress and pleasant images and cTBS stimulation over the DLPFC. The emotional pictures version of the task presents a series of picture pairs of distressing (e.g., crying child), neutral (e.g., book) and pleasant (e.g., smiling baby) emotional content using slides primarily taken from the International Affective Picture System (IAPS; Lang et al. 1997). Slides were selected based on previous studies to tap distress and pleasant content (Kelloung et al., 2008; McManis et al., 2001). This task consisted of 1 block of practice stimuli (12 picture pairs) followed by 3 experimental blocks, each containing 12 picture pairs. Each picture presentation consisted of three sequential components: (1) a 500 millisecond image of fixation cross appearing in the center of the screen, (2) a 500 millisecond simultaneous presentation of one of three potential

picture pairings: neutral-neutral, pleasant-neutral and distress-neutral, with stimuli centered and located immediately above and below the location of the fixation cross, and (3) a second image of fixation cross appearing in either the top or bottom picture location. Participants were instructed to respond as fast as they can and on every trial to select a key on the keyboard that corresponded to the location on the screen (up or down) where the dot-probe appeared. If no key was pressed within 5000 milliseconds, the response was recorded as incorrect.

The number and location of picture stimuli were counterbalanced across test trials in order to ensure that an equal number of emotional and neutral stimuli appeared in both top and bottom locations. Additionally, there were an equal number of emotional and neutral stimuli that were replaced versus not replaced by a dot-probe stimulus. The primary dependent measure for the current study was an attentional facilitation index. This facilitation index was calculated by subtracting the average response time (latency) to dot-probes replacing emotional pictures in distress-neutral and pleasant-neutral pairs from the average latency to probes replacing neutral stimuli in the various neutral-neutral picture pairs (12 pairs each). To control for potential location effects, such as an attentional preference for the top or bottom location of the screen, the following formula was used to calculate the facilitation indices that only compared neutral and emotional probes in the same location: Facilitation =1/2 x [(Neutral Only/Dot-probe Up - Distress Up/Dot-probe Up) + (Neutral Only/Dot-probe Down - Distress Down/Dot-probe Down)]. Consistent with prior uses of the task (e.g. Kimonis et al., 2016), incorrect responses and response times less than 100 milliseconds were not included in the calculation of facilitation indices. Facilitation scores greater than three standard deviations above or below the mean were truncated to 3 SDs. Given that emotional pictures typically facilitate allocation of attention, participants were generally expected to respond more quickly to probes replacing emotional images because these slides capture their initial attention, resulting in a pleasant facilitation index.

Results

Plan of analysis. Prior to the main analysis data was screened for outliers. Initially, we conducted repeated measures Analysis of Variance (ANOVA) with response times to the emotional dot-probe task as the dependent variable and emotion type as the within-factor (i.e., neutral, distress and pleasant). These analyses were used to investigate the effectiveness of the picture-type manipulation before proceeding with the main analysis. Second, using repeated measures ANOVA, we examined participants' response time differences on various types of

images as the within subject variable (neutral, distress and pleasant) with stimulation group as the between subject variable. These analyses were used to investigate how right and left DLPFC inhibition using the cTBS protocol might be affecting attention allocation toward emotional stimuli. Third, we used repeated measures ANOVA using stimulation groups as an independent variable to examine participants attention facilitation index scores calculated by subtracting the average response time to dot-probes replacing emotional pictures (distress and pleasant) from the average latency to probes replacing neutral stimuli. Partial eta squares (η^2 = .01-.06 small effect size, η^2 = .06-.14 medium effect size, η^2 > .14 large effect size; Cohen, 1988) are reported in the text. Interaction effects are depicted in figures along with 95% confidence intervals.

Descriptive statistics. Table 1 presents descriptive statistics among self-report measures of current symptoms of anxiety and depression which were measured at the beginning of the experiment. Before proceeding with the ANOVA comparisons, we tested the groups' differences between main mood disorder variables in order to control for mood disorders effects and groups differences. The four stimulation groups did not show significant differences based on age, depression or anxiety. Furthermore, we checked for gender effects since we had a larger number of females participants compare to males in each group. Post hoc statistical analysis confirmed that men and women did not respond differently in response to the emotional dot-probe task after cTBS, $F(3, 86)= 2.44$, $p=.07$, $\eta^2=.07$.

Manipulation check of Dot-Probe Task. To examine differences in reaction times (RTs) to distinct emotional stimuli (neutral, positive, threatening), we used repeated measure ANOVA in IBM SPSS 20.0 with emotion RT as the dependent variable and emotion type as within subjects factor. As expected, there was a significant within main effect of emotion $F(2, 86)= 77.46$, $p<.00$, $\eta^2=.47$, reflecting that participants responded faster during distressing (M=428.39, SE=8.32; $p<.00$) and pleasant images (M=422.64, SE=7.93; $p<.00$) compared to neutral images (M=472.57, SE=8.20).

Effects of cTBS on response times. Repeated measure ANOVAs were carried out on the reaction times with cTBS (Left, Right, Sham left, Sham right) as a between-subjects variable and emotion (pleasant, distressing and neutral) as a within-subjects variable. Although the main effect of cTBS was not significant $F(3, 86)= ,69$, $p=.55$, $\eta^2=.02$, there was a significant two-way Emotion x Stimulation interaction $F(6, 174)= 7.208$; $p=<.00$, $\eta^2=.20$. After real cTBS, participants responded faster to emotional stimuli compared to neutral, a phenomenon that was not observed for the sham groups. Significant interactions are depicted in figures along with 95% confidence intervals (figure 1).

Attentional facilitation indices. In order to explore our priori hypotheses, separated analyses for attention facilitation indices of pleasant and distressing stimuli was conducted. Findings suggested a significant within groups effect for attentional facilitation indices, $F(1, 90)= 5.58$, $p<.02$, $\eta^2=.06$, indicating that participants showed higher facilitation during pleasant stimuli ($M=49.94$, $SE=5.01$; $p<.02$) compared to distressing stimuli ($M=44.18$, $SE=4.80$). Between groups differences for type of stimulation were also identified. On average, participants receiving left and right stimulation showed higher overall attention facilitation to positive and distressing stimuli (these findings are demonstrated in fig. 2: average) compared to both sham conditions, $F(3, 90)= 8.38$, $p=.00$, $\eta^2=.22$. Importantly, there was no significant interaction between attentional facilitation indices and type of stimulation, $F(3, 90)= 1.27$, $p=.29$, $\eta^2=.04$. Pairwise comparisons (figure 2) revealed that real left cTBS ($M=50.41$, $SE=7.91$; $p<0$;$d=0.49$) and real right cTBS ($M=76.25$, $SE=$;$p<0$;$d=0.61$) resulted in significantly larger facilitation to pleasant images compared to sham left ($M=23.91$, $SE=8.09$) and sham right ($M=32.45$, $SE=7.74$). Post hoc comparisons also indicated that real left ($M=52.71$, $SE=7.84$; $p<0$; $d=0.42$) and real right ($M=67.12$, $SE=7.52$; $p<0$; $d=0.46$) cTBS groups resulted in significantly larger facilitation to distressing stimuli compared to sham left ($M=15.64$, $SE=8.02$) and sham right ($M=27.66$, $SE=7.68$).

Discussion

The present study provides the first empirical evidence showing that inhibitory cTBS over the DLPFC contributes to the modification of attention to emotional stimuli. The aim of this study was to investigate if neuromodulation of DLPFC (right and left) by cTBS would have an effect on attention towards distressing and positive stimuli. Thus, we used an emotional dot-probe task and presented pleasant, distressing and neutral images to test for shifts on attentional facilitation indices and RTs. As expected, in the RTs analysis of the dot-probe task, we found that in general participants responded faster during distressing and pleasant images compared to neutral images. More importantly, a significant interaction indicated that specifically those receiving real stimulation (both left and right), but not sham, showed significantly faster RTs to emotional compared to neutral images. In the attention facilitation indices, we found a faster facilitated identification of the probe in response to distressing images after both left and right DLPFC stimulation groups compared to the sham groups. This effect was also observed for both DLPFC hemispheres on pleasant images indicating larger vigilance to positive stimuli after cTBS. These findings provide support for neuroimaging data implicating the DLPFC in control of attention in relation to emotional information (Barbas,

2000) and further highlight the potential of cTBS to modify attention facilitation for emotional information.

Just as standard rTMS has demonstrated effects on brain activity and metabolism in neuroimaging studies (Siebner et al., 2009), similarly TBS has been reported to induce significant and long-lasting neuronal responses in motor cortical areas and more recently in prefrontal brain areas (Huang et al., 2005; Wozniak et al., 2014). In clinical practice, rTMS is applied over the left or right DLPFC and involves typically 45–min duration daily stimulation sessions applied over 4–6 weeks (Chen et al., 2013). Therefore, one main reason why we chose to further investigate TBS protocols is due to the brevity of its application. As described by imaging research, emotional stimuli (especially negative) are processed by a neural network consisting limbic and para-limbic regions and inter-connections with lateral prefrontal regions (Pedale et al., 2019). We demonstrated that right and left cTBS inhibition resulted in increased attention facilitation. These findings indicated that focus was towards emotional information and individuals responded faster on trials where probes replaced distressing and positive than neutral stimuli. Overall, these results suggest that a single cTBS session may boost automatic processes of emotional attention, eventually leading to facilitated engagement to emotional stimuli.

Considering the important role of frontal control areas in cognitive processing of emotional stimuli, we experimentally manipulated DLPFC activity using non-invasive cTBS. Dot-probe data evidenced that shifting hemispheric DLPFC activity towards the right or the left DLPFC led to a bias in favour of attention to emotional stimuli compared to neutral. Our findings confirm a regulatory influence of the DLPFC on emotional attention (Oschner and Gross, 2005), as our experimental manipulation clearly affected allocation of attention to probes replacing emotional images. According to the hemispheric asymmetry hypothesis (Davidson, 1992) and the asymmetric inhibition model (Grimhaw and Carmel, 2014) there is valence-specific specialization of the left-hemisphere to positive valence and the right-hemisphere to negative valence. In opposition to these theories our study provide evidence for the involvement of both DLPFC hemispheres in attention allocation to positive and negative emotional stimuli.

One can hypothesize that although no lateralized specialization effect to emotional attention was observed, our findings of increased speed on attention to emotional stimuli may reflect enhanced awareness following inhibition of the DLPFC. This is in line with previous reports of prefrontal modulatory influence on perception-related brain areas implicated in stimulus-driven processes of emotional attention (Banks, Eddy, Angstadt, Nathan, & Phan,

2007; Phan et al.,2005;Olofsson et al., 2008). Some studies implicate areas of the left prefrontal cortex in the inhibition of stimulus-driven processes of negative emotional information (e.g. Mak, Hu, Zhang, Xiao, & Lee, 2009). Others have found greater activity of right frontal areas associated with inhibitory processing stages of negative emotion (e.g. Leyman, De Raedt, Vanderhas-selt, & Baeken, 2009). If the brain structures involved in inhibition are lateralized either in the frontal right or left hemisphere, then it would be expected that reaction times to emotional stimuli and facilitation indices on the dot-probe task would be different between the healthy groups receiving left or right inhibition. However, as observed in this study, the reaction times in response to positive and distressing stimuli after cTBS to left and right hemispheres were approximately the same. One possible explanation in line with previous findings on brain activity after cTBS, is that DLPFC inhibition indirectly enhanced perceptual processing and autonomic attention, eventually leading to more effective processes of attention disengagement from emotional content stimuli (Keuper et al., 2018).

Perception-related brain areas including the DLPFC have been previously implicated in stimulus-driven mechanisms of emotional attention and regulation of affective processing (Sarter et al., 2005; Bressler et al., 2008; Bayle and Taylor, 2010). Two meta-analyses of neuroimaging data has shown that indeed frontal regions activation is increased when subjects engage cognitive strategies (i.e., reappraisal, detachment) during emotional processing and is reduced when subjects passively maintain their emotional state (Ochsner and Gross, 2005; Quirk and Beer, 2006). Functionally, the DLPFC activity have been associated with cognitive processes related to attention, including cognitive inhibition/control and voluntary affect regulation (Cabeza and Nyberg, 2000; Miller and Cohen, 2001). In addition, both animal and human lesion studies, has supported that DLPFC function is necessary for top-down effects to prevent emotion dysregulation (Izquierdo and Murray, 2005; Rosenkranz *et al*., 2003; Quirk and Beer, 2006). A previous behavioural study that investigated standard 1-Hz rTMS (inhibitory effect) on top-town control in a modified emotional Stroop task revealed that individuals receiving inhibitory rTMS over the right DLPFC were quicker on color naming of supraliminal fearful faces compared to sham stimulation (van Honk et al., 2002). We expected to replicate these findings following the cTBS protocol and this is important because we showed that theta burst, similarly with standard rTMS protocols, significantly affect emotional attention processing.

To date, only two other studies have explored effects of cTBS over DLPFC on emotional processing but only over the right hemisphere. In the first study, Keuper et al. (2018) recorded behavioural and electroencephalographic responses to subliminal and supraliminal

negative scenes versus neutral. Results showed that on a neurophysiological level, cTBS over the right DLPFC compared to sham increased occipital-parietal brain activity for both subliminal and supraliminal negative images suggesting that right DLPFC inhibition raised automatic processes of "emotional attention". In their EEG study, Cao et al. (2018) also demonstrated that cTBS over the right DLPFC decreases alpha band oscillations to happy face stimuli suggesting enhanced brain activity for happy facial expressions. Likewise, Notzon et al. (2017) reported increased neural activity to fearful faces in right occipital and right temporal regions, after standard inhibitory compared to excitatory rTMS. Our findings were consistent with these results demonstrating that a single cTBS session could modulate emotional attention processing in healthy individuals.

Strengths, Limitations, and conclusions

A strength of our study is that we conducted experimental manipulation at both the right and left DLPFC and this helps to elucidate the impact of cTBS in attentional emotion processing more fully. Another strength of our study design is that we included a cTBS sham condition since the presence of a control stimulation condition increase the potential generalization of the results. There are also several limitations and future directions that should mentioned. It should be noted that volunteers included in the current study were healthy even though we matched the groups on age, gender-ratio and had similar years of education. However, findings can be used as pilot data or can inform future interventions. For more direct test of our proposal of how cTBS can affect attentional processing, future studies with similar design should include individuals with impaired attentional bias. Additionally, imaging techniques were not used combined with behavioural tasks to more deeply understand the neural bilateral processes via which facilitation change was achieved, and further explore potential ways through which non-invasive stimulation affected attention processes. Future studies combining non-invasive stimulation and imaging techniques, which aim at elucidating the specific functional contribution of DLPFC regions on the interplay of emotion processing and attention would be of great interest. Finally, it is likely that multiple stimulation sessions in future studies will generate more clear results about lasting neural and behavioural changes. Therefore, it would be of great interest to replicate this study under multiple stimulation sessions design. In general the field would be greatly benefited by larger studies that can yield more robust estimate of the mechanisms of TBS applied to the prefrontal regions and what the clinical significance of these effects may be.

The present study has provided experimental confirmation that inhibitory cTBS over the DLPFC leads to increased attention facilitation to emotional stimuli. Decreased response

times indicated enhanced detection and attention of emotional stimuli. We suggested that this effect might reflect down-regulation mechanisms following DLPFC inhibition eventually leading to facilitated attention to positive and negative stimuli. It should be mentioned that the effect of cTBS on emotional processing confirms our recent findings that bilateral cTBS over the dlPFC improved emotional recognition accuracy of various emotional expressions (Konikkou, Konstantinou & Fanti, under review). Future research is needed to understand in more detail how targeted non-invasive brain stimulation via rTMS and TBS protocols may influence emotional processing and extend its applicability in clinical populations. A clearer picture of these mechanisms might have crucial implications for designing novel interventions for psychological disorders such as anxiety disorders linked to increased attention bias to negative cues (Bar-Haim et al., 2007) and antisocial disorders linked to reduced attention to emotional cues (Fanti, 2018). Another potential clinical implication is the potential of combining rTMS treatment in the future with attention modification programs designed to facilitate attentional disengagement from negative- stimuli or to enhance attentional engagement towards positive stimuli (Bar-Haim, 2010; Mogg, Waters, & Bradley., 2017). By combining these approaches, both top-down and bottom-up cognitive systems involved in emotion processing and empathic response might be normalized, enhancing attentional control strategies that are useful in dealing with emotional processing. Taken together, these initial findings and current literature indicates that DLPFC inhibition may enhance attention engagement to emotional stimuli and that the therapeutic use of cTBS may contribute to the treatment of emotional dysfunctions and processing biases.

STUDY 3

Theta burst transcranial magnetic stimulation over the dorsolateral prefrontal cortex affects emotional processing: Accounting for individual differences in Antisocial Behavior

Introduction

Prefrontal cortex (PFC) impairments have been associated with socio-emotional processing deficits (Adolphs, 2002; Coccaro et al., 2007; Shamay-Tsoory et al., 2003). Evidence from neuropsychological research shows that PFC structures interact with emotional neural circuits that underlie behavioral problems and affect the ability to recognize emotions by inhibiting or modulating their activation (Repple, et al., 2017). The involvement of the DLPFC in cognitive processing of emotions has been evident in head-injury and lesion studies, with findings documenting abnormal social-emotional functioning and impaired control of behavior (Fellows & Farah 2004; Butter & McDonald 1970). In congruence with these studies, noninvasive brain stimulation work demonstrated that modulation of PFC can induce changes on emotional perception and processing (Padberg et al., 2001; Winker et al., 2019). Considering the important role of the PFC in emotional processing, there is strong rationale for targeting this area for basic emotional research through neuro-stimulation techniques but also for promising therapeutic investigations. However, evidence for the potential of neuro-stimulation techniques acting as a treatment for disorders marked by deficits in emotional processing and frontal brain abnormalities (Blair, 2013) such as Antisocial Personality Disorder (APD) are lacking in the literature.

According to the DSM-5 (5th ed.; *DSM–5;* American Psychiatric Association [APA]. 2013), a key feature of APD is a pervasive disregard and violation of the rights of others. There are seven main features of APD consisting of criminal behaviour, deceitfulness, impulsivity, aggression and violence, reckless disregard for safety, irresponsibility, and lack of remorse. Individuals with disorders marked by antisocial behaviour frequently show deficits in emotional processing such as recognizing displays of facial affect. Antisocial behaviour, has been associated with specific deficits in the processing of facial emotion recognition and failure in understanding the social cues of other people which is essential for normal socialization (Marsh and Blair., 2008). Distress related cues, especially fearful and sad expressions have been shown to play an important role in appropriate interpersonal behavior (Billeci et al. 2019; Frick and White., 2008; Jones et al., 2009). Brain imaging literature has attribute these deficits in specified neural substrates, including PFC regions (Blair, 2013; Yang and Raine., 2009), involved in cognitive-emotional functions. As such, TMS is a promising tool for better understanding the relationship between affect processing and antisociality by altering the function of accessible cortical regions such as the PFC and observe the effects on different

tasks (Hartwigsen et al., 2015). Better understanding whether stimulating the PFC may enhance affect recognition would permit to further assess causal associations between antisocial behaviour and facial affect recognition deficits and will add on the limited literature on non-invasive stimulation and antisocial behavior.

Theoretical models attribute symptoms of antisocial behavior to core deficits in emotion processing that limit the capacity for empathic experience and prevent individuals from generating negative affect responses to aversive stimuli (Decety et al., 2007; Fanti, 2018; Fairchild et al., 2009). Consistent with this suggestion, individuals with antisocial behavior symptoms have demonstrated deficits in processing negative and positive facial expressions (Mitchell et al. 2006). Empirical neuroimaging findings indicate that disturbed affective processing of individuals with APS is associated with structural and functional PFC deficits (Anderson & Kiehl. 2012; Raine et al., 1998). A meta-analysis of 43 imaging studies linked *recognition* impairments of specific *emotions*, such as fear and sadness, among antisocial individuals with structural and functional reductions in various PFC regions, with a stronger effect for the left than right DLPFC (Yang & Raine 2009). This may be due to the DLPFC's broad connection to functions related to emotional processing, including executive functions and emotional attention. For example, right frontal regions has been associated with automatic processes of emotional attention (Fan et al., 2005; Fossella et al., 2002) and dorsomedial and lateral PFC regions has been associated with attention mechanisms for monitoring and resolving conflict among thoughts and feelings (Ochsner et al., 2002; Ochsner & Gross., 2005; Posner & Rothbart., 2007). Together, these studies suggest that there is evidence indicating the possible implication of the DLPFC on antisocial behavior and the processing of emotional stimuli.

Transcranial Magnetic Stimulation (TMS) is a promising, non-invasive and low-risk tool to experimentally investigate the causal involvement of the PFC during emotional processing in both healthy individuals and individuals with psychological problems (d'Alfonso et al., 2000; De Wit et al., 2015; Salehinejad et al., 2017; van Honk et al., 2002). TMS involves administering noninvasive magnetic pulses that temporarily suppress or excite the function of a brain region based on the stimulation pattern, frequency and intensity (Hallett, 2007). As such, TMS is a promising tool for testing hypotheses about the role of PFC regions in cognitive and emotional processing (Schwarzkopf et al. 2011). By altering the function of a prefrontal cortical region, we can simultaneously test whether the target PFC region plays a role in the behavior under observation (Hartwigsen et al., 2015). Importantly, previous studies have used noninvasive brain stimulation over the DLPFC in healthy subjects and clinical populations

(with a diagnosis of depression, violent offenders, or borderline personality disorder) and have reported significant beneficial effects on impulsivity, risk-taking and self-reported aggressiveness (Choy et al., 2019; Molero-Chamizo et al., 2019;Teti- Mayer et al., 2019).

A promising and newer patterned form of TMS is theta-burst stimulation (TBS), which applies 50 Hz stimulation repeated with a rate in the theta range of five times per second (Di Lazzaro, 2009; Huang et al., 2005). TBS is a novel stimulation pattern shown to induce significant and long-lasting neuronal conditioning responses in motor cortical studies, while electrophysiological effects in the PFC have also been observed (Grossheinrich et al., 2009). Intermittent train of TBS (iTBS) induces cortical facilitation, whereas continuous train of TBS (cTBS) decreases cortical excitability (Huang et al., 2005). Given the current evidence base, this novel pattern of stimulation that recently gained its FDA approval in 2018 for the treatment of depression (Blumberger et al., 2018), allows a treatment session to last less than 15 minutes compared to standard treatment sessions that last about 40-50 minutes (Chung et al., 2015). In depression, evidence for the effectiveness of excitatory TBS and non-inferiority to conventional TMS protocols exists but remain weak in other mental disorders (Chen et al., 2019). Nevertheless, TBS remains a promising instrument to target maladaptive brain networks because it is a more convenient intervention for patients and it is certainly a technique more affordable to treat a larger number of people in clinical use. The clinical relevance of TBS have been less systematically tested especially on PFC regions such as the DLPFC which was a main goal of the current research.

Studies that explored the effect of repetitive TMS over the DLPFC showed modification or enhancements during emotion recognition paradigms after treatment. Both left and right DLPFC stimulation has been related to affective modulation and changes to empathic responses (Gamond & Cattaneo 2016; Wang et al., 2014). Current results in nonclinical samples indicated that decreasing right DLPFC activation improves attention bias for threatening stimuli and alter emotion-related cognitive processes (Diefenbach et al., 2016). In addition, decreasing right PFC cortex activation has been found to improve inhibitory control of emotion during decision making (Knoch et al., 2006). Other brain stimulation studies that used excitatory stimulation over the left DLPFC indicated a reduction in emotional discomfort while viewing images demonstrating human pain (Boggio, Zaghi and Fregni 2009; Rego et al., 2015). One of the few studies that evaluated the lateralized role of DLPFC in cognitive empathy used both left-inhibitory /right excitatory and left excitatory/right inhibitory stimulation and found similar effects on pain perception and mood (Rego et al., 2015). In summary, these results suggest that both left and right DLPFC stimulation might affect emotional processing

although the differential role of the DLPFC hemispheres as a function of hemispheric asymmetry on different emotions is still unclear.

With regard to existing research that used theta burst protocols over the DLPFC to examine how this region affects emotional processing there are recent evidence supporting that inhibitory cTBS may affect emotional processing. Recently, the impact of cTBS which reduces neuronal excitability in the DLPFC was examined using electroencephalography during emotional face processing (Cao et al., 2018). Findings indicated that inhibitory cTBS does affect emotional processing and this effect is observed in changes in electric patterns in the brain and specifically on alpha band oscillations (Cao et al. 2018). In this study, the authors showed that cTBS delivered over the right DLPFC decreased alpha power oscillations which suggest increased activity at the cortical level (Coan & Allen. 2004) during the presentation of happy facial emotional stimuli. In another recent study that applied cTBS over the DLPFC during affective processing, right inhibition enhanced occipito-parietal brain activity for both subliminal and supraliminal negative images compared to neutral (Keuper et al., 2018). Adding to these findings standard inhibitory TMS has also been found to modulate early affective processing and reaction times for fearful faces in a facial expression identification task (Zwanzger et al., 2014). Thus, cTBS seems to be a promising stimulation to boost emotional processes such as automatic processes of emotional attention. However, even though these studies suggest the efficacy of cTBS approach it is still unknown whether it could be used to enhance emotional processing in individuals with antisocial behavior. Therefore, at this preliminary level we aimed for the first time to investigate the impact of inhibitory cTBS over the right and left DLPFC on facial emotion processing in a sample with differentiated symptoms of APD.

Current study

In the current study, we used TMS and specifically cTBS, which is able to induce reversible cortical inhibition or long term depression for up to one hour despite its lower stimulus intensity and shorter duration of stimulation (Paulus, 2005; Valllence et al., 2015). By doing so, we aimed to shed light on the possible causal role of the left and right DLPFC in emotional processing. In addition, we accounted for individual differences in antisocial behavior symptoms, in order to test differential activation patterns. We used cTBS to investigate the possible causal role of left and right stimulation in emotion recognition in a healthy group differentiated on symptoms of antisocial behavior. After the stimulation, participants completed a face recognition computerized task. There are no previous studies comparing right and left DLPFC stimulation that simultaneously tests for the effects of

antisocial behavior symptoms on emotional stimuli. As a result, the current study could shed light on the cognitive mechanisms underlying emotional processing. Given the asymmetric inhibition model of hemispheric differences proposed by Grimshaw and Carmel (2014), which describes that there is asymmetric frontal cortical and right prefrontal excitability may be associated with inhibiting the processing of positive or approach-related stimuli and left prefrontal activity may be associated with inhibiting negative or withdrawal related stimuli, we expected different effects between right and left DLPFC stimulation. We hypothesized that cTBS inhibition over the right DLPFC would result in increased recognition accuracy of positive expressions and left DLPFC would result in increased recognition accuracy of negative emotional expressions. Furthermore, we hypothesized that following active but not sham stimulation would improve more emotion recognition in individuals with high levels antisocial behavior symptoms compared to individuals with low levels.

Methods

Participants. Ninety-three young adults (31 males, mean age: *M*=22.10, *SD*=1.54, range 18-26 and 62 females, *M*=20,61, *SD*=1,34, range 18-23) were recruited for the purpose of the current study. They were medication-free, right-handed and had normal vision (for computer tasks). Exclusion criteria included history of psychiatric/neurological disorders including epilepsy, head trauma and migraine. Participants were also screened for depression using the Beck Depression Inventory-short form (BDI) and Beck Anxiety Inventory with an exclusion criterion of a score of >10. The study was approved by the Cyprus National Bioethics committee.

Procedure. This study was a double-blinded, randomized, sham-controlled study, where participants were randomly assigned to one of four different stimulation conditions: left cTBS (N=23), right cTBS (N=23), left sham (N=24), and right sham (N=23). Participants that met preliminary inclusion criteria began with an overview of the study and completed a written informed consent. The procedure was driven by the experimenter so that a quarter of the participants were assigned to the 'blue', 'green', 'yellow' and 'orange' group (unknown stimulation condition to the participant). Male and female participants were pseudo-randomly assigned to a color-group according to the order of arrival at the lab. Participants were told that they belong to the color-group indicated by the card they had chosen and that they will be presented with a face recognition task of different emotions after receiving a short TMS stimulation session (40 sec). Prior to the experiment, all participants were asked to complete a battery of Self-Report measures. Self-report assessment was followed by cTBS and then the emotion recognition task. Immediately after stimulation, participants were comfortably seated

in front of a 19’ computer screen (1024x768) at an approximate distance of 80 cm. Participants first completed a training phase (120 sec) of the task, to allow themselves to familiarize with the overall procedure. Faces were presented in random order and the E-Prime 2.0 software (Psychology Software Tools, Pittsburg, PA) was used for stimulation presentation and data collection.

cTBS Protocol - Real and Sham cTBS. Coil position was determined using standardized coordinates from the EEG (Steinmetz et al. 1989) International 10–20 system (with F4 corresponding to the right DLPFC stimulation target and F3 corresponding to the left DLPFC). The location and orientation of each participant’s coil placement was indicated on a nylon cap that participants wore throughout the single stimulation session. A figure-of-eight focal coil (70 mm diameter) was used. The coil was held in a fixed position by a mechanical arm and oriented so that the induced electric current flowed in a posterior–anterior direction. Stimulus intensities were set at 70% of active motor threshold (AMT). Previous experiments that used cTBS found significant inhibitory effects using as stimulation intensity 80% (e.g.,Huang et al., 2005) or 70% (Goldsworthy et al., 2013). We chose to use 70% intensity to prevent intense facial muscle twitching during stimulation. Each stimulation session TBS burst consisted of 3 pulses at 50 Hz, with each train being repeated every 200 ms (5 Hz) for 40 seconds (600 pulses). It has been shown that this stimulation paradigm suppresses cortical excitability. The number of pulses per participant used in the present study is consistent with the prototype protocol (see Huang et al., 2005).

Sham stimulation was delivered using an identical with the real Magstim figure-of-eight focal sham coil (70 mm diameter) that also produced identical stimulation noise. Sham Magstim figure-of-eight coil have been found to induce nearly zero electric-field under the coil's center (Smith & Peterchev, 2018) which make it a credible placebo procedure. The coil was held in a fixed position by a mechanical arm and oriented so that the induced electric current flowed in a posterior–anterior direction. Stimulus intensities were the same with the real stimulation condition and the same positioning procedure was followed using the 10-20 system for all participants.

Experimental task

Face Recognition task. A dynamic version of an emotion recognition task was created using standardized stimuli of dynamic, prototypical facial expressions from the Montréal Pain and Affective Face Clips (MPAFC) database (see Simon et al., 2008). Participants viewed a series of 96 1-s dynamic visual stimuli depicting a man or a woman (48 of each sex), whose facial expression morphed from neutral to one of four basic expressions: fear, happiness,

sadness, and pain (24 facial expressions were shown for each emotion). Eight clips were presented in random order for each emotion. Individuals viewed facial expressions on a computer screen and were instructed to label each emotion on a keyboard. After a practice phase consisting of each of the four expressions, participants were presented with the test stimuli in random order. Participants were scored according to whether or not they correctly identified the facial expression depicted (Bentler, 1990), and the final outcome variable used in the analysis was the number of accuracy errors that could range from 0-24 for each emotion.

Self-report Measures.

The *Adult Self-Report Inventory-4* (ASRI-4; Gadow, Sprafkin, & Weiss 2004) was used to assess ASPD, generalized anxiety, and depression symptoms as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM–5;* American Psychiatric Association [APA],2013). Symptoms on the ASRI-4 are rated on a 4-point Likert-type scale ranging from 0 (*never*) to 3 (*very often*). Although a single-session of TMS is usually not found to acutely affect mood in healthy volunteers (Baeken et al., 2006) it has been reported that mood and anxiety levels prior to stimulation (perhaps related to expectations concerning the TMS procedures) affects both cognitive-affective and cortisol responses to TMS (Baeken et al., 2011; Vanderhasselt et al., 2011). Therefore, for screening purposes participants completed also the anxiety and depression ASPD scales. The items were summed to create overall ASPD, anxiety, and depression symptom scores for the purposes of the current study. Research with clinical, college, and community samples has demonstrated that scores on the ASRI-4 show convergent and discriminant validity (Gadow et al., 2007; Kyranides, Fanti, Sikki, & Patrick, 2017). Even though behavioral symptoms of specific disorders are included in the ASRI-4, it does not provide additional diagnostic criteria; therefore, the responses do not indicate a clinical diagnosis but a continuity in symptom severity.

The *Inventory of Callous–Unemotional Traits* (ICU; Frick, 2004), which is designed to assess self-reported callous–unemotional (CU) traits, was also administered. The ICU comprises of 24 items (e.g., 'The feelings of others are important to you') that are rated on a 4-point Likert scale ranging from 0 (not at all true) to 3 (definitely true). CU traits, measured with the ICU, have been associated with aggression, delinquency, psychosocial and psychophysiological impairment (Fanti, 2003; Fanti et al., 2017). Previous research has provided evidence for the validity ($\alpha = .80$) of ICU scores in community and high-risk samples (Fanti et al., 2009; Kimonis et al., 2015).

Plan of Analysis

Independent sample t-tests were initially used to compare the ASPD groups on co-

occurring psychopathologies and callous unemotional traits. To address our main aim, we conducted repeated measures ANOVA in IBM SPSS 20.0 with type of stimulation and ASPD groups as the between-group independent variables and accuracy errors as the within-subjects factor. Significant interactions and repeated effects are depicted in graphs.

Results

ASPD groups

A median split of the data was conducted in IBM SPSS 20.0 on the basis of participants ASRI-4 pre-stimulation scores, in order to recode the continuous ASPD variable into a categorical one. Individuals above the median on ASPD symptoms (N=38; M=3.06; SD=1.35), labelled "High ASPD," greatly differed in severity of symptoms compared to those below the median (N=55; M=0.34; SD=.48, $t(91)$=13.73, p<.001), labelled "Low ASPD." In addition, Low and High ASPD groups were compared on several internalizing psychopathologies, including depression and anxiety, and callous-unemotional (CU) traits to test their dysfunction using independent sample t-tests. Test results provided evidence that there were significant differences between high ASPD and low ASPD groups on depression, $t(91)$= 3.72, p<.001, anxiety, $t(91)$= 3.68, p<.001, and CU traits, $t(91)$=3.34, p<.001 (Mean scores are reported in Table 1). Because the identified groups differed in these measures, they were included as covariates in further analysis.

TMS stimulation results

Repeated measures ANOVA was conducted in IBM SPSS 20.0 with type of stimulation and ASPD groups as the between-group independent variables and accuracy errors as the within-subjects factor. Before proceeding with the analysis we tested for potential covariates or additional main effects. Neither anxiety, $F(1, 82)$= .05, p=.82, nor depression, $F(1, 82)$= .46, p=.50, or CU traits, $F(1, 82)$= .60, p=.44, were significant covariates and were excluded from further analysis. In addition, we examined for any potential main, $F(1, 77)$= .05, p=.83, or interactive effects of gender (F ranged from .62 to 1.76), but no significant effects were identified. Findings from the repeated measures ANOVA suggested a significant within groups effect for accuracy errors, $F(3, 255)$= 58.23, p<.001, η^2=.41, indicating that participants showed lower accuracy errors during happy (M=.68, SE=.11) compared to fear (M=6.10, SE=.41; p<.001), pain (M=5.39, SE=.44; p<.001), and sad (M=5.34, SE=.35; p<.001) facial expressions. Between-groups differences for type of stimulation were also identified, $F(3, 85)$= 3.66, p<.05, η^2=.13. On average, participants receiving left stimulation showed lower overall accuracy errors (see fig. 1: average) compared to both sham conditions. Importantly, an interaction between accuracy errors and type of stimulation was identified, $F(9, 255)$= 2.19, p<.05, η^2=.07.

As shown in figure 1, those receiving stimulation (both left and right) showed lower accuracy errors for happy emotions compared to the sham left group, and lower accuracy errors for pain emotions compared to the sham right group. Finally, participants receiving left stimulation scored lower on accuracy errors in response to sad facial expressions compared to the left sham group.

Effects of ASPD groups. Participants high on ASPD symptoms in general made more errors (*M*=4.96, *SE*=.34) compared to those low on ASPD (*M*=3.80, *SE*=.27; *d*=.60; *p*<.05), *F*(1,85)=6.73, *p*<.05, η^2=.08. However, according to a two-way interaction between ASPD groups and type of stimulation (fig. 2), *F*(3,85)=3.38, *p*<.05, η^2=.12, this difference was only significant for the sham condition, but not for the stimulation conditions. These findings indicate that TMS stimulation decreased the difference in accuracy between ASPD groups. Additionally, we identified a three-way interaction between accuracy errors, type of stimulation and ASPD groups, *F*(9, 255)= 2.04, *p*<.05, η^2=.08. Findings suggested that none of the identified differences reported in figure 1 were significant among participants in the low ASPD group; however, these differences remained significant for the high ASPD group. As reported in figure 3, the same differences were identified for happy and sad emotions, but only participants receiving left stimulation differed from those in the sham right condition in response to pain emotions. Interestingly, individuals receiving left stimulation scored lower on accuracy errors in response to fear expressions, although these differences only approached significance (*p* < .10).

Discussion

The present study investigated the impact of inhibitory cTBS over the right and left DLPFC on facial emotion processing during the presentation of fearful, sad, happy and painful facial expressions. Our results showed that both left and right DLPFC stimulation was followed by better emotion recognition performance as demonstrated by lower accuracy errors for happy emotions compared to the sham left group, and lower accuracy errors for painful emotions compared to the sham right group. Finally, participants receiving left stimulation showed higher accuracy rates in response to sad facial expressions compared to the left sham group. Importantly, findings suggested that differences in accuracy rates remained significant only for the high ASPD group. Specifically, the high, but not the low, ASPD group showed better emotion recognition performance when receiving real stimulation over the left DLPFC for happy, painful and sad emotions. High ASPD individuals also showed higher accuracy rates when receiving right DLPFC stimulation to happy expressions. Findings also indicated that TMS stimulation decreased the differences in accuracy ratings identified among individuals

with low versus elevated ASPD symptoms.

An important contribution of this study is the finding that both left and right DLPFC regions are involved in emotion processing. A possible explanation for this effect can be derived from recent findings, which suggested that inhibitory repetitive transcranial magnetic stimulation (rTMS) of the DLPFC can modulate selective attention to emotional stimuli (Zwanger et al., 2014). Apart from the present study, DLPFC activation has been associated with improved performance in response to happy faces (Light et al., 2019) and alterations in responses to emotional faces (van Honk et al., 2002;Cao et al., 2018). Using inhibitory-rTMS, van Honk et al. (2002) found that the left and right PFC were involved in reducing the vigilant emotional response to unmasked versions of emotional faces, suggesting an important role in emotional processing. However, these studies did not include facial expressions depicting different emotions, and differed from the present study with respect to the experimental task employed to measure facial recognition processes. Our results provided an important contribution to the experimental rTMS research by evidencing the involvement of the left and right PFC for recognition processes of distinct emotional expressions.

Furthermore, our findings suggest that modulating the left DLPFC with rTMS may play a role in increasing emotion recognition of sad and painful facial expression in individuals with antisocial symptoms. The significant interaction between groups (high versus low ASPD) and emotion recognition, suggested that only the high ASPD group receiving active left cTBS showed a better performance in painful, sad, happy and overall face recognition. Compared to the low risk group, those in the high ASPD group also showed less accuracy errors in response to happy faces after right DLPFC inhibition. Antisocial symptoms in general have been associated with hypo-sensitivity to others' distress and empathy-eliciting information (Fanti, 2018). Consistent with this suggestion, individuals with behavioural problems demonstrated deficits in processing facial expressions associated with both negative and positive emotions (Mitchell et al., 2006). Recent evidence found that high levels of antisocial traits are related with impairments on processing the salient aspects of emotional facial stimuli (i.e., eyes) and especially emotions as associated with sadness and fear (Fanti et al., 2016; Kimonis et al., 2015). We are not aware of studies that measured the effects of multi-session TMS/cTBS as an intervention for individuals with ASPD or antisocial behaviour and emotional processing deficits. Our hypothesis would be that modulating the atypical pattern of neural activity of individuals with ASPD while viewing others emotional expressions may result in positive behavioural changes, which should be explored in future studies.

Our results supported the view that cTBS could play an important role in tackling some of the problems observed among individuals with antisocial symptoms related to emotional processing. In terms of clinical implications, these results suggest that TMS may be a potential clinical tool to facilitate emotional processing to happy but also sad and painful emotions. In the context of a single session, we could observe a cTBS related effect on improving errors accuracy. Regarding the participation of the left and the right DLPFC hemispheres in emotional processing our results indicate that both regions were involved in emotional processing with an effect of the right DLPFC in response to happy faces and an effect of the left DLPFC in response to happy, painful and sad expressions. The results may also allow for a speculation regarding the mechanisms by which cTBS contributes to improved emotional accuracy, which is via inhibitory effects on DLPFC. For example, some theories have described appraisal functions of the PFC on subcortical networks, such as evaluations of the value of emotional stimuli or situations that suppress distracting emotional influences and increases attention to emotional stimuli (Baeken et al., 2010; Etkin et al., 2011; Wager et al., 2008). At this point, this is a speculation that will need to be further investigated in future studies with designs that allow the testing of this hypothesis.

Potential limitations of our study also need to be discussed. Considering that the female participants in our sample outnumbered male participants and that participants were healthy individuals without an ASPD diagnosis, generalization of the present findings is limited. Therefore, this study is in need of replication in a sample with more male subjects, clinically diagnosed with ASPD. A similar approach was used by recent work using direct current stimulation and demonstrated that modulating activity of the PFC can reduce intentions to commit aggression in healthy individuals (Choy, Raine & Hamilton 2018). However, the identified ASPD groups in our study greatly differed in severity of symptoms. In addition, we compared the identified groups on co-occurring psychopathologies and callous-unemotional traits, finding that the groups scoring high on ASPD symptoms was at greater risk for both internalizing problems and psychopathic traits. These findings agree with prior work that ASPD increases the risk of anxiety and depression, which leads to societal maladjustment, substance use, and suicidal ideation (Goodwin & Hamilton, 2003). Further, prior work using similar samples verified the strong association between callous-unemotional traits and the diagnosis of ASPD group, suggesting that ASPD relates to low empathy and lower sympathy for others (Kimonis et al., 2013; Kyranides, Fanti, & Panayiotou, 2016). Finding that the high ASPD group in the current study is characterized by co-occurring internalizing problems and CU traits suggest that these individuals might be at greatest need for intervention. Nevertheless,

none of these variables were significant covariates, indicating that the identified effects were due to cTBS.

In addition, conducting multi-session cTBS at both left and right DLPFC would help to elucidate the impact of this type of stimulation and understand its long-term effects in modulating emotion processing more fully. Another limitation is the lack of neuroimaging data to demonstrate the effects of cTBS in other brain areas beside the DLPFC. Future pilot studies that can inform interventions are essential combining multi-session designs, neuroimaging and neuromodulation methods. Despite the limitations, the current study is among the first to consider left and right DLPFC stimulation and sham conditions, with a larger sample size compared to the majority of prior TMS work.

It also important to consider the possibility that TMS could be used to strengthen the effects of existing behavioural or cognitive interventions as well. It also important to consider the possibility that TMS could be used to strengthen the effects of existing behavioural or cognitive interventions as well. One example for future investigations is Attention Modification Therapy (AMT) towards emotional stimuli combined with TMS since our findings indicate that cTBS may boost emotion recognition. AMT is a novel treatment approach based on cognitive neuroscience research (Bar-Haim., 2010), and can be delivered cheaply and safely to large numbers of children and adults. Combining TMS with AMT may be an interesting intervention opportunity for altering attention bias towards emotional stimuli through which non-invasive brain stimulation could have the potential to become an enhancing tool. Furthermore, we investigated the effects of cTBS over both PFC hemispheres and identified that both left and right stimulation was followed by better emotion recognition. This demonstrates that we may suggest applying cTBS based on individualized pre-assessment procedures where left cTBS therapy will be delivered to participants indicating abnormal left PFC activity during emotional recognition tasks or the opposite for participants indicating abnormal right PFC activity. There is also the possibility when identifying the clinical effects of different protocols such as the cTBS to use it to minimize the adverse effects of pharmacology interventions, similarly with the use of TMS to participants with resistant depression that do not respond to drug treatment (Perera et al., 2016). Moreover, TMS is largely administered as a one size fits all therapy, without customizing the choice of different and more novel protocols such as TBS according to a patient's specific clinical profile or imaging-based estimates of dysregulation. Getting to know better the effects of novel protocols will give the chance to clinicians and TMS technicians to choose among a variety of stimulation protocols the most appropriate in each patient.

This study takes a step towards advancing knowledge about neural mechanisms that regulate emotional processing. Furthermore, our findings help in clarifying that treatment programs for antisocial behaviours may benefit by considering noninvasive brain stimulation techniques. Among other etiological mechanisms, the role of neural impairments on the development of aggression has been increasingly acknowledged (Fanti et al., 2019; Raine ,1998; Van Gooozen & Fairchild., 2008). Our findings further suggest a bilateral role of DLPFC involvement on emotional processing for others facial expressions of pain, sadness and happiness, especially among individuals with high antisocial symptoms. As a result, these findings advance our understanding of the networks involved in the emotional processing of facial stimuli, which possibly relate to differences in cognitive and affective empathy. Our novel findings suggest that the modulation of the right and left DLPFC can affect emotion recognition and may help on targeting atypical neural responses in antisocial populations.

GENERAL OVERVIEW AND CONCLUSION

The above sham-controlled studies were based on two decades of data in non-invasive brain stimulation field combined with neuroimaging findings based on the function of PFC in emotion processing. These findings are fundamental for the future work of our research group on identifying novel interventions for antisocial behaviour since we recently gained a grant from the Research Promotion Foundation in Cyprus. Our idea was to test two treatments: Attention Modification Therapy (AMT) towards emotional stimuli alone or combined with Transcranial Magnetic Stimulation for the treatment of antisocial behaviour. AMT is a novel treatment approach based on cognitive neuroscience research (Bar-Haim, 2010), and can be delivered cheaply and safely to large numbers of children and adults. No prior work investigated whether AMT or rTMS can reduce antisocial symptoms which makes this work promising and novel. However, since there are no previous studies using rTMS for the treatment of antisocial behaviour we needed to design these pilot studies to test the latest and more powerful stimulation version of rTMS which is theta burst protocols. We chose cTBS since it is the fastest version of stimulation (only 40 seconds) and has already shown some preliminary promising results in affective processing (Fu et al., 2017; Keuper et al., 2018; Roesmann et al., 2019). Furthermore, we investigated the effects of cTBS over both PFC hemispheres and identified that both left and right stimulation was followed by better emotion and attention processing. This demonstrates that we may suggest applying cTBS based on individualised pre-assessment procedures where left cTBS therapy will be delivered to participants indicating abnormal left PFC activity during emotional tasks or the opposite for participants indicating abnormal right PFC activity.

Antisocial behaviour is associated with a host of individual impairments (e.g., social, emotional, academic), distress to others (family, peers), and public and economic burden to society (Allen, Hwang, & Huijding., 2019). Given the level of individual impairment and negative societal impact, antisocial individuals are at greatest need of intensive treatment. Investigating the effectiveness of novel interventions such as neurostimulation therapy is critical to informing interventions designed to prevent or remediate these problems. We suggest that attention bias to emotional stimuli and emotion recognition deficits might be targeted by manipulating brain activity in different PFC areas. To our knowledge these are the first studies to assess cTBS effects on both PFC hemispheres on various emotional processing systems including physiological responses, PFC activity, attention control and facial emotion

recognition. Based on our findings cTBS seems to be a promising stimulation technique that we could apply in combination with AMT for our forthcoming treatment efforts.

Specifically, findings can have a significant impact on research by providing evidence for the clinical potential of theta burst interventions, while also can inform treatment for emotional systems responsible for psychopathology etiological pathways. So far, rTMS has been approved by the American FDA regulatory authorities as a therapeutic intervention for symptoms of depression in patients that failed to respond to other forms of treatment (Gaines et al., 2014). More recently, research has suggested that TMS holds potential to effectively alleviate symptoms of Obsessive compulsive disorder, migraines and strokes (Blom et al., 2011; Dionisio et al., 2018). In this perspective, we provided starting evidence highlighting the promises and pitfalls of cTBS as a viable therapeutic option as well. Although neurostimulation treatments with TBS protocols are still in their infancy our findings are promising and may lead to treatment advances. Regarding the dissemination for our results it is important to mention that our third study has been recently submitted and it is under review at a special issue of the Journal of Experimental Neurocriminology (Konikkou., Konstantinou & Fanti., under review). We hopefully plan to publish the rest of our research findings through scientific journals and relevant conference presentations as well.

Our studies discuss the possibility of one day being able to use neurostimulation methods as a prospective non-invasive treatment method to alter brain function in individuals with impaired affective processing. There is also the possibility when identifying the clinical effects of different protocols such as the cTBS to use it to minimize the adverse effects of pharmacology interventions, similarly with the use of rTMS in resistant depression. Moreover, rTMS is largely administered as a one size fits all therapy, without customizing the choice of different and more novel protocols such as TBS according to a patient's specific clinical profile or imaging-based estimates of dysregulation. Getting to know better the effects of novel protocols will give the chance to clinicians and rTMS technicians to choose among a variety of stimulation protocols the most appropriate in each patient. The only way to achieve this is through further investigation of novel protocols and larger studies including multiple stimulation sessions based on these initial results.

In this perspective, our pilot studies highlight the promises and pitfalls of a novel stimulation technique as a viable therapeutic option. Importantly, a future goal based on the current findings is the attempt to use rTMS combined with AMT. It is a novel hypothesis and our future investigation goal: To demonstrate whether by stimulating brain areas associated with attention and emotion processing deficits, rTMS can enhance the effectiveness of AMT.

These findings will allow future attempts to move away from a monolithic rTMS treatment approach to a combinative approach informed by the individual characteristics of heterogeneous groups. Thus, our findings are expected to have translational significance for designing future intervention programs.

Overall, uncovering the neuro-physiological mechanisms associated with the effects of cTBS over the PFC and demonstrating that a single cTBS was able to alter PFC activation but not physiological activity is expected to advance future implementation of cTBS in clinical research designs. Indicating how DLPFC inhibition by cTBS affected attention to emotional stimuli suggests that the therapeutic use of cTBS may contribute to the treatment of emotional dysfunctions related to attention processing biases. Finally using a novel neurostimulation protocol for the first time in a sample with differentiated antisocial symptoms may help on targeting attention and neural deficits related to emotion recognition in antisocial populations through cTBS. PFC areas show abnormalities in a variety of disorders associated with disturbed emotional and attention processing. Although there has been an increasing interest in exploring the use of accelerated rTMS treatment protocols in recent years, there are very limited number of randomised trials demonstrating its efficacy. In conclusion, a clearer picture of cTBS effects on PFC might have crucial implications for its application in clinical settings and it is particularly attractive because it requires short stimulation which can make a significant difference to the number of patients treated per day.

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Study 1 Tables

Table 1: *Demographic information per group, total N=40. Groups' differences on baseline questionnaires, mean and standard deviation are reported.*

		Sample	Right	Sham right		
Total *N*		40				
Gender *N*	Males	8	4	4		
	Females	32	16	16		
			M (SD)	M (SD)	F(1,39)	*p*
Age (years)			20,78 (1,55)	21,00 (1,67)	0.19	0.66
STAI-T			36,52 (5,29)	37,99 (8.05)	0.49	0.91
BDI-II			4,10 (2.12)	3,87 (2.46)	0.37	0.86

Note: STAI-T= State-Trait, BDI-II=Becks Depression Inventory.

Table 2: *Descriptive Statistics of HbO2 and Physiological Measures: Mean and Standard Deviation (SD).*

Stimulation	Emotion	Mean (SD) HbO^2	Mean (SD) SC	Mean (SD) HR
cTBS Right	Distressing	-005 (043)	12,13 (10,2)	85,1 (9,30)
	Pleasant	-024 (043)	11,60 (15,7)	82,4 (10,5)
	Neutral	-004 (045)	13,33 (14,8)	82,3 (9,43)
	Threatening	-011 (043)	12,61 (14,9)	84,6 (9,25)
Sham Right	Distressing	005 (044)	12,19 (9,11)	82,4 (10,1)
	Pleasant	020 (047)	10,16 (19,2)	80,9 (10,8)
	Neutral	-002 (046)	11,86 (19,2)	81,3 (10,5)
	Threatening	000 (041)	11,51 (9,87)	82,3 (9,76)

Note: HbO2= Oxygenated Hemoglobin, cTBS= continuous theta burst stimulation.

Study 2 Tables

Table 1: *Demographic information per group, total N=91. Groups' differences on baseline questionnaires, mean and standard deviation are reported.*

		Sample	Left	Right	Sham left	Sham right		
Total *N*		91						
Gender *N*	Males	32	7	7	9	9		
	Females	59	17	16	13	13		
			M (SD)	M (SD)	M (SD)	M (SD)	F(1,90)	*p*
Age (years)			20.00 (1.16)	21.17 (1.74)	21.13 (1.78)	22.00 (3.23)	1.04	0.37
STAI-T			39.71 (10.36)	37.37 (8.99)	37.33 (9.02)	38.05 (7.66)	0.35	0.79
BDI-II			3.29 (2.40)	3.09 (2.12)	4.34 (2.06)	4.03 (3.02)	0.24	0.88

Note: *STAI-T= State-Trait Anxiety Inventory, BDI-II=Becks Depression Inventory.*

Table 2: *Descriptive Statistics of Reaction Times: Mean and Standard Deviation (SD)*

Training	Emotion	Mean (RTs)	SD (RTs)
cTBS Left	Distressing	440.70	87.27
	Pleasant	442.09	94.34
	Neutral	499.95	98.34
cTBS Right	Distressing	426.15	58.97
	Pleasant	415.08	62.13
	Neutral	503.51	76.31
Sham Left	Distressing	424.63	64.77
	Pleasant	416.35	58.91
	Neutral	440.27	59.66
Sham Right	Distressing	425.69	92.25
	Pleasant	422.90	96.32
	Neutral	453.61	82.90

Note: cTBS= continuous theta burst stimulation.

Study 3 Tables

Table 1: *Descriptive Statistics and Correlations between the variables under investigation (n=93)*

	Anxiety		Depression		CU	
	High ASPD	Low ASPD	High ASPD	Low ASPD	High ASPD	Low ASPD
N	38	55				
Anxiety			.66**	.50**	-.02	.13
ASPD			.04	.27*	.34*	.18
Depression					-.07	.28*
Descriptive Statistics						
Mean	42.13	35.64	17.25	12.18	22.04	16.50
SD	10.73	6.21	6.93	6.12	7.63	8.12

Note. SD = standard deviation, ASPD=Antisocial Personality Disorder symptoms CU= Callous Unemotional traits.
**p < .05. **p < .01.*

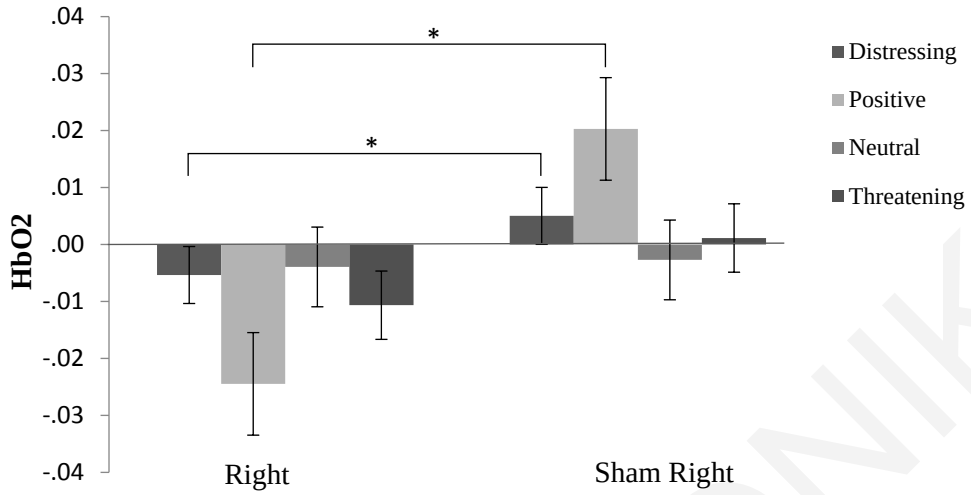
Table 2: *Descriptive Statistics and Correlations between ASPD scores and accuracy errors on the dynamic emotion recognition task*

	Fear	Happy	Pain	Sad	Total errors
ASPD	.10	.35**	.04	-.01	.14
Descriptive Statistics					
Mean					
ASPD high	6.05	.97	5.73	5.51	22.24
ASPD low	4.87	.35	4.95	5.29	18.04
SD					
ASPD high	4.52	1.42	4.18	3.47	12.50
ASPD low	3.06	.58	4.05	3.15	8.03

Note. SD = standard deviation, ASPD=Antisocial Personality Disorder symptoms.
***p < .01.*

Study 1 Figures

Figure 1: *Significant effects of cTBS stimulation over the right PFC in images type manipulation. Y-axis represent HbO2 signal when comparing emotional conditions (Distressing, Positive, Neutral and Threatening)*



Note: * p<0.05.

Figure 2: *No significant effects of cTBS stimulation over the right DLPFC on skin conductance. Y-axis represent skin conductance reactivity when comparing emotional conditions (Distressing, Positive, and Threatening).*

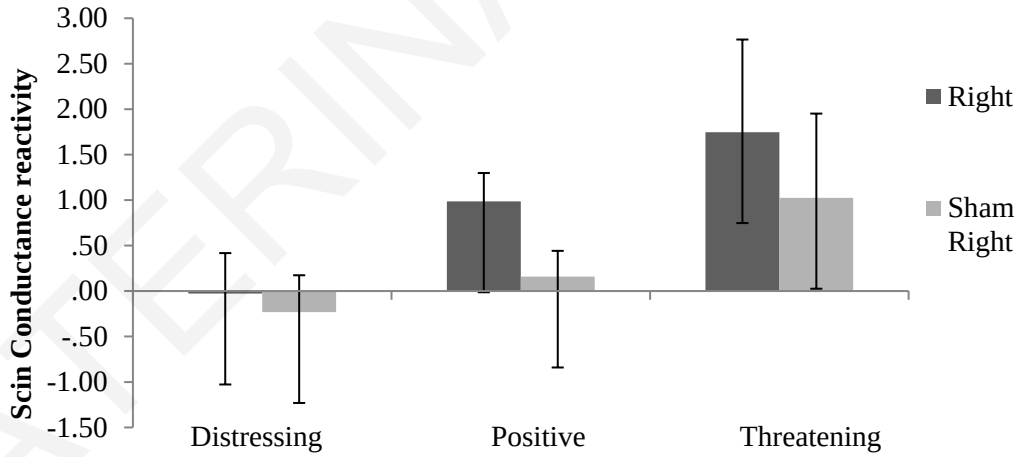
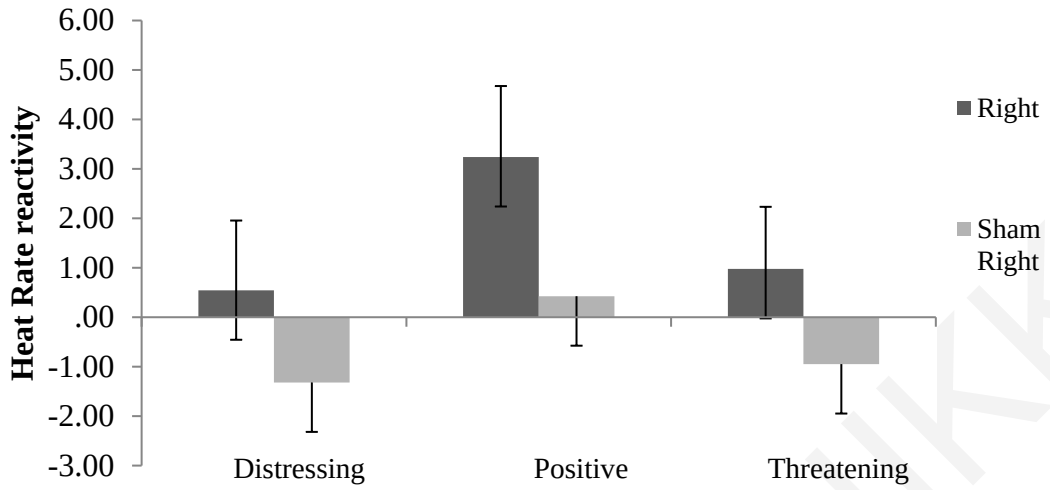
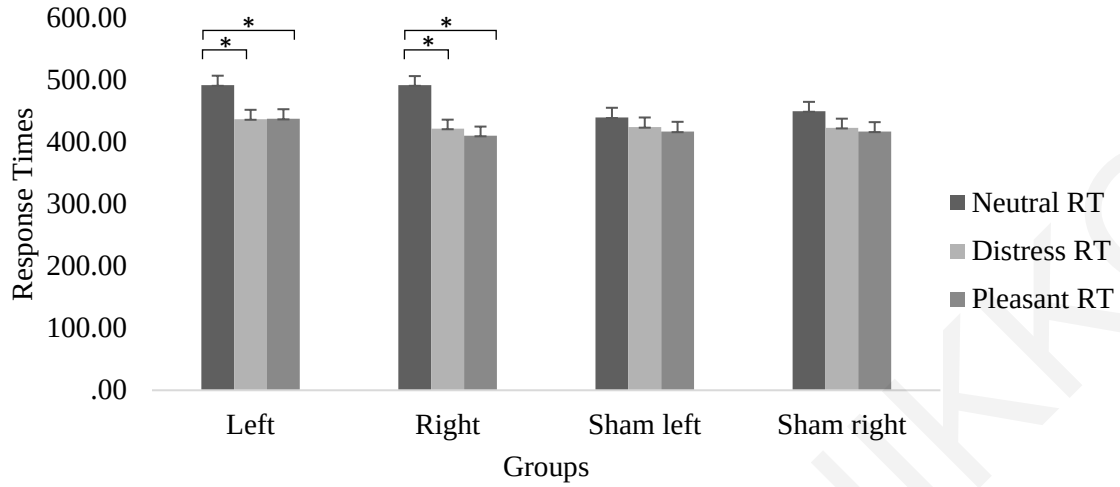


Figure 3: *No significant effects of cTBS stimulation over the right PFC over heart rate reactivity. Y-axis represent heart rate reactivity when comparing emotional conditions (Distressing, Positive and Threatening).*



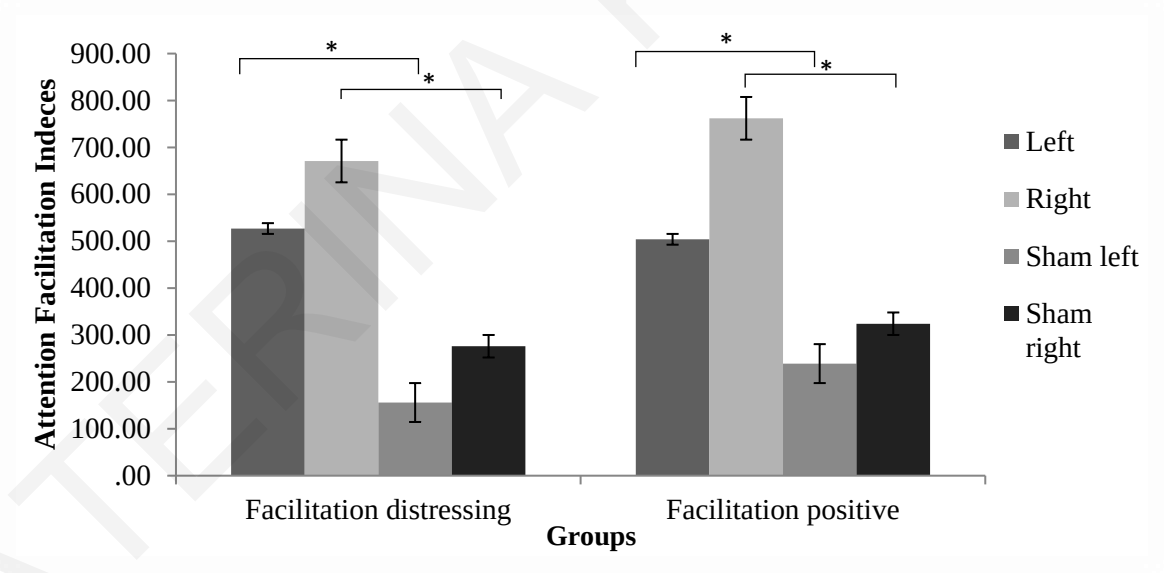
Study 2 Figures

Figure 1: *Average and emotion specific differences on response times for neutral, distressing and pleasant images.*



Note: indicate significant difference between various emotional stimuli types (p<.05) and the two-way interaction between emotions and type of stimulation among participants.*

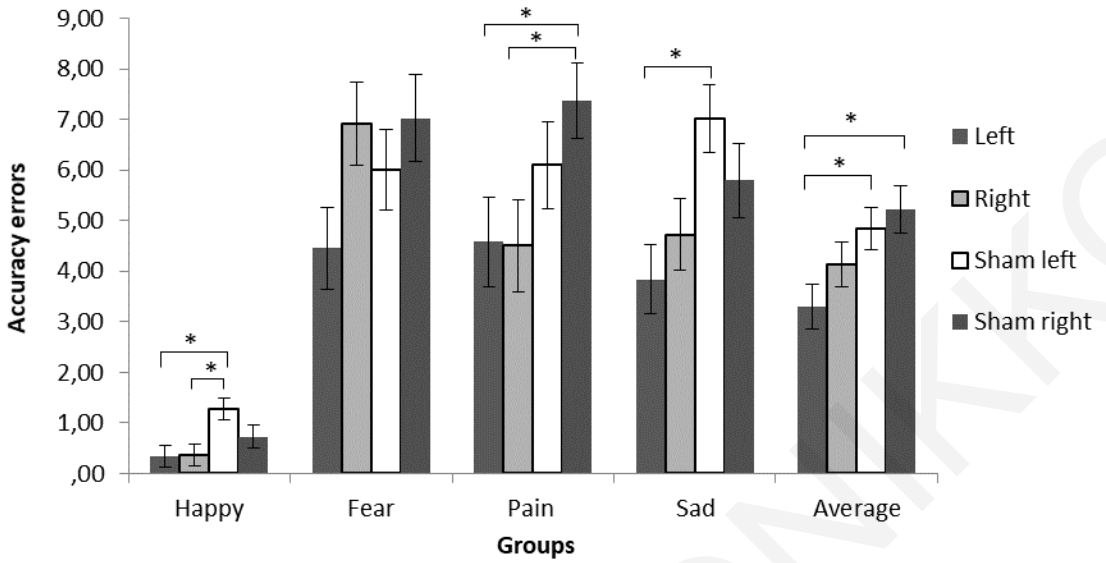
Figure 2: *Average and emotion specific differences on facilitation indices for distressing and pleasant images*



Note: indicate significant difference between different stimulation groups (p<.05).*

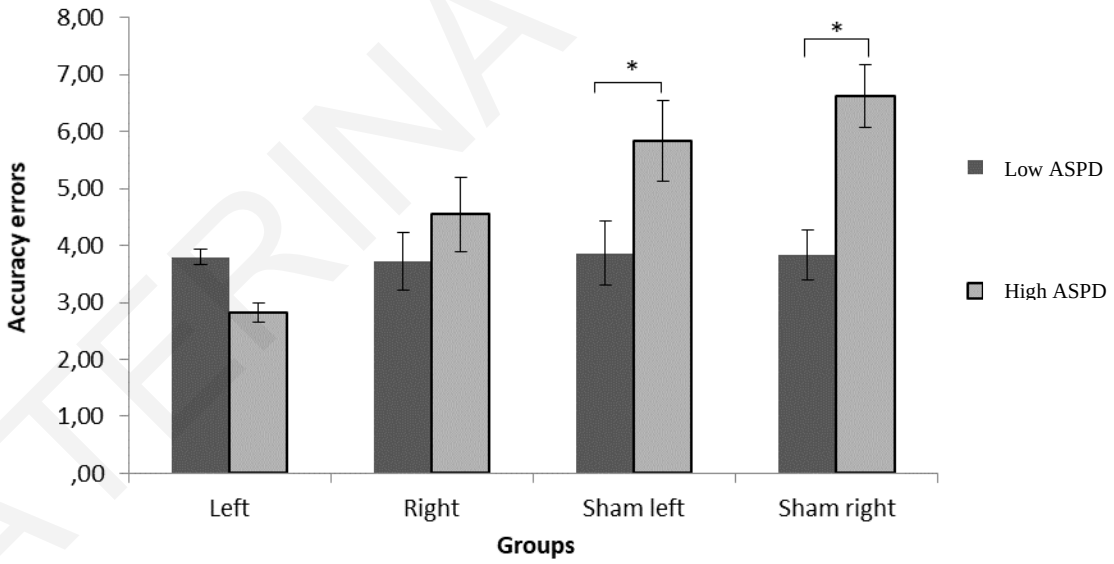
Study 3 Figures

Figure 1. *Average and emotion specific differences for each condition.*



*Note: * indicate significant difference between various stimulation groups (p<.05).*

Figure 2. *The interaction between ASPD groups and type of stimulation predicting accuracy errors.*



*Note:*indicate significant difference between low and high ASPD groups (p<.05).*

Figure 3. *The three-way interaction between emotions, ASPD groups and type of stimulation, depicting significant differences among participants high on ASPD symptoms.*

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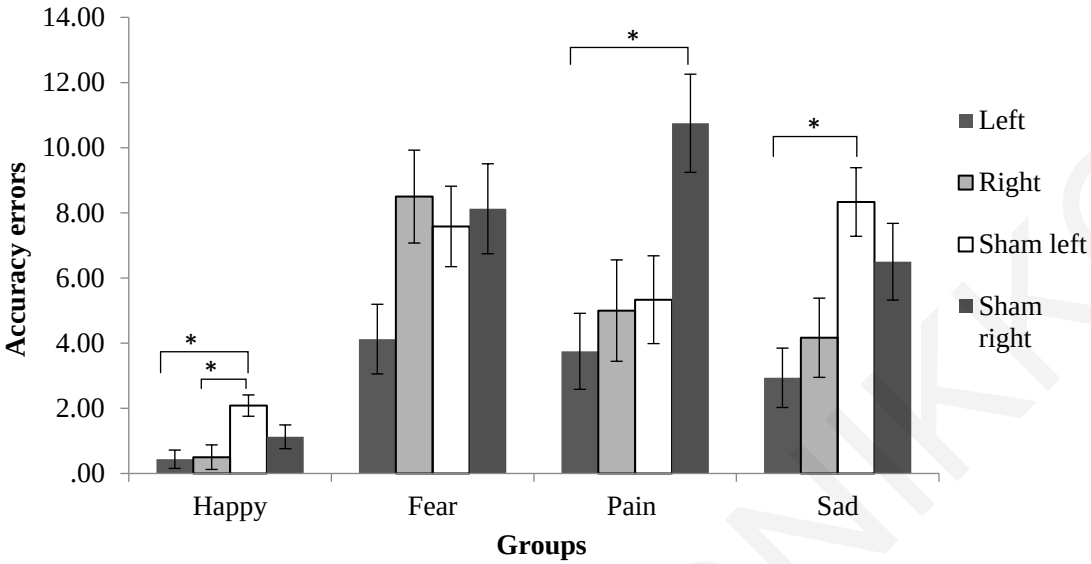

*Note: *indicate significant difference between low and high ASPD groups (p<.05).*

Appendix

The International Affective Picture System (IAPS) identification numbers are as follows. Positive: 1710, 1750, 1920, 2000, 2010, 7330, 7350, 7410, 8496, 8540. Distress: 2095, 2276, 2703, 2800, 2900, 3220, 3301, 9041, 9220, 9421. Neutral: 2190, 2200, 2210, 7000, 7002, 7006, 7009, 7010, 7025, 7035. Threatening: 1050, 1205, 1300, 1321, 1931, 2100, 2110, 2120, 2682, and 6250.