The effects of repetitive Transcranial Magnetic Stimulation on empathy and impulsivity in healthy adults

Cheng-Chang Yang, MSc.

Thesis submitted to the University of Nottingham
for the degree of Doctor of Philosophy

September 2018

TABLE OF CONTENTS

LIST OF APPENDICES

INDEX OF TABLES

INDEX OF FIGURES

ABBREVIATIONS

AAT	Adjusting Amount Task
ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
AMT	Active motor threshold
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASD	Autism spectrum disorder
BIS-11	Barrett Impulsiveness Scale, version 11
BPD	Borderline personality disorder
CI	Confidence interval
CPT	Continuous Performance Test
cTBS	Continuous Theta Burst Stimulation
DBT	Dialectic Behaviour Therapy
DLPFC	Dorsolateral prefrontal cortex
DW	Decreased win
EEG	Electroencephalography
EMG	Electromyography
FDI	First dorsal interosseous
FW	Fixed win
GNG	Go/No-Go Task
HF-rTMS	High-frequency Transcranial Magnetic Stimulation
IFG	Inferior frontal gyrus
IRI	Interpersonal Reactivity Index
ISI	Interstimulus interval
IST	Information Sampling Task
iTBS	Intermittent Theta Burst Stimulation
LDLPFC	Left dorsolateral frontal cortex
LF-rTMS	Low-frequency Transcranial Magnetic Stimulation
LTD	Long-term depression
LTP	Long-term potentiation
M1	Primary motor cortex
MDD	Major depressive disorder
MEP	Motor evoked potentials
MI	Motor impulsivity
mPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
MSO	Motor stimulator output
MT	Motor threshold

NMDA-R	N-methyl-D-aspartate receptor
OCD	Obsessive–compulsive disorder
OFC	Orbitofrontal cortex
PICOS	Population, intervention, comparator, outcome, and study design
ppTMS	Paired-pulse Transcranial Magnetic Stimulation
pre-SMA	Pre-supplementary motor area
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic review and Meta-Analysis Protocols
PTSD	Posttraumatic stress disorder
QCAE	Questionnaire of Cognitive and Affective Empathy
QPS	Quadripulse stimulation
RDLPFC	Right dorsolateral prefrontal cortex
rFEF	Right frontal eye field
RI	Reflection/ cognitive impulsivity
rIFG	Right inferior frontal gyrus
RMET	Reading the Mind in the Eyes Test
RMT	Resting motor threshold
rTMS	Repetitive Transcranial Magnetic Stimulation
SCWT	Stroop Colour Word Test
SMA	Supplementary motor area
SpTMS	Single-pulse Transcranial Magnetic Stimulation
SSD	Stop signal delay
SSRT	Stop-signal reaction time
SST	Stop Signal Task
SUDs	Substance use disorders
TBS	Theta Burst Stimulation
tDCS	Transcranial direct current stimulation
TI	Temporal impulsivity
TMS	Transcranial Magnetic Stimulation
ToM	Theory of Mind
TPJ	Temporoparietal junction
UPPS-P	UPPSP-P impulsive behaviour scale
vmPFC	Ventromedial prefrontal cortex

ABSTRACT

Both impulsivity and empathy are considered crucial in clinical, in particular forensic, populations. A neuroscientific technique, namely repetitive transcranial magnetic stimulation (rTMS), has proven its therapeutic utility in a variety of neuropsychiatric disorders and may be effective in modulating empathy and impulsivity. This thesis aimed to examine the effects of rTMS on empathy and impulsivity in healthy adults via two systematic reviews with meta-analyses and two empirical rTMS studies, thereby contributing to the relatively small pool of knowledge in the field.

The first systematic review and meta-analysis reviewed the literature on the effects of rTMS on empathy in healthy adults, and included 18 studies contributing to 24 effect sizes. The findings revealed an overall small effect favouring active rTMS over sham stimulation on cognitive empathy in healthy individuals. Differential effects across the domains of empathy, namely affective and cognitive empathy (also referred to as theory of mind (ToM)), were evident. Meta-regression revealed no significant between-study heterogeneity in respect of sex ratio, mean age, number of pulses, and stimulation intensity. In conclusion, the study found that rTMS may have discernible effects on different components of cognitive empathy.

The second systematic review and meta-analysis which examined the effects of rTMS on impulsivity in healthy adults included 27 articles consisting of 50 effect sizes. Results indicate that rTMS has distinct effects on different impulsivity subdomains. A small and significant effect was found in respect of modulating motor impulsivity and a moderate effect was found in regards to

temporal impulsivity. However, insufficient data was available to ascertain the effects of rTMS on reflection impulsivity.

The first empirical study investigated the effects of excitatory rTMS at the rIFG of 20 healthy male adults in modulating motor and reflection impulsivity. It employed a single-blind randomised crossover design, and it also examined the relationship between trait and behavioural measures of impulsivity. Unexpectedly, no significant effect was found on either motor or reflection impulsivity, after including scores on trait impulsivity as covariates in the analyses. In accord with the extant literature, there were no significant associations between self-report (trait) and behavioural measures of impulsivity.

The final study applied intermittent theta burst stimulation (iTBS) at the left dorsolateral prefrontal cortex (LDLPFC) to modulate cognitive empathy and both temporal and reflection impulsivity in 23 healthy adults, using a single-blind randomised crossover design. Non-significant post-iTBS effects on both cognitive empathy and impulsivity were found. Baseline trait measures of empathy and impulsivity were included in the analysis as covariates in order to control for the impact of pre-stimulation individual differences on the iTBS modulation.

Despite the mixed results, I argue that rTMS can potentially be used to modulate empathy and impulsivity. Future studies in the field should address some of the limitations highlighted in this project, for instance, in terms of localisation of stimulation sites, stimulation parameters and sample sizes, to determine the utility of TMS.

DECLARATION

The literature review, data collection, analyses and the conclusions drawn are the result of my own work. All other authors have agreed that the data can be used in my PhD thesis. All instruments used in the current study remain the copyright of their respective authors and proprietors.

No portion of the work referred to in the thesis has been submitted in support of an application for any degree at this or any other institution of learning. Sections of this thesis have been presented in the following conference presentations and published in peer-review journals:

Peer-reviewed publications:

Yang, C.-C., Khalifa, N., & Völlm, B. (2018). The effects of repetitive transcranial magnetic stimulation on empathy: A systematic review and meta-analysis. *Psychological Medicine*. *48*(5), 737-750. doi: 10.1017/S003329171700232X (Chapter 4)

Yang, C.-C., Völlm, B., & Khalifa, N. (2018). The effects of rTMS on impulsivity in normal adults: a systematic review and meta-analysis. *Neuropsychology Review*. doi: 10.1007/s11065-018-9376-6 (Chapter 5)

Yang, C.-C., Khalifa, N., & Völlm, B. (2018). Excitatory repetitive transcranial magnetic stimulation applied to the right inferior frontal gyrus has no effect on motor or cognitive impulsivity in healthy adults. *Behavioural Brain Research*.*347*, 1-7. doi: 10.1016/j.bbr.2018.02.047 (Chapter 6)

Conference presentations:

Yang, C.-C., Khalifa, N., & Völlm, B. (2017). *The effects of rTMS on impulsivity in adults: a systematic review and meta-analysis*. Poster presented at the IMH Research Day, The Institute of Mental Health, Nottingham, UK.

Yang, C.-C., Khalifa, N., Völlm, B. & Lankappa, S. (2017). *The role of right inferior frontal gyrus in impulsivity: insights from high-frequency repetitive transcranial magnetic stimulation*. Poster presented at the 2nd International Brain Stimulation Conference, Barcelona, Spain.

Yang, C.-C., Khalifa, N., & Völlm, B. (2016). *The potential to alter your impulsivity: current evidence from repetitive transcranial magnetic stimulation*. Poster presented at the East Midlands University Association's Annual Conference, Loughborough, UK.

REMARKS ON PRESENTATION OF THESIS IN ALTERNATIVE FORMAT

This thesis is presented in the 'Alternative format' in accordance with the guidelines provided by the University of Nottingham, January 2016. It contains sections written in a format suitable for submission for publication in a peer-reviewed journal. The results of the research conducted have or will be submitted for publication in externally refereed contexts such as journals and conference proceedings. I can confirm that this thesis has been finished under supervision and with support and revisions from my supervisors.

The structure of the thesis follows a general introduction and description of the aims and hypotheses of the research. The main body of the thesis contains four chapters presenting the research conducted, concluded by a general discussion that draws together the various findings of the work into a coherent synthesis and indicates directions for future research.

ACKNOWLEDGEMENTS

I am deeply grateful to my supervisors, Dr Najat Khalifa and Professor Birgit Völlm for the expertise that they have shared with me and their support to motivate me to complete this PhD thesis. I am also very grateful to Dr Sudheer Lankappa for his permission to use the ECT suite and TMS devices as well as his medical backup. I would especially like to thank Dr Katy Jones and Professor Hamish McAllister-Williams for their critical comments in my viva. I would also like to thank Dr Shining Chou for taking over as the principal supervisor at the last moment in my PhD.

My sincere thanks go to Dr Sarina Iwabuchi for her mentoring and teaching how to perform TMS. In addition, I have to mention Dr Boliang Guo for his helpful guidance on systematic reviews and meta-analyses. I would also like to acknowledge Adrian Pantry for his administrative assistance throughout my study in University of Nottingham.

Special thanks go to all the PhD students in Room A10, who fulfilled my boring academic life in a supportive and encouraging way throughout these years. I would also like to express my sincere gratitude to participants in my two studies for their participation and dissemination of the study information. I would like to thank my funding sponsor, Ministry of Education, Taiwan, for the generous financial support.

Lastly but most importantly, I would like to show my deepest gratitude to my beloved wife for her selfless caring and support even during the time of hardship. Without her strong faith in me, my dream of studying abroad would never have begun nor have ever been accomplished. Special thanks go to my dear family members for their understanding, encouragement, and support during the four years.

CHAPTER 1 : INTRODUCTION

1.1 OVERVIEW

Empathy and impulsivity are both multi-facet concepts and crucial topics in clinical and forensic populations. For example, impulsivity and low empathy are common features in Cluster B personality disorders (American Psychiatric Association, 2013) and have often been identified as two of the main risk factors of violence (Bjørkly, 2013; Chamorro et al., 2012; Jolliffe & Farrington, 2004; van Langen, Wissink, van Vugt, Van der Stouwe, & Stams, 2014). These issues demonstrate the importance of the study to reduce impulsivity and improve empathy.

Traditionally, two broad categories of treatment, namely pharmacological and psychotherapeutic approaches, have been used to address impulsivity (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). The efficacy of lithium, anticonvulsants, and antipsychotics for impulsive aggression have been supported among studies, but unfortunately they may be associated with frequent or significant side effects that decrease its use (Moeller et al., 2001; Neto & True, 2011). With respect to the psychotherapeutic approach, Dialectic behaviour therapy (DBT) is increasingly recognised as an effective psychological intervention for people with emotional regulation problems (Carmel, Rose, & Fruzzetti, 2014). For example, Verheul et al. (2003) randomly assigned 58 women with borderline personality disorder (BPD) to either 12 months of DBT or usual treatment and found that patients in the DBT group had fewer episodes of impulsive self-harm after treatment. However,

the at least one-year time commitment limits the DBT implementation (Carmel et al., 2014; Neto & True, 2011).

For Interventions to improve empathy, a majority of studies have focused on sexual and violent offenders according to the underlying rationale that increased empathy will have an inhibitory effect upon the individual's motivation to offend (Day, Casey, & Gerace, 2010). A variety of psychotherapeutic programme modules, like role playing and forgiveness therapy, have been introduced to promote victim or general empathy. However, systematic evaluation of the efficacy of these treatment approaches is sparse with somewhat mixed evidence to support intervention (Day et al., 2010). Recent evidence from systematic reviews further suggests that current treatment approaches may be ineffective (potentially harmful) to sexual offenders (Dennis et al., 2012; Duggan & Dennis, 2014).

Aforementioned limitations of traditional intervention to impulsivity and empathy have motivated the development of adjunctive, or alternative therapeutic interventions, using neuroscientific approaches (e.g., Glenn & Raine, 2014). Non-invasive neuromodulation techniques, such as transcranial magnetic stimulation (TMS), particularly the repetitive form (rTMS), may have the potential to fill an important gap in this area. In recent decades, the neuromodulation of empathy and impulsivity has attracted some attention in rTMS studies (Hetu, Taschereau-Dumouchel, & Jackson, 2012; Juan & Muggleton, 2012 for reviews). Although there is a growing body of literature focusing on effects of rTMS on empathy and impulsivity, the results remain

equivocal. There is an urgent need to conduct further studies in the field to determine the effects of TMS on both impulsivity and empathy.

1.1.1 Research strands

There are eight major strands to this PhD research. Chapter 1 provides a brief overview of the literature regarding empathy, impulsivity, and TMS. Chapter 2 provides an outline of the aims and hypotheses of the thesis. Chapter 3 presents general information regarding the methodological approach adapted in the project. Chapter 4 describes the findings of a systematic review and meta-analysis of the literature concerning the effects of rTMS on empathy. Chapter 5 entails another systematic review and meta-analysis of the literature on the effects of rTMS on impulsivity. Chapter 6 concerns a proof of concept study that examined the effects of TMS on impulsivity in healthy volunteers. Chapter 7 concerns an empirical study on the effects of TMS on both empathy and impulsivity in a non-clinical population. Chapter 8 summaries and discusses the findings obtained from the aforementioned chapters.

1.2 EMPATHY

Human behaviour can be influenced by one's interpretation of others' behaviour, and modified through interpersonal interactions. Such processes require empathy, the ability to understand, to predict and to respond to social contexts appropriately. Therefore, empathy is viewed as a form of social cognition which plays an important role in interpersonal interactions involving human beings.

1.2.1 Definition

The term empathy has its origins in the late nineteenth century German literature. It originates from *Einfühlung*, a term used to describe the way people wilfully project themselves into a work of art to aesthetically appreciate its qualities. Its original meaning was then transformed and utilised in contemporary psychology (Wispé, 1987).

Empathy is viewed as a combination of perception of self, others, and interpersonal processes. As a broad concept, empathy has been variously defined in the literature (see Table 1-1). Batson (2009) identified eight diverse but interrelated conceptualizations of empathy from the literature: (i) knowing another person's cognitive and emotional internal state; (ii) adopting the posture or matching the neural responses of another; (iii) feeling as another person feels; (iv) intuiting or projecting oneself into another's situation; (v) imagining another's thoughts and feelings; (vi) imagining how one would think and feel in the other's situation; (vii) feeling distress when seeing another's suffering; and (viii) feeling for another person who is suffering. Despite the ongoing debate about the definition of empathy, these seemingly divergent definitions share a core concept, that is sensitivity to, and understanding of, the mental states of others (Smith, 2006).

1.2.2 Components of Empathy

Empathy is a multidimensional construct. There appears to be an agreement among researchers (e.g., Davis, 1983; Dvash & Shamay-Tsoory, 2014; Reniers, Corcoran, Drake, Shryane, & Völlm, 2011) that empathy encompasses two distinct components; cognitive and affective. Cognitive

empathy reflects the ability to understand another's emotions and feelings, and affective empathy reflects the ability to share another's emotional state, and to experience feelings of the other person. The two component construct is in accord with recent neuroscientific findings (Dvash & Shamay-Tsoory, 2014). Meanwhile, some researchers (e.g., Blair, 2005) have argued in favour of a third component for empathy, namely motor empathy, which is defined as the tendency to automatically mirror facial expressions, vocalisations, postures, and actions of an observed individual.

1.2.3 Theory of Mind

Theory of Mind (ToM), also referred as “mentalisation”, is a similar concept and often overlaps with empathy. Similarly, the definition of ToM is incongruent across the literature. For example, Premack and Woodruff (1978) suggest that ToM reflects the ability to attribute mental states (e.g., thoughts, feelings, beliefs, intentions) to accurately predict and explain another person's behaviour. Frith and Frith (1999) propose that ToM reflects the intuitive ability to attribute thoughts and feelings to others. Shamay-Tsoory, Tomer, Berger, Goldsher, and Aharon-Peretz (2005) regard ToM as the ability to understand and predict the behaviour of other people through the process of making inferences regarding their mental states: in terms of their knowledge, intentions, and beliefs. It is suggested that these abilities are acquired progressively from a false belief, the understanding that someone can have a belief that is incorrect; then through to the ability to attribute other’s beliefs concerning the beliefs of a third person; and onto the ability to infer others’ mental states in complex social contexts (Aboulafia-Brakha, Christe, Martory,

& Annoni, 2011). It is suggested that ToM has a cognitive component and an affective component, whereby cognitive ToM refers to the ability to infer others' beliefs and affective ToM refers to the capability to understand other people's emotional states (Shamay-Tsoory & Aharon-Peretz, 2007). Recently, ToM has been recognised by some authors as the cognitive component of empathy owing to the accumulation of neuroscientific evidence in support of the concept (Dvash & Shamay-Tsoory, 2014). Figure 1-1 shows the proposed model describing empathy as a superordinate of ToM.

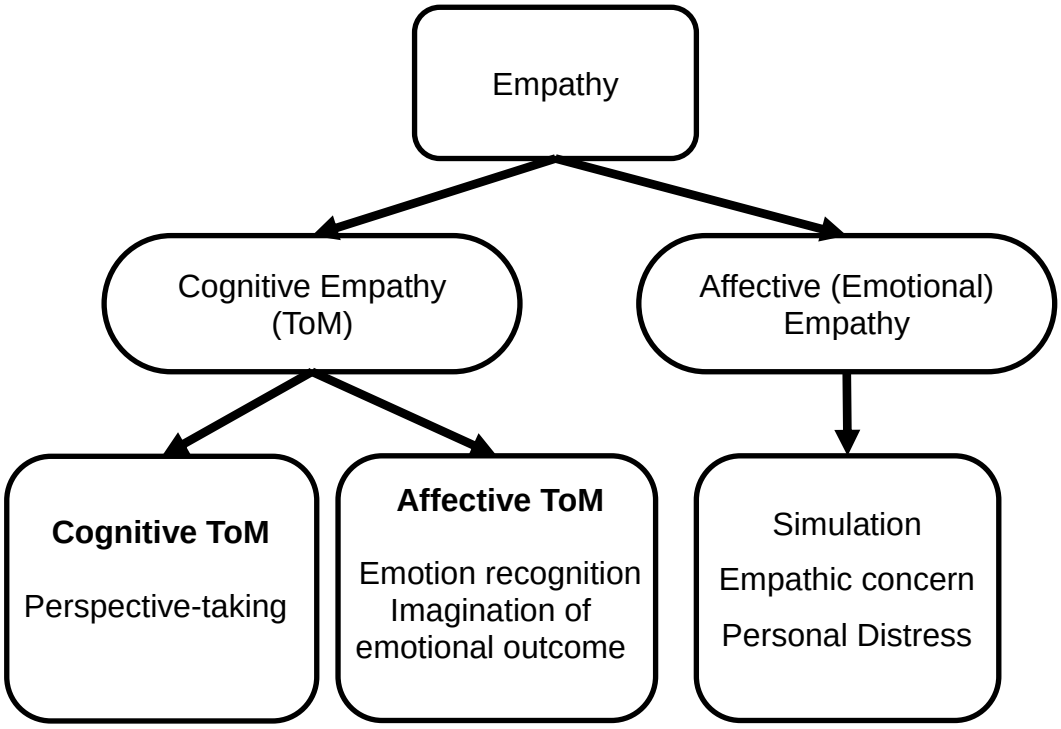


Figure 1-1 The proposed model describing the relationship between empathy and ToM

Table 1-1 Examples of empathy definitions in the literature

Researcher (year)	Proposed definition of empathy
Hogan (1969)	"the intellectual or imaginative apprehension of another's condition or state of mind without actually experiencing that person's feelings"
Mehrabian and Epstein (1972)	"the heightened responsiveness to another's emotional experience"
Davis (1983)	“reactions of one individual to the observed experiences of another”
Hoffman (1987)	“an affective response more appropriate to someone else’s situation than to one’s own”
Eisenberg (2000)	“an affective response that stems from the apprehension or comprehension of another’s emotional state or condition and is similar to what the other person is feeling or would be expected to feel.”
Preston and de Waal (2002)	“A super-ordinate category that includes all sub-classes of phenomena that share the same mechanism. This includes emotional contagion, sympathy, cognitive empathy, helping behaviour, etc.’’
Baron-Cohen, Richler, Bisarya, Gurunathan, and Wheelwright	“Empathy is not only about others' emotional states but also entails emotional responsiveness to them: Empathizing is the drive to identify another person's emotions and thoughts, and to

(2003)	respond to them with an appropriate emotion."
Decety and Jackson (2004)	"The naturally occurring subjective experience of similarity between the feelings expressed by self and others without losing sight of whose feelings belong to whom. Empathy involves the affective experience of the other person's actual or inferred emotional state and some minimal recognition and understanding of another's emotional state."
Smith (2006)	"Empathy refers to sensitivity to, and understanding of, the mental states of others."
Völlm, Taylor, et al. (2006)	"The ability to infer and share the emotional experiences of another"
Reniers et al. (2011)	"A comprehension of other people's experience (cognitive empathy) as well as the ability to vicariously experience the emotional experience of others (affective empathy)."
Dvash and Shamay-Tsoory (2014)	"The link between knowing the thoughts and feelings of others, experiencing them, and responding to others in caring, supportive ways."

1.2.4 Measurements

A number of tools have been developed to measure empathy, reflecting the ways empathy has been conceptualised. These tools fall into two broad categories; self-report and behavioural measures. There currently exists a considerable number of self-report (trait) measures of empathy. Table 1-2 summaries the most popular self-reported instruments designed for assessing empathy.

Behavioural measures are designed to measure affective empathy and cognitive empathy (i.e., ToM). Table 1-3 presents the most commonly used tasks, measuring different subtypes of ToM.

Behavioural measures are also being used to measure affective empathy or motor empathy, using physiological indicators measured while individuals are exposed to emotional stimuli aimed at inducing the empathic process. These include, for example, functional neuroimaging, heart rate variations, facial electromyographical activity and skin conductance. However, the use of psychophysiological indicators is still an evolving field within empathy research (Neumann, Chan, Boyle, Wang, & Westbury, 2015; Neumann & Westbury, 2011).

1.2.5 Neural substrates of empathy

Recent advances in neuroscience implicated a broad range of brain regions in empathy. One recent functional magnetic resonance imaging (MRI) based meta-analytic study (Fan, Duncan, de Greck, & Northoff, 2011) implicated the dorsal portion of anterior cingulate cortex (ACC), anterior midcingulate cortex,

supplementary motor area (SMA) and bilateral anterior insula in processing of empathic tendencies in humans. More specifically, the dorsal anterior midcingulate cortex has been implicated in tasks engaging cognitive empathy, and the right anterior insula in tasks engaging affective empathy.

Furthermore, researchers have also explored the neural mechanisms implicated in ToM. Several brain regions have been implicated in cognitive ToM, including medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (DLPFC), temporoparietal junction (TPJ) and temporal poles (Carrington & Bailey, 2009; Frith & Frith, 1999; Reniers, Völlm, Elliott, & Corcoran, 2014; Völlm, Richardson, et al., 2006). Brain areas implicated in the regulation of affective ToM include mPFC, particularly the ventral portion (Sebastian et al., 2012; Shamay-Tsoory & Aharon-Peretz, 2007; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009), inferior frontal gyrus (IFG), ACC, and amygdala (Gonzalez-Liencres, Shamay-Tsoory, & Brune, 2013; Shamay-Tsoory et al., 2009).

1.2.6 Clinical issues regarding empathy

1.2.6.1 Neuropsychiatric disorders

Low or impaired empathy has been associated with a variety of structural and functional abnormalities, and as cardinal features of several neuropsychiatric disorders, including, but not restricted to, psychopathy, antisocial personality disorder (Dolan & Fullam, 2004), schizophrenia (Bragado-Jimenez & Taylor, 2012), major depressive disorder (MDD; Schreiter, Pijnenborg, & aan het Rot, 2013), autistic spectrum disorders (ASD; Shimoni, Weizman, Yoran, & Raviv, 2012), temporal lobe epilepsy (Li et al., 2013), Alzheimer's disease (Laisney

et al., 2013), Parkinson's disease (Yu et al., 2012) and other neurodegenerative diseases (Poletti, Enrici, & Adenzato, 2012). Moreover, impaired empathy has been regarded as the core feature underpinning impairment of social functioning in individuals with psychopathy (Soderstrom, 2003), schizophrenia (Michaels et al., 2015), and ASD (Ruggieri, 2013).

1.2.6.2 Forensic issues

Empathy is thought to play a pivotal role in the violence inhibition system (Blair, Mitchell, & Blair, 2005) and low empathy is often referred to as a risk factor for violence and general offending behaviour (Jolliffe & Farrington, 2007). An early systematic review examining the relation between empathy and antisocial behaviour identified that the level of empathy was negatively related to aggression, externalising, and antisocial behaviour (Miller & Eisenberg, 1988). Evidence has been provided in support of a strong connection between offending and affective (Jolliffe & Farrington, 2007; Lovett & Sheffield, 2007) or cognitive (Jolliffe & Farrington, 2004) empathy from systematic review articles. More recently, one meta-analytic study (van Langen et al., 2014) found a strong relationship between low cognitive empathy and offending behaviour, but a weak association between low affective empathy and offending behaviour.

Table 1-2 Most widely used self-reported empathy measurements

Instrument	Author (year)	Domain of empathy	Description	Comments
Hogan Empathy Scale	Hogan (1969)	Cognitive empathy	64-items, 31 items selected from the Minnesota Multiphasic Personality Inventory, 25 extracted from the California Psychological Inventory and 8 original items. Four separate dimensions included: social self-confidence, even-temperedness, sensitivity, and nonconformity	Questionable test-retest reliability and low internal consistency
Questionnaire Measure of Emotional Empathy	Mehrabian and Epstein (1972)	Affective empathy	33-items divided into 7 subscales (Susceptibility to emotional contagion, Appreciation of the feelings of unfamiliar and distant others, Extreme emotional responsiveness, tendency To be moved by others' positive emotional experiences, tendency to be moved by others' negative emotional experiences, Sympathetic tendency, Willingness to be in contact with others who have problems) using a 9-point Likert scale from strongly disagree (-4) to strongly agree (+4)	May more accurately reflect general emotional arousal rather than empathy
Interpersonal Reactivity Index	Davis (1983)	Cognitive and affective empathy	28 items using 5-point scales, 4 sub-scales (Perspective Taking, Fantasy, Empathic Concern, Personal Distress), each with 7 items	A broad definition of empathy used; some items assessing sympathy. Personal Distress subscale may not assess a

				central component of empathy
Balanced Emotional Empathy Scale	Mehrabian (2000)	Affective empathy	30 items using a 9-point agreement-disagreement scale; fifteen of these items are positively worded whereas 15 are negatively worded	Only assesses emotional empathy; norms vary significantly with gender
Empathy Quotient	Baron-Cohen and Wheelwright (2004)	Cognitive and affective empathy	60 items (40 empathy and 20 filler items) using a 4-point scale from strongly agree to strongly disagree	Designed for use with ASD; assessing a general capacity for empathic responding
Basic Empathy Scale	Jolliffe and Farrington (2006)	Cognitive and affective empathy	20 items, to be answered on a 5-point Likert scale ranging from strongly disagree to strongly agree	Developed from adolescent groups
Griffith Empathy Measure	Dadds et al. (2008)	Cognitive and affective empathy	23 items rated on a 9-point Likert-type scale to assess parents' level of agreement with statements concerning their child	Informant-based measure of child and adolescent empathy; low internal consistency of the cognitive component
Toronto Empathy Questionnaire	Spreng, McKinnon, Mar, and	Cognitive and affective	16 items, to be rated on a 5-point scale from never to always	Only single factor obtained and it conceptualises empathy as a primarily

Questionnaire of Cognitive and Affective Empathy (QCAE)	Levine (2009) Reniers et al. (2011)	empathy Cognitive and affective empathy	31 items, 6 items selected from the Interpersonal Reactivity Index, 8 from the Impulsiveness Venturesomeness Empathy Inventory, 15 from the Empathy Quotient and 2 from the Hogan Empathy Scale. 5 factors (Perspective taking, Online simulation, Emotional contagion, Proximal responsivity, Peripheral responsivity), using a 4-point Likert scale ranging from strongly disagree to strongly agree	emotional process Built to capture the contemporary construct of empathy

Table 1-3 Commonly used ToM tasks

Instrument	Author (year)	Type of ToM	Description	Comments
Facial Emotion Recognition Test	Ekman and Friesen (1976)	Affective ToM	Participants are asked to choose which of the following emotions correspond to the facial expression of photographs of faces shown: 'happiness' , 'fear' , 'anger' , 'disgust' , 'surprise' , 'sadness' or 'neutral'	Measuring basic levels of affective ToM
False-Beliefs Tasks	Baron-Cohen, Leslie, and Frith (1985); Baron-Cohen (1989)	Cognitive ToM	First-order false-belief items involve attribution about other's false belief with regard to real events whereas second-order false-belief items are related to what people think about other people's thoughts. Three types of questions (belief, reality, memory) are asked	Verbal abilities may contribute to the quality of the answers
Happé's Stories	Happé (1994)	Cognitive ToM	16 short stories (half ToM items and half non-ToM passages), each followed by a test question	Verbal abilities may contribute to the quality of the answers
Cartoons' Tasks	Corcoran, Cahill, and Frith (1997); Happé, Brownell, and Winner (1999);	Cognitive ToM	A series of comic strips are presented to the participant, who is then required to choose the logical ending. The number of items and conditions (human characters or non-human characters) varies among different versions	Scoring may be trained since a perfect score is required for a full and explicit explanation

	Brunet, Sarfati, Hardy-Bayle, and Decety (2000)			
Faux Pas Test	Stone, Baron-Cohen, and Knight (1998)	Cognitive and affective ToM	20 stories are read to the participant, 10 with a faux pas (someone mistakenly saying something they should not have) and 10 control stories. Questions are then asked to determine whether the participant recognised the faux pas	Some items may concern moral judgements
Reading the Mind in the Eyes Test (RMET)	Baron-Cohen, Wheelwright, Hill, Raste, and Plumb (2001)	Affective ToM	The participant is asked to describe the emotional/mental state of a person based on only an image of their eyes from 36 items, in a fixed-choice paradigm	A widely used task with good psychometric properties
Yoni task	Shamay-Tsoory and Aharon-Peretz (2007)	Cognitive and affective ToM	The participant needs to judge mental states of the cartoon character called Yoni based on eye gaze and non-verbal cues. 64 trials are divided into three conditions: 24 trials of affective ToM, 24 cognitive ToM and 16 physical conditions	Consisting of first- and second-order cognitive and affective mental state inferences

ToM: Theory of Mind

1.3 IMPULSIVITY

Impulse control is an important aspect of behaviour in our everyday life. Identifying examples of impulse control is not difficult, such as resisting the temptation of having one more drink, buying unnecessary extra items at the grocery store, or just stopping and chatting to a stranger you have just met on the street. However, little consensus exists on the definition of impulsivity (Evenden, 1999b).

1.3.1 Definition

A number of definitions of impulsivity have been proposed with overlapping or similar components (Table 1-4). For example, Evenden (1999b) suggested that impulsivity covers ‘‘actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes’’. Bari and Robbins (2013) viewed impulsivity as the inability to withhold or stop a response, preferring immediate gratification, making premature decisions without gathering sufficient information, and the tendency of novelty/sensation-seeking to engage in risky behaviours. Fineberg et al. (2014) defined impulsivity as “a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or to others”. Caswell, Bond, Duka, and Morgan (2015) propose that “impulsivity encompasses a range of behaviours that include making premature decisions, preferring immediate gratification and having difficulties inhibiting motor responses”. Besides descriptions of behaviour or actions, some consider impulsivity as a constellation of negative personality traits (e.g., Patton,

Stanford, & Barratt, 1995). Although definitions of impulsivity vary among researchers, there is a general agreement that impulsivity should be considered as a multifactorial construct with independent subdomains (Evenden, 1999b; Whiteside & Lynam, 2001).

Table 1-4 Examples of impulsivity definitions in the literature

Researcher (year)	Proposed definition of impulsivity
Buss and Plomin (1975)	"a multidimensional temperament with inhibitory control, or the ability to delay the performance of a behaviour"
Dickman (1990)	dysfunctional impulsivity: "a tendency to engage in rapid, error prone information processing because of an inability to use a slower, more methodical approach under certain circumstances"; functional impulsivity: "to engage in rapid error prone information processing when such a strategy is rendered optimal by the individual's other personality traits"
Depue and Collins (1999)	"a heterogeneous cluster of lower-order traits that includes terms such as impulsivity, sensation seeking, risk taking, novelty seeking, boldness, adventuresomeness, boredom susceptibility, unreliability, and unorderliness"
Evenden (1999b)	''actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes''
Moeller et al., (2001)	"a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individuals or to others"
Whiteside and Lynam (2001)	"an artificial umbrella term that actually encompasses four distinct facets of personality associated with

	impulsive behaviour" (i.e., urgency, lack of premeditation, lack of perseverance, and sensation seeking)
Bari and Robbins (2013)	"the inability to withhold or stop a response, preferring immediate gratification, making premature decisions without gathering sufficient information, and the tendency of novelty/sensation-seeking to engage in risky behaviours"
Fineberg et al. (2014)	"a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or to others"
Caswell et al. (2015)	"a range of behaviours that include making premature decisions, preferring immediate gratification and having difficulties inhibiting motor responses"

1.3.2 Subdomains

Traditionally, researchers who regarded impulsivity as a personality trait proposed a multi-faceted construct for impulsivity. For example, Eysenck and Eysenck (1977) identified four specific factors under the broad heading of impulsiveness, namely narrow impulsiveness, risk-taking, non-planning, and liveliness. Later, Patton et al. (1995) identified three components for impulsivity; attention, motor activation and lack of planning. This model has been incorporated into the widespread self-report questionnaire, the Barratt Impulsiveness Scale, version 11 (BIS-11) with three subscales: attentional impulsivity, motor impulsivity and non-planning impulsivity. The concepts of motor impulsivity and non-planning impulsivity of the BIS-11 are similar to the Eysenck and Eysenck (1977) subdomains of impulsiveness narrow and non-planning, respectively (Patton et aI., 1995). Similarly, findings from recent laboratory studies view impulsivity as a multi-dimensional concept (Caswell, Celio, Morgan, & Duka, 2016; Evenden, 1999b) whereby three different facets have been proposed: a) motor impulsivity (MI), also used interchangeably with response disinhibition, the inability to inhibit a behavioural response; b) delay-discounting (also referred to as temporal impulsivity; TI), the failure to delay gratification; and c) reflection/cognitive impulsivity (RI), the tendency to make premature decisions without sampling enough information (Verdejo-Garcia, Lawrence, & Clark, 2008).

1.3.3 Measurements

With respect to measurements of impulsivity, these can be classified based on the dimension to be evaluated, that is trait/ state dependent impulsivity

(Iribarren, Jimenez-Gimenez, Garcia-de Cecilia, & Rubio-Valladolid, 2011), or on the format of evaluation, that is, self-report inventory/ behavioural task (Evenden, 1999b; Moeller et al., 2001).

1.3.3.1 trait vs state impulsivity

Trait impulsivity is defined as a relatively stable predisposition of the individual which is more or less always present and permeates most of the individual's behavioural styles. State impulsivity covers transient variations on affecting the internal state of the individual that somehow deviate from usual behaviour and that influence actions and thoughts for a limited time. These changes are dependent on biological or specific environmental situations (Bari & Robbins, 2013; Iribarren et al., 2011).

1.3.3.2 Self-reported vs behavioural tasks

There are two main approaches to measuring impulsivity: self-report inventories and behavioural tasks (Moeller et al., 2001). Self-report inventories are traditional measures of impulsivity, which mainly aim to identify different facets of impulsivity (Caswell et al., 2016). A number of self-report personality inventories include impulsivity as one of their subscales. Besides, several self-report measurements dedicated to measuring impulsivity have been developed (Table 1-5). In contrast, behavioural tasks of impulsivity are designed to index behaviourally observable impulsive responding (Caswell et al., 2016). Brief summaries of the most commonly used behavioural measures of impulsivity are presented in and Table 1-6. Although trait impulsivity is usually measured by self-report inventories and state impulsivity is usually measured by behavioural tasks, they are not simply

synonymous and these terms should be used with care. For example, the choice preference measured by delay discounting tasks is based on both past experience and future expectations, which concur to form a stable representation of the "self" (Bari & Robbins, 2013). Evidence is accumulating that self-report and behavioural measures of impulsivity do not correlate to each other in both healthy (Caswell et al., 2016; Enticott, Ogloff, & Bradshaw, 2006) and clinical populations (Strasser et al., 2016). One potential explanation for this is that they may measure different concepts or different aspects of the same concept (Caswell et al., 2015). Another explanation is that laboratory tasks are often considered more objective and are less likely influenced by an individual's biases and inaccuracies than self-report measures (Enticott et al., 2006). Moreover, self-report instruments require respondents to have sufficient insight to rate their impulsive tendencies accurately. This is important as insight might be impaired or questionable in impulsive individuals (Verdejo-Garcia et al., 2008). However, behavioural measures are not immune to biases in that they do not account for the social aspects of impulsivity and do not measure long-term patterns of behaviour (Moeller et al., 2001).

1.3.4 Neural substrates of impulsivity

The aforementioned components of impulsivity are thought to be underpinned by different biological mechanisms (Evenden, 1999a, 1999b). Although a considerable amount of animal research in this field has provided important insights into the neural underpinnings of impulsive behaviour, only human studies will be discussed here considering the direct relevance to the

research topics of this thesis. The heterogeneity of different components of impulsivity has been further examined and depicted with different neural underpinnings in recent studies in neuroscience (Grant & Kim, 2014).

Several brain areas have been implicated in MI (Fineberg et al. 2014). Multiple tiers of evidence from neuroimaging and lesion studies have demonstrated that MI is sub-served by a fronto-subcortical network encompassing the right inferior frontal gyrus (rIFG) and its subcortical connections to basal ganglia (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Chambers, Garavan, & Bellgrove, 2009; Wilbertz et al., 2014). In this circuit, the ACC, pre-supplementary motor area (pre-SMA), the premotor cortex and primary motor cortex are the sites involved before movement commands descend the corticospinal tract (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Chambers et al., 2009; Meyer & Bucci, 2016).

It has been suggested that three distinct sets of neural regions of a fronto-limbic network are involved in TI; ventromedial prefrontal cortex (vmPFC), ACC, and basal ganglia where basal ganglia and vmPFC are involved in valuation and ACC and vmPFC account for cognitive control (Peters & Buchel, 2011). Disconnections between these implicated neural regions are also likely to be crucial since reduced white matter integrity within this network has been reported in healthy volunteers with higher TI (Peper et al., 2013). Other neural substrates have been implicated in TI, such as the DLPFC and orbitofrontal cortex (OFC). When an individual chooses larger but delayed rewards over immediate rewards, activation in the DLPFC is evident (McClure, Ericson, Laibson, Loewenstein, & Cohen, 2007). The role of OFC in

TI remains controversial. Activation in the OFC has been associated with favouring large but delayed rewards over immediate rewards (Winstanley, Theobald, Cardinal, & Robbins, 2004) and steeper discounting (Rudebeck, Walton, Smyth, Bannerman, & Rushworth, 2006).

In contrast, the neurobiological underpinning of RI appears to have received less attention in the literature. Some studies show that the vmPFC plays a crucial role in disadvantageous decision-making (Bechara, 2004; Clark & Manes, 2004) and risk-taking (Cohen, Berkman, & Lieberman, 2013). Given that the vmPFC (including inferior frontal gyrus) is highly interconnected with insula and DLPFC, these brain regions are thought to be important in RI. For example, stronger functional connectivity between the rIFG and the anterior insula has been noted in risk-seeking individuals compared to risk-averse individuals during performing risk preference tasks (Cox et al., 2010). Hyperactivity in rIFG has been found in risk-averse participants while selecting less risky options (Christopoulos, Tobler, Bossaerts, Dolan, & Schultz, 2009).

1.3.5 Clinical issues

1.3.5.1 Neuropsychiatric disorders

Impulsivity plays a prominent role in psychopathology (Cyders, 2013) as it has been regarded as a symptom of several neuropsychiatric disorders, such as substance use disorders (SUDs), schizophrenia (Matsuzawa, Shirayama, Niitsu, Hashimoto, & Iyo, 2015), bipolar affective disorder, obsessive compulsive disorder (OCD; Endrass et al., 2010), borderline personality disorder (BPD), antisocial personality disorder, attention deficit hyperactivity

disorder (ADHD), and impulse-control disorders (American Psychiatric Association, 2013; Fineberg et al., 2014; Musser, Galloway-Long, Frick, & Nigg, 2013). The heterogeneity of impulsivity is also evident with different phenotypes of impulsive behaviour being identified in different neuropsychiatric disorders (Castellanos-Ryan & Séguin, 2015; Evenden, 1999a).

1.3.5.2 Forensic-psychiatric problems

Impulsivity may partly explain the high rates of offending behaviour and suicide associated with some of these disorders particularly BPD (Brevet-Aeby et al. 2016) and SUDs (Khemiri, Jokinen, Runeson, & Jayaram-Lindstrom, 2016). In addition, impulsivity in early life is regarded as a significant predictor of future physical health and delinquent behaviour (Moffitt et al. 2011). Furthermore, impulsivity has been included as a core criminogenic factor in classical criminology theories (Gottfredson & Hirschi, 1990) and is a crucial aspect in the HCR-20 (Douglas, Hart, Webster, & Belfrage, 2013), a well-validated risk assessment for violence. Impulsivity is an important risk factor of violence among both healthy (Chamorro et al. 2012) and clinical populations (Bjørkly, 2013).

Table 1-5 Commonly used self-report measurements of impulsivity

Instrument	Author (year)	Domain of impulsivity	Description
Sensation Seeking Scale	Zuckerman, Eysenck, and Eysenck (1978)	Sensation seeking	40 items using forced-choice (true or false) format consisting of 4 sub-scales: thrill and adventure seeking, disinhibition, experience seeking, and susceptibility to boredom
Dickman Impulsivity Inventory	Dickman (1990)	Dysfunctional Impulsivity; Functional Impulsivity	23 items using forced-choice (true or false) format consisting of 2 sub-scales: Dysfunctional Impulsivity (to act with relatively little forethought when this causes problems) and Functional Impulsivity (to act with relatively little forethought when this is optimal)
Barratt Impulsiveness Scale (BIS-11)	Patton et al. (1995)	Motor, attentional, non-planning	30 items using 4-point Likert-ratings (1 = never/rarely, 2 = occasionally, 3 = often, 4 = almost always/always) consisting of 3 sub-scales: motor, attentional, and non-planning impulsivity
Urgency, Premeditation, Perseverance, Sensation Seeking Impulsive Behaviour Scale (UPPS)	Whiteside and Lynam (2001)	Negative urgency, (lack of) premeditation, (lack of) perseverance, sensation seeking	45 items using 4-point Likert-ratings (1 = agree strongly, 2 = agree some, 3 = disagree some, 4 = disagree strongly) consisting of 4 sub-scales: negative urgency, (lack of) premeditation, (lack of) perseverance, and sensation seeking
UPPS-P Impulsive Behaviour Scale (UPPS-P)	Lynam, Smith, Whiteside, and Cyders (2006)	Negative urgency, (lack of) premeditation, (lack of) perseverance, sensation seeking, and positive urgency	59 items using 4-point Likert-ratings (1 = agree strongly, 2 = agree some, 3 = disagree some, 4 = disagree strongly) consisting of 5 sub-scales: negative urgency, (lack of) premeditation, (lack of) perseverance, sensation seeking, and positive urgency

Table 1-6 Summary of behavioural measures of impulsivity

Type of impulsivity Task or approach	Author (year)	Description	Measure of impulsivity
Motor impulsivity			
Stroop colour-word interference task (SCWT)	Stroop (1935)	Subjects are asked to name the ink colours of words referring to colours; (1) congruent condition: ink colour of word is same as colour name; (2) incongruent condition: ink colour and colour name are different	Interference index
Continuous Performance Test (CPT)	Conners (2000)	Subjects are presented with stimuli for a short time (usually 100-200ms) at a rate of -1 per 2 seconds and are asked to respond to target stimuli	Commission errors
Go/NoGo task (GNG)	Gordon (1983); Gordon and Caramazza (1982)	Subjects are presented with a series of stimuli and are asked to respond to any stimulus on the screen except for one. In Go blocks, all letters are targets; in NoGo blocks, a predetermined percentage of stimuli are non-targets	Commission errors on NoGo blocks
Stop Signal Task (SST)	Logan and Cowan (1984); Logan (1994)	Participants are presented with series of visual stimuli and are asked to respond to the direction of arrow stimuli by pressing different buttons unless a stop signal is presented after a short delay	Stop-signal reaction time (SSRT)
Temporal impulsivity			

Adjusting Amount Task (AAT)[a]	Du, Green, and Myerson (2002); Frye, Galizio, Friedel, DeHart, and Odum (2016)	Participants are presented with a series of paired-choices to indicate their preference of receiving a small amount of money now or a large amount of money after a delay. The amount of the immediate alternative in the following trial will be adjusted according to the previous decision.	A measure of discounting of delayed rewards (k)
Intertemporal Choice	Stephens and Anderson (2001)	Subjects are presented with hypothetical choices between a small amount of money now or a large amount of money after a delay. As the delay to the larger amount of money increases, preference for this option usually decreases	The rapidity by which the reward is discounted
Monetary Choice Questionnaire (MCQ)	Kirby (2009); Kirby, Petry, and Bickel (1999)	A pen-and-paper task in which participants choose between hypothetical large delayed rewards and smaller more immediate rewards. Participants are requested to complete 27 items	A measure of discounting of delayed rewards (k)
Self-control Choice Task	Cherek and Lane (1999)	Subjects are told about potential earnings before the task. Both the A (small reward with fixed short delay) and B (large reward with varied delay) letters appear on the screen at the beginning of each trial. The subject selects a letter by pressing the corresponding button on the response panel	Number of impulsive choices

Cognitive/Reflection impulsivity			
Matching Familiar Figures Test (MFFT)	Kagan (1965); Cairns and Cammock (1978)	Subjects have to select one picture that is identical to the target picture from a set (8 variants) of highly similar pictures in 12 (Kegan's version) or 20 trials	Latency to the first response and accuracy or the amount of errors
Information Sampling Task (IST)[b]	Clark, Robbins, Ersche, and Sahakian (2006)	Participants open a 5*5 matrix of boxes to reveal two colours underneath before selecting the colour in the majority. There are two (fixed win, decreased win) conditions available, each consisting of 10 trials	P(correct), the probability of uncertainty
Iowa Gambling Task (IGT)	Bechara, Damasio, Damasio, and Anderson (1994)	Subjects are presented with 4 virtual decks of cards that yield a large immediate reward but a very likely large loss in the future and decks of cards that yield a small immediate reward but smaller losses in the future. They are instructed to win as much money as possible	Higher net scores reflect more advantageous decision-making performance on the task
Balloon Analog Risk Task (BART)	Lejuez (2002)	The participant is presented with a balloon and told to earn money by pumping the balloon up by clicking a button. All collected points will be lost if the balloon pops. The number of trials is 30 but can be adjusted	Adjusted average number of pumps on unexploded balloons

[a] Refer to Chapter 7 for detailed information

[b] Refer to Chapter 6 and 7 for detailed information

1.4 TRANSCRANIAL MAGNETIC STIMULATION

1.4.1 Overview of transcranial magnetic stimulation

Since Barker and his colleagues (Barker & Freeston, 1985; Barker, Freeston, Jalinous, Merton, & Morton, 1985; Barker & Jalinous, 1985) first introduced TMS to modulate the activity of cortical neurons using time-varying magnetic fields, TMS has become one of the most commonly used non-invasive brain stimulation techniques in the past three decades (Rossini et al., 2015). With regard to the physics of TMS, an electric pulse is sent through the conductive wiring within the TMS coil and declines within a brief time period (<1 ms). Based on Faraday's law, the rapid changing of the current produces a magnetic field (up to about 2.5 Tesla) which in turn induces an electrical current in the surrounding cortical tissue below the coil (Barker & Freeston, 1985; Hallett, 2000). Consequently, the effect of TMS can be regarded as an interaction between the induced current and the brain areas beneath the stimulation site (Rotenberg, Horvath, & Pascual-Leone, 2014).

This electromagnetic induction follows the inverse cube law which states that the power of the magnetic field decays exponentially as the distance from the original current increases. Therefore, the induced electric current in the brain also decreases rapidly as it moves away from the coil with a maximum penetration depth of 1.5 to 2 cm from the scalp (Hallett, 2000; Rotenberg et al., 2014). Although currently available coils have been designed for deeper brain stimulation, superficial brain areas closer to the skull will always receive stronger energy than deeper brain regions, such as the basal ganglia and thalamus (Roth, Amir, Levkovitz, & Zangen, 2007).

TMS can be categorised by the frequency of pulse delivery. In single-pulse TMS (spTMS) the pulse is delivered one at a time; paired-pulse TMS (ppTMS) refers to pulses generated in pairs and separated by a variable time interval, while rTMS means the stimuli are delivered in trains (Rossi, Hallett, Rossini, Pascual-Leone, & The Safety of TMS Consensus Group, 2009; Sandrini, Umilta, & Rusconi, 2011). These types of TMS are applied for different purposes. For example, spTMS is usually used for mapping motor cortical outputs, studying central motor conduction time, and studying brain-behaviour causal relations. Whereas ppTMS can be used to stimulate single or two different brain regions, providing measures of intracortical facilitation and inhibition (Rossi et al., 2009). With respect to rTMS, two rTMS protocols, ‘‘conventional” and ‘‘patterned”, can be differentiated and are described in latter sections.

1.4.2 TMS physiological mechanisms

1.4.2.1 The motor evoked potential

TMS applied over the motor cortex preferentially activates interneurons in a plane parallel to the brain surface, it leads to a transynaptic activation of pyramidal cells evoking descending volleys in the corticospinal tracts. Motor-neuron activation in response to corticospinal volleys induced by TMS evokes a motor-evoked potential (MEP) on electromyography (EMG) recorded by using surface electrodes applied over the muscle belly (Klomjai, Katz, & Lackmy-Vallée, 2015; Sandrini et al., 2011). The peak-to-peak amplitude of the MEP reflects the efficiency of horizontally oriented axons, corticospinal neurons as well as the ease with which motor neurons and

muscle fibres can be depolarised; and it has been used to estimate the excitability of corticospinal pathways (Klomjai et al., 2015).

1.4.2.2 Cortical plasticity induced by rTMS

It is assumed that the ability of rTMS to induce changes in cortical excitability outlasting the period of stimulation contributes to cortical plasticity (Hoogendam, Ramakers, & Di Lazzaro, 2010). Currently, the physiological basis of rTMS after-effects is poorly understood. However, it is generally believed that the mechanisms underlying rTMS after-effects resemble long-term potentiation (LTP) and long-term depression (LTD) found in animal studies (Klomjai et al., 2015). Excitatory rTMS has been shown to induce LTP-like effects, whereas inhibitory rTMS typically leads to LTD-like effects (Thut & Pascual-Leone, 2010). Studies have attempted to extend findings regarding synaptic plasticity in animal experiments to the rTMS neuromodulation effects in humans (Hoogendam et al., 2010; Pascual-Leone et al., 2011).

In animal studies, LTP reflects an increase in the synaptic efficacy that can last for days or even weeks and months induced by brief high-frequency stimulation. Conversely, LTD reflects a long lasting weakening of a neuronal synapse following low-frequency stimulation (Hoogendam et al., 2010). On the cellular basis, in the CA1 region of the hippocampus, which is the most frequently studied region, LTP and LTD originate from the synapses of the axons of CA3 neurons and the dendritic spines of CA1 pyramidal neurons. The N-methyl-D-aspartate receptor (NMDA-R) placed post-synaptically has an intrinsic cation channel, which is blocked by magnesium ions when the cell

is at its normal resting membrane potential. Only when the postsynaptic neuron is sufficiently depolarised, the blockage will be removed, the NMDA-R will be opened, and calcium ions will then enter the post-synaptic neuron to initiate LTP induction (Hoogendam et al., 2010; Klomjai et al., 2015).

With respect to LTD, its induction reverses the LTP effects or LTD is induced “de novo”. It is suggested that LTD induction also results from NMDA-R activation, which leads to elevated concentration of calcium ions post-synaptically. Contrary to LTP induction, which would be due to a large and fast increase in the calcium ion concentration, LTD induction would arise from a small and slow increase in the calcium ion concentration. (Hoogendam et al., 2010; Klomjai et al., 2015).

1.4.3 TMS parameters

1.4.3.1 Motor Threshold

According to the committee of the International Federation of Clinical Neurophysiology (Rossini et al., 1994; Rossini et al., 2015), the motor threshold (MT) is defined as the lowest intensity (given as percentage of maximum stimulator output, MSO) of primary motor cortex (M1) stimulation required to induce a reliable MEP in the target muscle through a spTMS. This can be defined as a visible muscle twitch or an EMG response in the target muscle (usually the first dorsal interosseous, FDI). The twitch-based MT estimation is easier to perform, but this MT obtained by visual inspection is normally slightly higher (0% to 27.8%) than the EMG-based MT (Westin, Bassi, Lisanby, & Luber, 2014). MT can be determined while the target test muscle is at rest, namely resting motor threshold (RMT) or while the muscle is

at a slight tonic contraction, namely active motor threshold (AMT). There are mainly two approaches of measuring the MT (Groppa et al., 2012; Rossini et al., 2015). One approach, called the relative frequency method (Groppa et al., 2012; Rossini et al., 1994), starts with the lowest intensity of 30% of MSO with the coil placed over the optimal site of stimulation and gradually increasing in intensity in steps of 5% MSO until TMS consistently elicits MEPs in at least 5 out of 10 trials. Another method, called the adaptive threshold hunting, uses an S-shaped metric function to predict or estimate for each pulse in the sequence a TMS intensity that yields a 50% probability of evoking an MEP (Rossini et al., 2015). Such a process can be done by running a computerised maximum-likelihood threshold tracking algorithm (Awiszus, 2003). Both of the methods described above are recommended to derive an accurate MT estimation for either clinical or research purpose (Rossini et al., 2015), although some have proposed higher accuracy and time-saving in the adaptive method (Awiszus, 2011; Qi, Wu, & Schweighofer, 2011).

1.4.3.2 Online vs offline

Due to the short duration of the effect, spTMS or brief trains of rTMS is generally delivered “online”, where both stimulation and task performance are administered concurrently (Sandrini et al., 2011). The main advantage of this approach is that it has a good temporal resolution, which allows researchers to study the causal chronometry in brain-behaviour relations (Rossi et al., 2009). However, this online approach may not be appropriate if the timing to deliver the TMS pulse is not well understood (Walsh & Cowey, 2000). The “offline” mode has usually been used to examine the behavioural effects after

stimulating a specific brain area (or network) in healthy participants, or to examine the therapeutic effects through modulating brain activity in patients with specific neuropsychiatric disorders (Thut & Pascual-Leone, 2010). The disadvantage of the offline mode is that it requires the use of a task that lasts no longer than the duration of the after-effect and temporal involvement of a cognitive process will be ignored (Sandrini et al., 2011).

1.4.4 rTMS protocols

The application of rTMS was introduced in 1989 using repetitive pulses or trains of stimuli at various frequency delivered to the same cortical region for several seconds (Rossini et al., 2015). In contrast with spTMS, rTMS has the potential to change and modulate cortical excitability lasting beyond the stimulation period (Klomjai et al., 2015). The conventional rTMS protocol is used when each pulse is generated apart by identical inter-stimulus intervals (ISI), and the trains of stimuli are delivered at a fixed frequency. On the other hand, a patterned rTMS protocol refers to repetitive application of short rTMS bursts at a high frequency interleaved by short pauses of no stimulation (Rossi et al., 2009).

1.4.4.1 Conventional rTMS

Examples of conventional rTMS are shown in Figure 1-2. Emerging consensus considers low-frequency rTMS (LF-rTMS) as ‘‘inhibitory’’ stimulation and high-frequency rTMS (HF-rTMS) as ‘‘excitatory’’ stimulation. It is currently agreed (Rossini et al., 2015) that “low frequency” is defined as the frequency of one or less stimulus in every second (≤ 1Hz). Previous studies show that the duration of the after-effects from LF-rTMS on

neurophysiological markers or behavioural measures is at least half the duration of the stimulation train (Eisenegger, Treyer, Fehr, & Knoch, 2008; Robertson, Theoret, & Pascual-Leone, 2003). However, the cut-off for “high frequency” is not defined clearly. Some researchers (e.g., Sandrini et al., 2011) proposed pulses delivered at the frequency of more than 1 Hz, whereas others (e.g., Klomjai et al., 2015; Lefaucheur et al., 2014; McKinley, Bridges, Walters, & Nelson, 2012; Rossi et al., 2009; Rotenberg et al., 2014; Thut & Pascual-Leone, 2010) suggested that ≥ 5 Hz is the proper cut-off since it may reliably lead to excitatory effects in the brain, with some nuances as a function of the intensity of stimulation and the number of pulses delivered. When the number of pulses delivered is low, HF-rTMS of subthreshold intensity tends to produce suppressive effects whereas suprathreshold stimuli tend to produce facilitatory effects (Lefaucheur et al., 2014). However, longer trains of HF-rTMS tend to consistently produce excitatory effects and such after-effects of HF-rTMS typically last for 30 minutes (Thut & Pascual-Leone, 2010).

1.4.4.2 Patterned rTMS

Theta-burst stimulation (TBS) is regarded as a form of patterned rTMS (see Figure 1-2) comprising of trains of magnetic pulses with different ISIs and intensities (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). The TBS paradigm was originated from animal models, delivering bursts of three pulses at 50Hz repeated every 200ms. The term “theta” comes from the frequency of bursts, 5 Hz, which is in the range of theta rhythm. There are two different patterns of TBS that are commonly used with opposite effects,

namely continuous (cTBS) and intermittent (iTBS). In cTBS, a 40 second train of uninterrupted TBS is given (600 pulses) with a stimulus intensity of 80% MT, leading to a LTD-like decrease in cortex excitability (Rossini et al., 2015). In contrast, iTBS consists of a 2 s train of TBS repeated every 10 seconds for a total of 190 seconds (600 pulses) with the same MT, producing LTP-like plasticity in the cortex (Huang et al., 2005; Rossi et al., 2009). The estimated time of after-effects until recovery can last for more than an hour in the context of its lower intensity and shorter duration of stimulation (Huang et al., 2005; Thut & Pascual-Leone, 2010). This makes TBS particularly useful for neuromodulation research due to its prolong effects on cortical excitability that exceed those seen with conventional rTMS protocols (Huang et al., 2005; Rossini et al., 2015; Thut & Pascual-Leone, 2010), and its relative safety efficacy (Oberman, Edwards, Eldaief, & Pascual-Leone, 2011).

Quadripulse stimulation (QPS) is another effective form of patterned rTMS which has been introduced more recently. It is thought to induce stable and reliable long-term effects (Hamada et al., 2007; Hamada et al., 2008). The QPS protocol consists of trains of four monophasic TMS pulses separated by an ISI of 5 ms or 50 ms with an interburst interval of 5 s (i.e., 0.2 Hz) for 30 min. It finally gives 360 bursts (1440 pulses) in one session. Neuroimaging studies (e.g., Watanabe et al., 2014) further supported its bidirectional effects on cortical excitability. QPS may possess a strong potential in neuroplasticity research; however, given that only a limited number of studies exist, accumulating evidence is needed (Rossini et al., 2015).

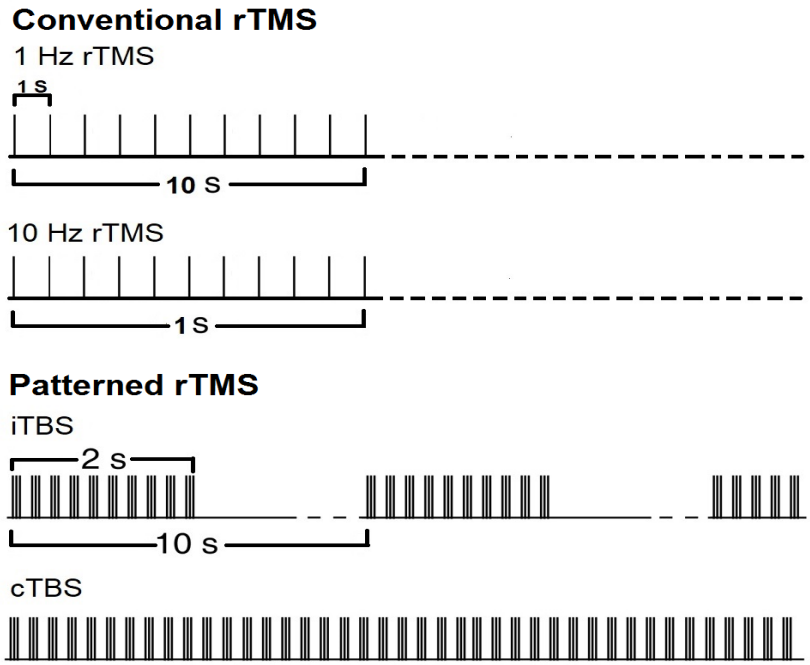


Figure 1-2 Graphical illustration of the conventional and patterned stimulation protocols
From the top: examples of 10 s of repetitive transcranial magnetic stimulation (rTMS) at 1 Hz (first trace), 1 s of rTMS at 10 Hz (second trace), intermittent theta burst stimulation pattern (iTBS) at the third trace and continuous theta burst stimulation pattern (cTBS) at the fourth trace

1.4.5 Localisation methods

There are several ways to localise the target brain regions. Landmark methods are the traditional ways to perform rough localisation. The 10–20 international system of electroencephalography (EEG) electrode placement is the most commonly used landmark method (Rotenberg et al., 2014). Several regions can be therefore targeted, such as DLPFC (left: F3, right: F4), M1 (left: C3, right: C4), vertex (Cz), and IFG (left: F7, right: F8). Alternative landmark methods are also utilised. For example, DLPFC is usually defined as 5 cm anterior to the area for activation of the first dorsal interosseus (Pascual-Leone, Rubio, Pallardó, & Catalá, 1996) For obtaining M1, the area of 5 cm lateral to the vertex has been suggested (Groppa et al., 2012). In addition, a landmark method using the canthus and tragus as referential spots

for IFG has been proposed (Gough, Nobre, & Devlin, 2005). Recently, several neuro-navigation systems have been developed utilising either infrared or ultra-frequency pulses to recognise a participant's anatomical landmarks with structural or functional brain MRI (Rotenberg et al., 2014; Ruohonen & Karhu, 2010). This technique has benefited from the advanced frameless stereotaxic systems allowing to target individual sites precisely with high resolution brain images (Luber & Lisanby, 2014).

1.4.6 TMS Equipment

The design and components of TMS devices are relatively straightforward and universal. Each machine consists of a main stimulator and a stimulating coil (Wagner, Valero-Cabre, & Pascual-Leone, 2007). The main stimulator is composed of several components, including a charging system to generate the current, an energy storage capacitor to generate, store, and discharge energetic pulses, a circuitry to recharge energy, and a high-power switch to connect the circuit (Barker & Freeston, 1985; Barker et al., 1985).

1.4.6.1 Stimulating coils

TMS coils can be designed in a variety of shapes and sizes. It is housed in a plastic mould and different coil geometries produce corresponding differences in the shape of the induced magnetic field (Rossi et al., 2009). Circular coils are relatively powerful with the maximal current near the outer edge of the coils but lack focality (Rossini et al., 2015). Figure-of-eight-shaped (also named butterfly) coils are most commonly used. They allow greater focality and producing maximal current at the intersection of the two round components (Hallett, 2007; Rossi et al., 2009) than other coils. The

disadvantage of the figure-of-eight coils is the limited penetration of the induced current because the diameter of the loops is relatively smaller than the circular coil (Hallett, 2007). Other coils for deep brain stimulation have larger dimensions than conventional coils, and provide a significantly slower decay rate of the electric field with distance, at the expense of reduced focality (Deng, Lisanby, & Peterchev, 2014). The double cone coil is formed by two adjacent 110mm circular windings in diameter fixed at an angle of 100° angle, and allows direct stimulation of deeper brain regions (Deng et al., 2014). Because of its deep penetration, this coil has been used for activation of the pelvic floor and lower limbs motor representation at the interhemispheric fissure, for cerebellar stimulation as well as for activation of the ACC through stimulation of the medial frontal cortex (Deng et al., 2014; Rossini et al., 2015). Another configuration is termed the H-coil, with complex windings that allow a slower fall-off of the intensity of the magnetic field with depth (Hallett, 2007; Zangen, Roth, Voller, & Hallett, 2005). Considering that the maximal stimulation intensity is always at the surface of the brain, it is not recommended to stimulate brain regions under the coil more than 4 cm in depth (Deng et al., 2014). Commercialised water-, oil- and forced-air cooling coils have been utilised in studies for long stimulation periods with high intensity to minimise overheating during the pulse generation (Rossi et al., 2009). For conducting sham-controlled studies, a variety of sham coils are available from all manufacturers of TMS machines. The sham coils are identical to the active coils in appearance, generating noises and vibrations. These features are designed to mimic the real stimulation, but without magnetic output.

1.4.7 Safety issues

While the TMS technique is non-invasive and is virtually painless, it is not totally risk-free. Safety concerns of TMS administration have been raised considering heating, magnetisation, induced voltages, and implanted electrodes (Najib & Horvath, 2014; Rossi et al., 2009).

1.4.7.1 Side effects

Transient headache and neck pain are the most commonly reported side effects of TMS, experienced by 20-40% of participants undergoing TMS (Machii, Cohen, Ramos-Estebanez, & Pascual-Leone, 2006; Najib & Horvath, 2014). In addition, transient hearing change is common due to persistent noise but preventable if earplugs are worn during TMS (Rossi et al., 2009). It is also transient and reversible. The induction of seizure is the most serious acute risk but occurs in an extremely small proportion (around 0.1%) of participants (Oberman et al., 2011). Syncope/fainting during TMS can be seen for several reasons but may not be directly linked to TMS (Rossi et al., 2009). Anxiety, psychological discomfort, and physical discomfort induced vasodepressor (neurocardiogenic) syncope is usually suspected in these cases although the incidence rate of syncope has been reported as less frequent than seizure (Najib & Horvath, 2014). Other side effects, such as transient hypomania, transient cognitive changes, and toothache have been reported but considered as very rare in occurrence (Najib & Horvath, 2014; Oberman et al., 2011; Rossi et al., 2009).

1.4.7.2 Parameters regarding safety issues

It is generally agreed that spTMS is safe if used with precautions (Hallett, 2007), although some studies have reported syncope events during spTMS with low intensity, for instance, to determine the motor threshold (e.g., Kalbe et al., 2010). On the other hand, the protocols of rTMS have been more frequently reported to induce side effects (Rossi et al., 2009). Protocols with low frequency, low stimulation intensity, short train durations and long inter-train intervals are considered as carrying less risk (Machii et al., 2006; Najib & Horvath, 2014). Theoretically, seizures are more likely to be induced by high-frequency rTMS with short intervals between trains of stimulation either during or after the stimulation due to increased cortical excitability (Oberman et al., 2011; Rossi et al., 2009). However, there are case reports describing induced seizures during inhibitory rTMS (e.g., Oberman & Pascual-Leone, 2009). TBS protocols are considered safer than the conventional rTMS protocols because the lower stimulation intensity and the shorter duration of stimulation may reduce the risk of seizure attacks regardless of the delivery of high-frequency bursts (Oberman et al., 2011; Oberman & Pascual-Leone, 2009). In one recent meta-analysis (Oberman et al., 2011), involving 776 healthy participants and 225 clinical patients in over 4500 TBS sessions, only one seizure event has been reported, standing for only 0.02% of participants. Transient headache and neck pain are still the most typically manifested side effects in TBS studies, but the incident frequency is only around 3% of the participants compared to the 40% in conventional rTMS protocols (Rossi et al., 2009).

1.4.7.3 Contraindications

The only absolute contraindication to TMS is the presence of metal objects in the head, including implanted cranial electrodes, a cochlear implant, metal plates or surgical clips (Rossi et al., 2009). Other conditions of increased or uncertain risk should be highlighted: a past history of syncope or seizure, epilepsy, and cerebral lesion, as well as current use of psychotropic medication. Individuals with a history of syncope or epilepsy are at higher risk of seizure induction (Schrader, Stern, Koski, Nuwer, & Engel, 2004) though some disagree with this argument (Bae et al., 2007; Rotenberg et al., 2009). Patients with any types of brain lesion are advised not to receive TMS due to the issue of induced current shunting. Because a person's seizure threshold may be lowered after taking some sorts of medication, such as antidepressants, a full and detailed medication history-taking is highly recommended. Besides aforementioned conditions, rTMS is best avoided in children and pregnant women for a conservative stance (Najib & Horvath, 2014).

1.4.7.4 Safety screening and monitoring

In order to prevent the risk of induced seizures, it is necessary for investigators and practitioners to use a standardised questionnaire to screen potential rTMS candidates (Rossi, Hallett, Rossini, & Pascual-Leone, 2011; Rossi et al., 2009). If the safety guidelines established by Rossi et al. (2009) are followed rigorously, the risk of induced seizure attacks due to TMS should be low (Najib & Horvath, 2014; Oberman et al., 2011). Although TMS paradigms utilised across studies vary, it is strongly recommended that both

physical health and cognitive functions are examined before and after stimulation.

1.4.8 rTMS in clinical practice

1.4.8.1 Symptom reductions in clinical populations

Over the past two decades, TMS, especially rTMS, has proven its utility in clinical practice in a range of neuropsychiatric disorders (Lefaucheur et al., 2014; Rossini et al., 2015; Wassermann & Zimmermann, 2012), including depression (Sabesan et al., 2015), obsessive–compulsive disorder (OCD; Trevizol et al., 2016), post-traumatic stress disorder (PTSD; Karsen, Watts, & Holtzheimer, 2014), schizophrenia (Dougall, Maayan, Soares-Weiser, McDermott, & McIntosh, 2015), and Parkinson's disease (Goodwill et al., 2017). The most striking therapeutic benefits have been found in relation to depression whereby active rTMS produced a greater decrease in depressive severity, higher response rates, and increased remission rates compared to patients receiving sham-controlled rTMS (Gaynes et al., 2014). In patients with OCD, active rTMS has revealed superior ameliorating effects to sham rTMS on OCD symptoms regardless of the rTMS frequency selected and brain regions stimulated (Trevizol et al., 2016). Similarly, active rTMS appears to be an effective treatment for PTSD in a limited number of clinical trials. PTSD symptom reduction has a trend to correlate with the total number of TMS pulses received (Karsen et al., 2014). In regards to schizophrenia, rTMS showed less promising therapeutic effects both for clinical improvements and positive symptoms (Dougall et al., 2015). With respect to Parkinson's disease, evidence from a recent meta-analytic study showed an overall significant

positive effect, favouring active rTMS over sham stimulation on motor function (Goodwill et al., 2017). To be concluded, it seems that rTMS may be regarded as an alternative therapeutic technique for patients with specific neuropsychiatric disorders. However, the stimulation parameters (intensity, frequency, and duration) and paradigm often selected arbitrarily among clinical trials makes it usually difficult to address the therapeutic effects from rTMS (Dougall et al., 2015; Sandrini et al., 2011).

1.4.8.2 Cognitive enhancement

Evidence has also been accumulating in relation to the cognitive enhancement effects of rTMS as indexed by improved accuracy or decreased response time in a variety of cognitive task performances (Demirtas-Tatlidede, Vahabzadeh-Hagh, & Pascual-Leone, 2013; Luber & Lisanby, 2014). For healthy individuals, one recent meta-analytic study (Hsu, Ku, Zanto, & Gazzaley, 2015) found an effect size of 0.42 on cognitive outcome measures from 14 studies involving a total of 331 healthy older adults (aged above 60) after they underwent rTMS or tDCS protocols.

For neuropsychiatric disorders, most of current studies specifically focused on neuropsychiatric disorders with a cardinal feature of cognitive dysfunction, such as major depression, Alzheimer's disease, and Parkinson's disease (Demirtas-Tatlidede et al., 2013; Goodwill et al., 2017; Hsu et al., 2015; Luber & Lisanby, 2014). In depression, the vast majority of previous rTMS studies targeted the DLPFC, which is involved in a large variety of cognitive domains comprising attention, memory, executive functions, psychomotor speed, and social cognition. However, remarkable post-rTMS effects have not been

shown in respect of all cognitive domains regulated by the DLPFC. Given that improved verbal memory, one of the neuropsychological functions closely related to the clinical severity of depression (Douglas & Porter, 2009), has been consistently reported, some attributed such an improvement to rTMS-induced therapeutic effects on clinical improvement in depression (Demirtas-Tatlidede et al., 2013). In Alzheimer's disease, significant improvements in different cognitive outcome measures after rTMS have been reported across studies regardless of the time of follow-ups (Demirtas-Tatlidede et al., 2013; Hsu et al., 2015). In contrast with this, the findings of beneficial rTMS effects on cognition have not been replicated in patients with Parkinson's disease (Goodwill et al., 2017). In general, the cognitive enhancement properties of TMS have been limited to improving immediate task performances (Luber & Lisanby, 2014). Prolonged beneficial effects from rTMS may be achieved after receiving multiple TMS sessions (Thut & Pascual-Leone, 2010). In sum, research into the cognitive enhancement properties of TMS remains in its infancy (Luber & Lisanby, 2014).

1.4.8.3 Empathy

Studies concerning the use of TMS to modulate ToM or empathy almost exclusively used rTMS (Hetu et al., 2012; Schuwerk, Langguth, & Sommer, 2014). Two recent narrative reviews in the field (Hetu et al., 2012; Schuwerk, Langguth, et al., 2014) suggested that rTMS has the potential to contribute to enhancing ToM and empathy with its exclusive capacity to modulate the neural systems underpinning these constructs. Studies involving healthy

individuals predominantly used inhibitory rTMS to investigate the functional neurobiological basis of empathy and ToM. For example, Costa, Torriero, Oliveri, and Caltagirone (2008) found that LF-rTMS impaired cognitive ToM when applied over the DLPFC and TPJ. Krause, Enticott, Zangen, and Fitzgerald (2012) found that deep rTMS at mPFC disrupted affective ToM for 16 healthy adults with high empathy, but improved affective ToM for those with low empathy. These authors further suggested that LF-rTMS effects on affective ToM are dependent on baseline empathic abilities. Nevertheless, HF-rTMS has been used by others to modulate impaired empathy or ToM in some clinical populations, especially those with ASD and MDD. For example, Berlim, Mcgirr, Beaulieu, and Turecki (2012) used HF-rTMS at the left DLPFC (LDLPFC) in 14 patients with MDD to modulate affective ToM. Although depressive symptoms were significantly ameliorated after the daily administration of rTMS for 4 weeks, no remarkable post-rTMS changes in empathy were found. However, given that a significant interaction between post-rTMS change in affective ToM and depressive symptoms was revealed, these authors suggested that the rTMS effect on affective ToM could be associated with clinical improvement over time in patients with MDD.

Another randomised sham-controlled rTMS trial (Enticott et al., 2014) employed deep HF-rTMS over the bilateral dorsal portion of mPFC to patients with ASD with 2 weeks of daily weekday treatment. This study indicated that deep HF-rTMS can significantly improve social relatedness in patients with ASD but no post-rTMS changes could be found in relation to measures of empathy or ToM. Since less promising rTMS effects on empathy have been revealed in clinical populations and clinical trials in this field are sparse, it is

not possible to draw firm conclusions about the therapeutic effects of rTMS in the field (Schuwerk, Langguth, et al., 2014).

In addition, previous studies (e.g., Enticott et al., 2014; Keuken et al., 2011; Krause et al., 2012; Lev-Ran, Shamay-Tsoory, Zangen, & Levkovitz, 2012) have reported variations in the TMS parameters selected, the tasks used to measure ToM and empathic abilities and experimental designs across studies.

1.4.8.4 Impulsivity

Existing reviews have paid attention to the excitatory or inhibitory effect of rTMS on various domains of impulsivity (e.g., Brevet-Aeby, Brunelin, Iceta, Padovan, & Poulet, 2016; Juan & Muggleton, 2012). For MI, structures involved in MI, namely the DLPFC, the pre-SMA and the IFG, have been investigated using rTMS, with predominant inhibitory rTMS protocols. Studies showed that excitatory rTMS applied to the left or right DLPFC led to improvements in MI as indexed by reduced reaction times in the Stroop Colour Word Test (SCWT; Kim, Han, Ahn, Kim, & Kim, 2012; Vanderhasselt, De Raedt, Baeken, Leyman, & D'haenen, 2006; Vanderhasselt et al., 2007) and decreased commission errors in a Continuous Performance Test (CPT; Hwang, Kim, Park, Bang, & Kim, 2010). The role of the pre-SMA in MI has been also highlighted in inhibitory rTMS studies, as manifested by prolonged stop-signal reaction time (SSRT; Obeso, Robles, Munoz-Marron, & Redolar-Ripoll, 2013) or response slowing (Lee et al., 2016) in a Stop Signal Task (SST). Previous studies persistently showed increased SSRT in SST with applications of inhibitory rTMS protocols at the rIFG (Chambers et al.,

2007; Chambers et al., 2006; Obeso et al., 2013; Verbruggen, Aron, Stevens, & Chambers, 2010), with the exception of the negative findings in Lee et al. (2016).

Studies in TI are relatively few and mainly focused on DLPFC, but the results are less congruent. Cho et al. (2010) utilised cTBS and iTBS over the right DLPFC whereby only cTBS reduced delay discounting. The effects of cTBS at the right DLPFC was further supported by Cho et al. (2012). Studies targeting the left DLPFC found that HF-rTMS selectively decreased discounting of monetary gains (Sheffer et al., 2013) while LF-rTMS induced preferential choosing of immediate rewards representing elevated TI (Figner et al., 2010).

Studies concerning RI are sparse. Knoch et al. (2006) found that individuals were significantly inclined to risky decision-making after LF-rTMS at right but not left DLPFC.

1.4.9 Conclusion

Empathy and impulsivity are both multi-dimensional constructs with strong relevance to treating neuropsychiatric disorders and in forensic populations. Considering their neural underpinnings, TMS, especially rTMS, may have the potential to modulate empathy and impulsivity in clinical populations. However, the evidence base for the effects of rTMS on empathy and impulsivity is still thin. Conducting a systematic review and meta-analysis of the literature on the effects of rTMS on empathy and impulsivity is merited.

CHAPTER 2 : AIMS AND HYPOTHESES

As mentioned in the introduction section of this thesis, empathy and impulsivity both have diverse neurobiological underpinnings and have been viewed as cardinal features of a range of neuropsychiatric conditions and as key risk factors for violence. In addition, rTMS has been suggested as a potential therapeutic modality for treatment of neuropsychiatric disorders. Therefore, the broad aim of this thesis was to examine the evidence of the effects of rTMS on empathy and impulsivity. The specific objectives of the theses were to:

1. Review the evidence base for use of rTMS to modulate empathy
2. Review the evidence base for use of rTMS to modulate impulsivity
3. Examine the efficacy of rTMS to modulate both empathy and impulsivity in healthy controls.

2.1 HYPOTHESES

Hypothesis 1: Given that empathy is a multidimensional construct with distinct underpinnings, it was hypothesised that rTMS would have differential effects on different domains of empathy. This hypothesis was tested by conducting a systematic review and meta-analyses (see Chapter 4).

Hypothesis 2: Similarly, it was hypothesised that rTMS would have differential effects on different domains of impulsivity. This hypothesis was also investigated by a systematic review and meta-analyses (see Chapter 5).

Hypothesis 3: This was driven by findings from the first systematic review and meta-analyses. I examined the effects of rTMS at rIFG on modulating different domains of impulsivity in healthy individuals (Chapter 6). I hypothesised that HF-rTMS would significantly improve motor and cognitive domains of impulsivity.

Hypothesis 4: This was driven by findings from the first and second systematic reviews and meta-analyses (Chapters 4 and 5). I examined the effects rTMS at LDLPFC on both empathy and impulsivity. I hypothesised that rTMS would significantly reduce temporal and reflection impulsivity and facilitate empathy in healthy individuals (Chapter 7).

The rationale for choosing healthy participants is three fold. First, both impulsivity and empathy are on a continuum with normality. As such effective interventions involving healthy individuals could potentially be extended to clinical populations. Second, the vast majority of studies conducted in the field involve healthy individuals, and there is a dearth of studies involving clinical populations. Third, research into the effects of TMS on empathy and impulsivity is still in its infancy. More definitive studies are required in this area before extending research into clinical populations.

CHAPTER 3 : GENERAL METHODS

3.1 SYSTEMATIC REVIEW

A systematic review is an approach to collate current empirical evidence filtered by pre-determined eligibility criteria to investigate a specific research question. Reliable conclusions can be drawn after using rigorous, systematic methods for identifying, appraising, and synthesising evidence to minimise the risk of bias (Liberati et al., 2009a). Systematic reviews facilitate the development of clinical practice guidelines and provide critical information to inform clinical decision-making (Moher et al., 2015). Four crucial characteristics of a systematic review should be highlighted: (a) clear objectives with an explicit, reproducible methodology; (b) systematic search with pre-specified criteria to identify all eligible studies; (c) quality assessment to evaluate the validity of the findings of the included studies; and (d) systematic presentation and synthesis of the characteristics and findings of included studies (Moher et al., 2015; Shamseer et al., 2015). This thesis followed the reporting guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Liberati et al., 2009a; Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009) and its modified version for protocols (PRISMA-P; Moher et al., 2015; Shamseer et al., 2015) to report the findings from systematic reviews and meta-analyses.

3.1.1 Data extraction

For data extraction, a dedicated form (Appendix 1) was used for the two systematic reviews. Information concerning study objectives, characteristics

of participants, inclusion/exclusion criteria, study design, experimental processes, rTMS protocols, outcome variables, effect sizes, and the type of statistical tests used was extracted.

3.1.2 Quality assessment

The quality assessment tool for quantitative studies (National Collaborating Centre for Methods and Tools, 2008) was selected as the tool of quality assessment (Appendix 2). The tool is recommended by the Cochrane Group for its proper feasibility in systematic reviews of effectiveness (Armstrong, Waters, & Doyle, 2011). This tool encompasses the domains of selection bias, study design, confounders, blinding, data collection method, withdrawals and dropouts, intervention integrity, and statistical analyses. Only the first six domains can be quantitatively rated in a three-level scale: strong, moderate, weak. A global rating of quality is assigned to each study based on the number of weak ratings in the six domains: strong (no weak ratings), moderate (one weak rating), weak (two or more weak ratings). It takes between 10-15 minutes to evaluate each study using this tool.

Other details regarding keywords selection, literature search, and electronic databases can be found in Chapters 4 and 5.

3.2 META-ANALYSIS

Meta-analysis is a set of mathmatical techniques used to obtain a single summarised effect size from a number of different reports (Thompson & Higgins, 2002). It is usually included in systematic reviews to provide more

precise estimates of the effects by combining information from all relevant studies (Liberati et al., 2009a).

3.2.1 Effect size

In a meta-analysis, the effect size is a value reflecting the magnitude of the treatment effect or the strength of a relationship between two variables. The effect size can be referred to as odds ratios, risk ratios, risk differences, standardised mean differences or correlations (Borenstein, Hedges, Higgins, & Rothstein, 2009b). Given that the outcome variables in the meta-analyses were performance on behavioural tasks, standardised mean differences were used for representing effect sizes. The sample estimate of the standardised mean difference is often called Cohen's *d* (Cohen, 1988) which can be calculated as $d = \frac{\overline{X}_1 - \overline{X}_2}{S_{within}}$. In the numerator, X_1 and X_2 are the sample means in the two groups. In the denominator, S_{within} is the within-groups standard deviation, pooled across groups. However, when a *d* is obtained from small samples, it tends to overestimate the absolute value of the true effect. Therefore, Hedges (1981) proposed an unbiased estimate, namely Hedges' *g*, where *g* can be calculated approximately as $g = \left(1 - \frac{3}{4df-1}\right) \times d$ with *df* indicating the degrees of freedom. Moreover, considering that a majority of rTMS studies recruited for the meta-analyses in the thesis were cross-over design with repeated measurements in both treatment (i.e., active stimulation) and control (i.e., sham stimulation) conditions, the aforementioned equations for obtaining effect sizes may not apply. Morris (2008) has examined three methods of deriving effect sizes in studies with

repeated measurements. The best method proposed and used in the thesis is calculating an effect size based on the mean pre-post change in the treatment group minus the mean pre-post change in the control group, divided by the pooled pre-treatment standard deviation.

3.2.2 Fixed-effect versus random-effects models

Most meta-analyses are based on either the fixed-effect model or the random-effects model (Deeks, Higgins, & Altman, 2011). For the fixed-effect model, it is assumed that only one true effect size exists in all the studies in the analysis; therefore, all observed variations in effects are due to sampling error. By contrast, for the random-effects model, the true effect is assumed to vary from study to study considering the characteristics of the studies (Borenstein, Hedges, & Rothstein, 2007). The major difference of the two models in obtaining the effect size is weighting the included studies. Since the true effect size is assumed identical for all studies in the fixed-effect model and the only source of the between-study variation is sampling error, the larger studies providing better estimates would be assigned more weights and the information in the smaller studies tends to be ignored by assigning them relatively low weights. By contrast, the goal of the random-effects model is to estimate the mean of a distribution of effects, and therefore a small study would not be discounted (Borenstein et al., 2009b). Given that the meta-analyses performed in this thesis includes a series of studies conducted by different researchers in different samples, it is not appropriate that all the studies should be considered equivalent (Borenstein et al., 2007). Therefore, the random-effects model is selected in the thesis.

3.2.3 Forest plot

The results of a meta-analysis are usually represented in a forest plot. Figure 3-1 exhibits an example of forest plots extracted from Chapter 5. The left column shows the study name and relevant information. In the middle of the figure, the dots are the mean effect sizes with the horizontal lines indicating 95% confidence intervals. The values are also shown in the second right column. The column on the right side indicates the weights assigned to each study. The solid vertical line crossing zero indicates no difference between the studies, and the dashed vertical line represents the overall mean effect. The diamond at the bottom indicate the limits of the 95% confidence interval of the overall mean effect size.

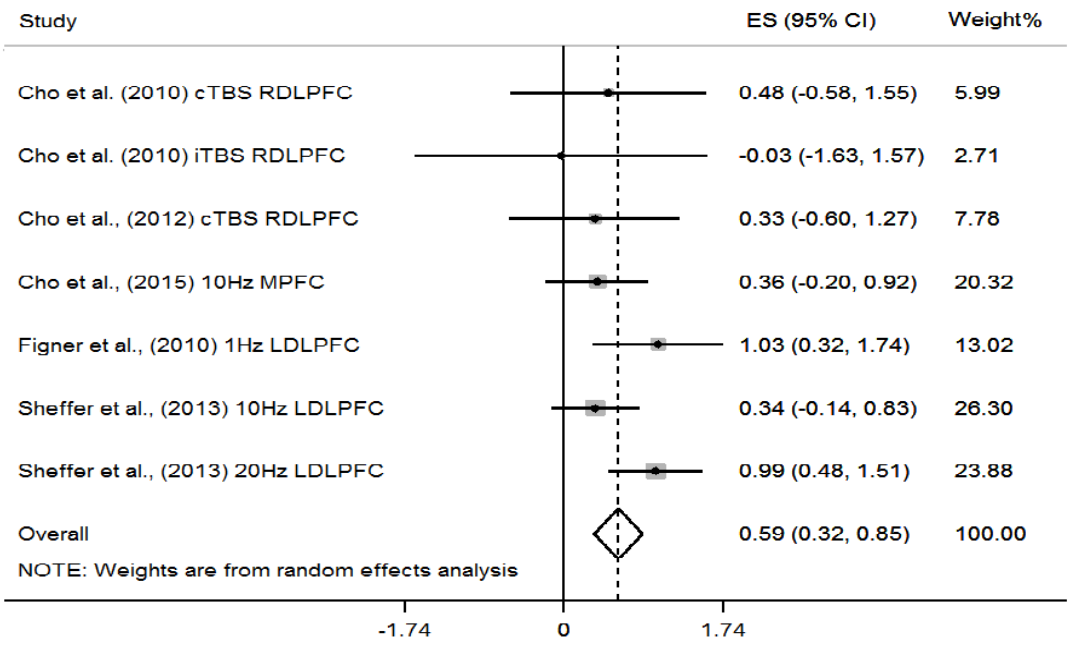


Figure 3-1 An example of a forest plot

3.2.4 Heterogeneity

3.2.4.1 Identifying and quantifying heterogeneity

Three statistics, namely I^2, Q, and tau-squared (T^2), were used in this thesis to quantify the level of heterogeneity between studies. I^2, an index of heterogeneity proposed by Higgins, Thompson, Deeks, and Altman (2003), is calculated as $I^2 = 100\% \times \frac{(Q - df)}{Q}$, where Q is the Cochran's heterogeneity statistic calculated by summing each study's weighted squared deviations from the average of the meta-analysis estimate (Higgins & Thompson, 2002) and *df* is the degrees of freedom. I^2 ranges between 0% and 100% with a value of 0% indicating no observed heterogeneity and a value of greater than 50% representing moderate heterogeneity (Deeks et al., 2011). While I^2 is a measure of relative heterogeneity, T^2 is the variance of the true effect sizes, as an estimate of absolute heterogeneity (Borenstein, Hedges, Higgins, & Rothstein, 2009a). When the observed variance increases or the variance within-studies decreases, T^2 will increase accordingly (Borenstein et al., 2007).

3.2.4.2 Subgroup analyses

Subgroup analyses involve dividing all the participant data into subgroups by categorical study characteristics, such as sex, age, education levels, or geographical locations for investigating heterogeneous results which is conceived to result from particular subgroups (Deeks et al., 2011). When there are only two subgroups, statistical significance can be suggested by non-overlap of the confidence intervals of the two summary estimates. The

significance of differences between subgroups can also be statistically examined by converting the categorical variables into dummy variables (which can only take values of zero or one) in the meta-regression model (Borenstein et al., 2009b).

3.2.4.3 Meta-regression

By contrast, meta-regression allows the effect of either continuous or categorical characteristics to be investigated, and multiple factors can be examined simultaneously with a sufficient number of studies (Thompson & Higgins, 2002). The term “meta-regression” refers to the covariates used in the regression model at the level of the study (e.g., average age) rather than the level of the participant (e.g., individual age). The regression coefficient indicates the way the outcome (dependent) variable changes with the specific moderator with a statistical significance level (Deeks et al., 2011). Generally, at least ten participants for each covariate is recommended for performing a regression; therefore meta-regression should not be considered if the number of included studies is less than ten (Borenstein et al., 2009b)

3.2.5 Bias

The funnel plot (see Figure 3-2 as an example) is often used to assess bias, where the publication bias (i.e., studies with statistically significant findings would be more possibly submitted and more easily to be published) is one of the prominent reasons for bias (Hoffman, 2015). For continuous outcome variables, the horizontal scale represents the mean result (usually Cohen’s *d* or Hedges’ *g*) and the vertical scale shows the standard error of the effect size (Egger et al., 1997). Therefore, effect estimates from small studies will

distribute widely at the bottom of the plot, while studies with a larger sample size will spread narrowly on the top. The plot should approximately resemble a symmetrical funnel in the absence of bias; however, if the studies are biased, for example, due to lack of small studies with positive and large effect sizes, then the funnel plot becomes asymmetrical with a gap in the right corner of the bottom (Sterne, Egger, & Moher, 2011). The asymmetry of a funnel plot may be examined by visual inspection but can also be tested by two statistical methods, the Egger test (Egger, Davey Smith, Schneider, & Minder, 1997) and the Begg and Mazumdar rank correlation test (Begg & Mazumdar, 1994). Moreover, Duval and Tweedie (2000) has proposed a "trim and fill" technique to deal with remarkable asymmetry by modelling the data assuming they were symmetrically distributed with the same mean value. However, this technique is less recommended by the Cochrane Group (Sterne et al., 2011) due to its unrealistic assumption that a funnel plot should be symmetrical.

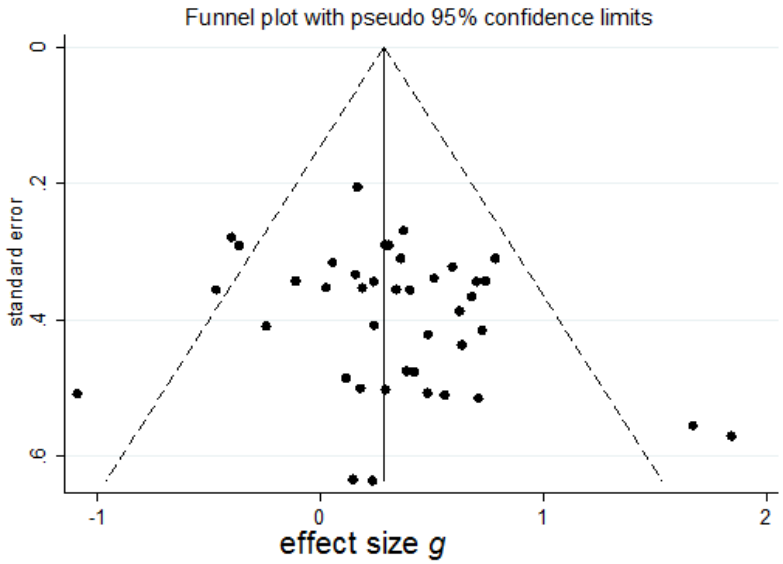


Figure 3-2 An example of funnel plots
The dashed lines indicate the funnel and the solid vertical line represents the pooled mean effect. Each dot represents one study.

3.3 TMS METHODS

All TMS sessions were conducted in the ECT suite, Queens Medical Centre, Nottingham, England, UK.

3.3.1 Equipment

Figure 3-3 shows the devices for the TMS session: a vital signs monitor, a commercialised chair manufactured by Magstim, a stand supporting the coil for rTMS, and a set of TMS machine and its accessories. A Magstim Rapid stimulator2 (The Magstim Company Ltd, Wales, UK) was used in all experiments in the thesis, which produces a biphasic waveform and a magnetic field of up to 2.5 Tesla (Figure 3-4a). The Magstim Company's figure-of-eight coil (Figure 3-4b), air-cooling figure-of-eight coil (Figure 3-4c), and sham coil (Figure 3-4d) were used in this thesis for spTMS, active rTMS, and sham rTMS, respectively.

3.3.2 RMT determination

Once participants were seated upright and relaxed, the TMS session commenced. The coil was placed tangentially to the scalp with the handle facing backwards at approximately 45° to the midline (see Figure 3-5b). The method to localise M1 followed the suggestion by Groppa et al. (2012). For each participant, spTMS was administered to obtain RMT based on previously established protocols (Rossini et al., 1994; Rossini et al., 2015) with the initial intensity at 30% MSO in increments of 5% until twitchings were observed in 5 of 10 consecutive trials over the right thumb.

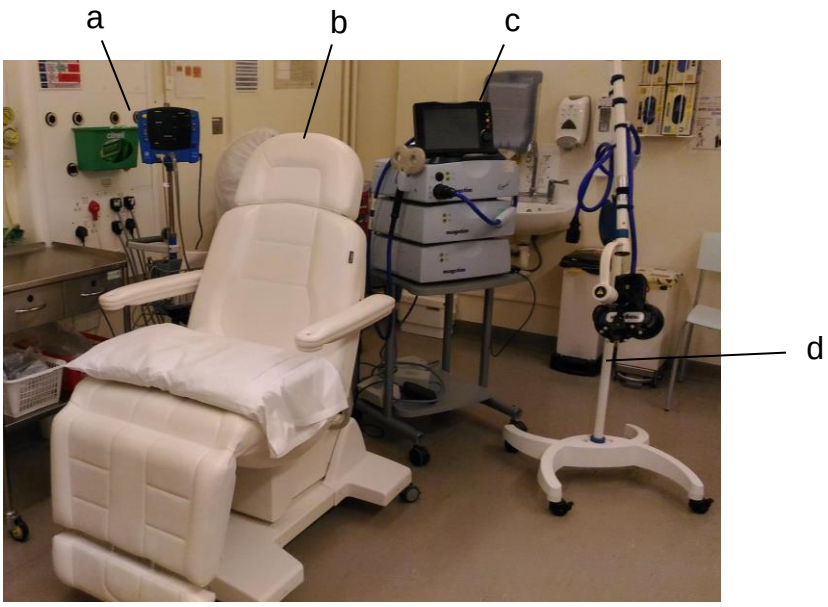


Figure 3-3 Devices for TMS sessions

a. A vital signs monitor collecting data of heart rate, oxygen saturation, and blood pressure
b. A commercialised chair with a pillow for participants
c. A TMS machine connected with a hand-held figure-of-eight coil
d. A stand with an air-cooling coil

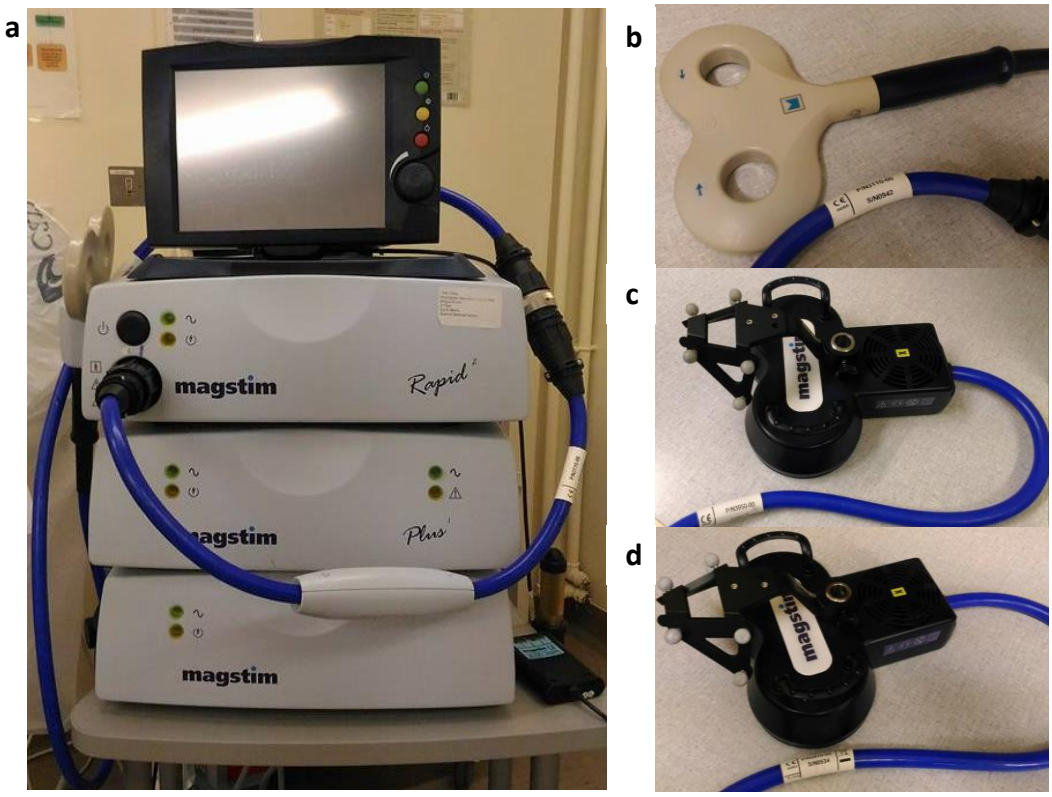


Figure 3-4 TMS machine and coils used in the thesis

a: Magstim rapid2 stimulator; b: coil for spTMS; c: active coil; d: sham rTMS coil

3.3.3 Localisation methods

Two stimulation sites were selected in the thesis. In Chapter 6, rIFG was selected as the region of interest for stimulation. The localisation method (Figure 3-5a) followed the suggestion by Gough et al. (2005). This localisation method has been further confirmed by using frameless stereotaxy structural MRI scans obtained from normal individuals (Waldowski, Seniow, Lesniak, Iwanski, & Czlonkowska, 2012). In Chapter 7, LDLPFC was used as the stimulation site landmarked by the method shown in Figure 3-5b. This method proposed by Pascual-Leone et al. (1996) for LDLPFC localisation has been commonly used for employing rTMS in treating medication-resistant depression in clinical settings.

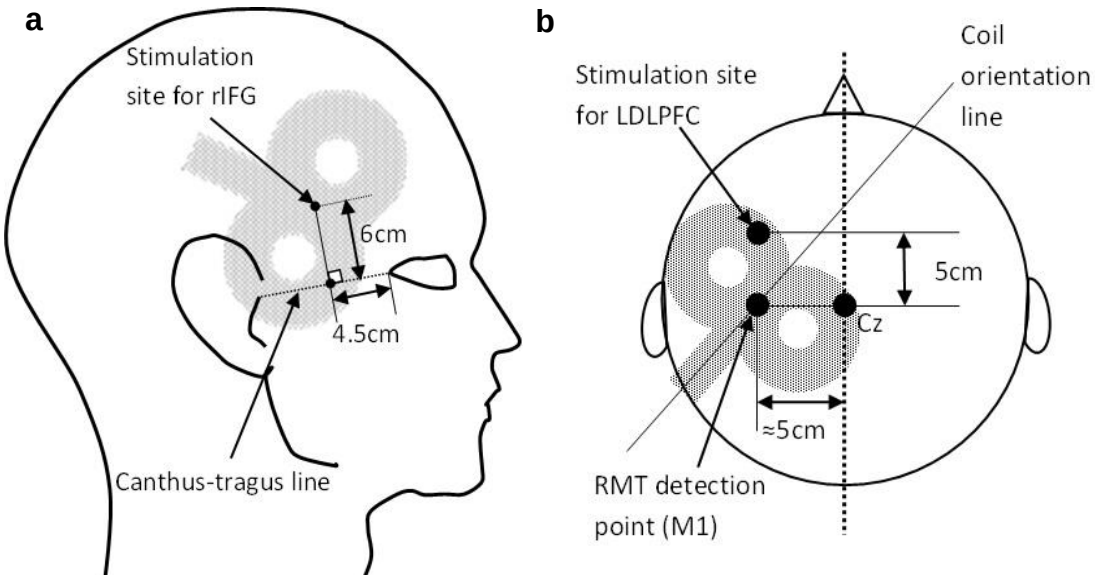


Figure 3-5 Localisation methods for the stimulation sites

a. The right inferior frontal gyrus (rIFG)
b. The primary motor cortex (M1) for determination of the resting motor threshold (RMT) and the stimulation site for the left dorsolateral prefrontal cortex (LDLPFC)

3.3.4 Safety screening and monitoring

Before entering the TMS session, participants were all screened using a standardised questionnaire (Appendix 3) following the established safety guidelines (Rossi et al., 2011; Rossi et al., 2009) to prevent the risk of seizure induction. All participants had checked their heart rate, blood pressure, and oxygen saturation before and after the stimulation. The tolerability to each stimulation session was also examined by recording participants' subjective complaints and the researcher's observation (Appendix 4).

CHAPTER 4 : THE EFFECTS OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ON EMPATHY AND THEORY OF MIND: A SYSTEMATIC REVIEW AND META-ANALYSIS

This chapter is presented in the format of a published paper as outlined in 'Remarks on Presentation of Thesis in Alternative Format' namely Yang, C.-C., Khalifa, N., & Völlm, B. (2018). The effects of repetitive transcranial magnetic stimulation on empathy: A systematic review and meta-analysis. *Psychological Medicine*. *48*(5), 737-750. doi: 10.1017/S003329171700232X

Cheng-Chang Yang

Najat Khalifa

Birgit Völlm*

Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham

4.1 ABSTRACT

Empathy is a multi-dimensional concept with affective and cognitive components; the latter is often referred to as Theory of Mind (ToM). Impaired empathy is prevalent in people with neuropsychiatric disorders, such as personality disorder, psychopathy, and schizophrenia, highlighting the need to develop therapeutic interventions to address this. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive therapeutic technique that has been effective in treating various neuropsychiatric conditions, can be potentially used to modulate empathy. To our knowledge, no systematic reviews or meta-analyses in this field have been conducted. The aim of the current study was to review the literature on the use of rTMS to modulate empathy in adults. Seven electronic databases (AMED, Cochrane library, Embase, Medline, Pubmed, PsycInfo, and Web of Science) were searched using appropriate search terms. Twenty-two studies were identified, all bar one study involved interventions in healthy rather than clinical populations, and 18 of them, providing results for 24 trials, were included in the meta-analyses. Results showed an overall small, but statistically significant, effect in favour of active rTMS in healthy individuals. Differential effects across cognitive and affective ToM were evident. Subgroup analyses for cognitive ToM revealed significant effect sizes on excitatory rTMS, online paradigms, and non-randomised design trials. Subgroup analyses for affective ToM revealed significant effect sizes on excitatory rTMS, online paradigms, and non-randomised design trials. Meta-regression revealed no significant sources of heterogeneity. In conclusion, rTMS may have discernible effects on different components of empathy. Further research is

required to examine the effects of rTMS on empathy in clinical and non-clinical populations, using appropriate empathy tasks and rTMS protocols.

Keywords

Empathy; neuromodulation; neuroplasticity; theory of mind; transcranial magnetic stimulation

4.2 INTRODUCTION

Successful human socialisation is heavily influenced by the abilities to detect and understand cognitive and emotional processes in others. These abilities are referred to as Theory of Mind (ToM) and empathy (Gallese, 2003; Keuken et al., 2011; Krall et al., 2016; Young, Camprodon, Hauser, Pascual-Leone, & Saxe, 2010). Clinicians and researchers use these terms interchangeably, but there is no universal consensus on their definitions and constructs. For example, some authors regard empathy as a two-component construct with affective and cognitive components (e.g., Reniers et al., 2011) whilst others (e.g., Blair, 2005) have proposed a three-component construct by adding a motor component to reflect the act of mirroring the motor responses of the observed person (motor empathy).

Some commentators view cognitive empathy as synonymous to ToM which is the ability to attribute mental states, such as desires, intentions and beliefs, to others (Frith & Frith, 1999). Some authors have favoured a ToM model with two distinct components, namely affective and cognitive (e.g., Kalbe et al., 2010). Others have suggested that empathy and ToM encompass similar underlying abilities that are discernible at the neural level (e.g., Reniers et al., 2014). More recently, Dvash and Shamay-Tsoory (2014) argued in favour of a two-component construct of empathy, namely emotional and cognitive empathy (also refered to as ToM), with distinct neuroanatomical underpinnings (Figure 4-1). According to this model cognitive empathy (ToM) has two distinct subcomponents, namely affective ToM and cognitive ToM.

Several brain regions have been implicated in cognitive ToM, including medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (DLPFC), temporoparietal junction (TPJ) and temporal poles (Carrington & Bailey, 2009; Frith & Frith, 1999; Reniers et al., 2014; Völlm, Richardson, et al., 2006). Brain areas implicated in the regulation of affective ToM include mPFC, particularly the ventral portion (Sebastian et al., 2012; Shamay-Tsoory & Aharon-Peretz, 2007; Shamay-Tsoory et al., 2009), inferior frontal gyrus (IFG), anterior cingulate cortex, and amygdala (Gonzalez-Liencres et al., 2013; Shamay-Tsoory et al., 2009).

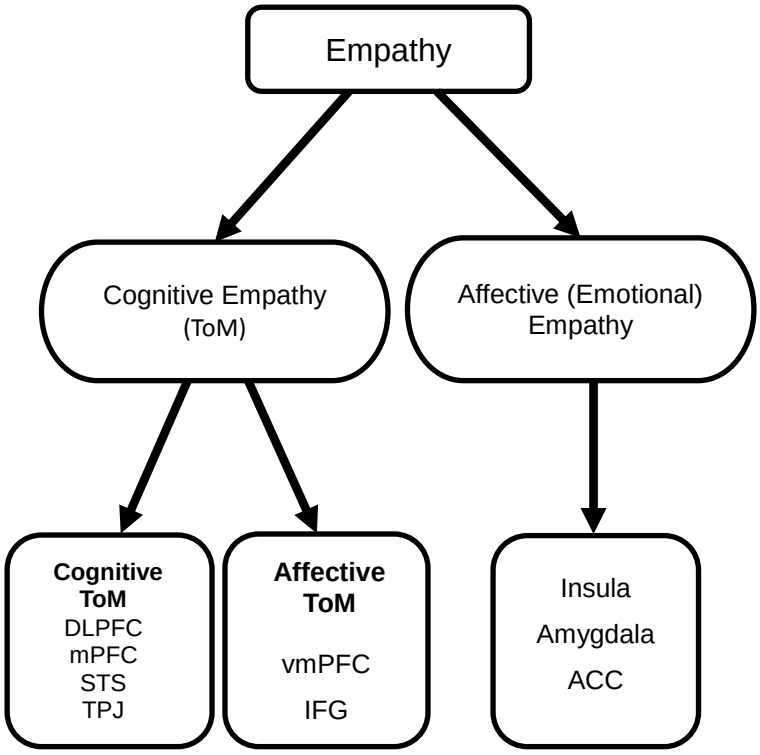


Figure 4-1 Empathy system adapted from Dvash and Shamay-Tsoory (2014)
Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex; STS, superior temporal sulcus; ToM, Theory of Mind; TPJ, temporoparietal junction; vmPFC, ventromedial prefrontal cortex

Self-report inventories commonly used to measure empathy include the Hogan Empathy Scale (Hogan, 1969), the Interpersonal Reactivity Index (IRI; Davis, 1983), the Balanced Emotional Empathy Scale (Mehrabian, 2000), the Empathy Quotient (Behan, Stone, & Garavan, 2015), and the Questionnaire of Cognitive and Affective Empathy (QCAE; Reniers et al., 2011). Behavioural measures of cognitive empathy (i.e., ToM) are primarily performance-based and include such tasks as first-order (Baron-Cohen et al., 1985) and second-order false-belief (Baron-Cohen, 1989) tasks for assessing cognitive ToM, the Reading the Mind in the Eyes (RMET) for evaluating affective ToM (Baron-Cohen et al., 2001), and the Faux Pas Recognition test (Stone et al., 1998) and the Yoni task (Shamay-Tsoory & Aharon-Peretz, 2007) for assessing both affective and cognitive ToM.

Impairment of social functioning consequent upon impaired empathy has been reported in a range of neuropsychiatric conditions, including psychopathy, antisocial personality disorder (Dolan & Fullam, 2004), schizophrenia (Bragado-Jimenez & Taylor, 2012), major depressive disorder (MDD; Schreiter et al., 2013), autistic spectrum disorder (ASD; Shimoni et al., 2012), temporal lobe epilepsy (Li et al., 2013), Alzheimer's disease, Parkinson's disease (Yu et al., 2012), and other neurodegenerative diseases (Poletti et al., 2012). Empathy is highly correlated with violence (Jolliffe & Farrington, 2004) and plays a pivotal role in the violence inhibition system (Blair et al., 2005). Thus, enhancement of empathy has been regarded as a major treatment goal in criminogenic programmes (Day et al., 2010; Reidy, Kearns, & DeGue, 2013). However, conventional psychological interventions for empathy enhancement have proved less effective in certain offender

groups, particularly those with psychopathy (Reidy et al., 2013), highlighting the need to develop alternative therapeutic interventions to enhance empathy, of which transcranial magnetic stimulation (TMS), especially its repetitive format (rTMS), is an example (Glannon, 2014; Glenn & Raine, 2008).

TMS is a non-invasive technique used to deliver brief, high-intensity magnetic pulses to the brain inducing localised neuronal depolarization to regulate cortical excitability that underlies the modulation of cortical networks (Luber & Lisanby, 2014). In general, high frequency (≥ 5 Hz) rTMS and its newer version, intermittent theta burst stimulation (iTBS), facilitate cortical excitability, whereas low frequency (about 1 Hz) rTMS and continuous theta burst stimulation (cTBS) contribute to opposite effects (Huang et al., 2005; Pascual-Leone, Walsh, & Rothwell, 2000; Wassermann & Zimmermann, 2012). rTMS has been used to treat a variety of neurological and psychiatric diseases (see Wassermann & Zimmermann, 2012) and to enhance cognitive functions in healthy volunteers (see Hsu et al., 2015) and in people with MDD (Serafini et al., 2015). Table 4-1 provides more information about the effects of TMS in clinical populations (Wassermann & Zimmermann, 2012). Additionally, rTMS has been used to modulate empathy with some promising effects (see Hetu et al., 2012; Schuwerk, Langguth, et al., 2014). However, findings are inconsistent likely due to differences in the tasks used to measure empathy, experimental designs, targeted brain regions, and rTMS parameters, including the paradigms used (i.e., online or offline), stimulus intensity (measured as a percentage of resting motor threshold [RMT] or of maximum stimulator output [MSO]), frequency and number of pulses.

We therefore aimed to conduct a systematic review and meta-analysis of the literature on the effects of rTMS on empathy in healthy and clinical populations to integrate the evidence base and to determine if certain TMS parameters or brain regions selected are associated with stronger effects on specific domains of empathy. Whilst effective interventions involving healthy individuals could potentially be extended to clinical populations, as we shall describe later in this review, all the studies included in this review, bar one study, involved interventions in in healthy groups. Due to the overlaps between the concepts of empathy and ToM, in this review we have conceptualised empathy in accordance with the model proposed by Dvash & Shamay-Tsoory (2014) as outlined above. We followed PRISMA-P guidelines (Moher et al., 2015; Shamseer et al., 2015) in the reporting of this review where applicable.

Table 4-1 rTMS effects in clinical populations

Population	Effects
Depression	rTMS at DLPFC yields a medium to large effect size on reducing the severity of depressive symptoms.
Schizophrenia	Low-frequency rTMS significantly reduces intensity of auditory hallucinations but is less efficient in improving negative symptoms.
Obsessive compulsive disorder	High-frequency rTMS may reduce compulsions; the finding has not been replicated consistently across studies.
Posttraumatic stress disorder	High-frequency rTMS may have positive and sustainable therapeutic effects on anxiety.
Parkinson's Disease	High-frequency rTMS may have beneficial effects on motor disorders
Alzheimer disease	High-frequency, offline rTMS may contribute to small short-term improvement in cognitive functioning

DLPFC: dorsolateral prefrontal cortex; rTMS: repetitive transcranial magnetic stimulation

Table is summarised from Wassermann & Zimmermann (2012)

4.3 METHOD

4.3.1 Data sources

Using the terms ”transcranial magnetic stimulation” or ”TMS“ combined with “theory of mind”, “ToM”, “empath$”, “mentali$”, “role taking”, or “perspective taking”, a systematic search of the literature on the effects of TMS on empathy was conducted on 25 May 2016 of seven electronic databases (AMED, Cochrane library, Embase, Medline, PsycInfo, Pubmed, Web of Science). The International Clinical Trials Registry Platform, Dissertation Abstracts, Google, and the library catalogues of the University of Nottingham were also searched to identify grey literature in the field. No filters were added regarding the age of study participants, publication time or language of publication (see Appendix 5 for search syntax). References of eligible articles were searched manually for potentially eligible studies missed by the electronic searches.

4.3.2 Study selection

Empirical studies were included in the review if they: (1) involved adult participants without dementia or other major neurological conditions; (2) used rTMS as an active intervention; (3) had a comparison group or control condition; and (4) used behavioural tasks to assess empathy (Appendix 6). Of the 508 papers originally identified, 22 met the inclusion criteria (see Figure 4-2 and Appendix 6) and were quality assessed using the quality assessment tool for quantitative studies (National Collaborating Centre for Methods and Tools, 2008) on the domains of selection bias, study design, confounders,

blinding, data collection method, withdrawals and dropouts, intervention integrity, and statistical analyses.

Of the 22 studies included in the review, four (Balconi, Crivelli, & Bortolotti, 2010; Hoekert, Vingerhoets, & Aleman, 2010; Lev-Ran et al., 2012; Uddin, Molnar-Szakacs, Zaidel, & Iacoboni, 2006) were excluded from the meta-analyses due to lack of sufficient data to allow effect size calculation and only after exhausting attempts to obtain this information from the authors.

4.3.3 Data extraction and analyses

A standardised form (Appendix 1) was used to extract information concerning authors, study objectives, sample characteristics, inclusion/exclusion criteria, study design, experimental processes, rTMS protocols, outcome variables, and analytic strategy.

We originally intended to conduct separate meta-analyses of studies involving clinical populations and healthy individuals using the random-effects model and, where applicable, in accordance with the model proposed by Dvash & Shamay-Tsoory (2014) with its components: cognitive empathy (i.e., ToM, including cognitive ToM and affective ToM) and affective empathy. However, this has not been possible due to there being only one study in the field (Enticott et al., 2014). Therefore, the meta-analyses presented in this review include only studies involving healthy participants. Measures of cognitive ToM included the cognitive component of the Yoni task, moral judgement, false-belief tasks, and action-understanding tools. Measures of affective ToM included the RMET, tasks of facial expression recognition, the affective component of the Yoni task, affective go/no-go tasks, the faux pas test and

emotional egocentricity. While it can be argued that facial expression recognition is not a test of empathic abilities, the model proposed by Dvash & Shamay-Tsoory (2014) regards emotional recognition as a component of affective ToM. This view has been supported by other commentators (e.g., Poletti et al., 2012), Therefore, tasks measuring emotional recognition, such as facial expression recognition taks, were included in the review.

Effect size was regarded as positive if the active rTMS effect was in the predicted direction and negative if it was in the opposite direction. Moreover, when a study entailed multiple stimulation sites, each trial of the different stimulation sites was used as the unit of analysis for the purpose of meta-analysis. A pooled effect size was used if a study provided multiple outcomes (e.g., accuracy and reaction time, score of each subscale, or short-term and long-term performance). Only the comparison between experimental and sham group (condition) was selected when a trial consisted of more than one control group or condition (e.g., one group receiving rTMS at a control site and another receiving sham stimulation). Effect sizes represented as Hedges' *g* and 95% confidence intervals (CI) were calculated according to the differences between experimental (real stimulation) and control (sham stimulation) conditions in post-stimulation evaluations or "online" performance divided by pooled standard deviation.

The *Q* and I^2 statistics (Higgins & Thompson, 2002; Higgins et al., 2003) were used to assess consistency between studies. The *Q* statistic represents the level of heterogeneity while the I^2 index specifies the total variation from between-study variance. A *P* value ≤ .05 and an I^2 value of greater than 40%

were deemed as indicative of moderate heterogeneity. Funnel plots (Egger & Smith, 1995), the Egger test (Egger, Davey Smith, et al., 1997), and Begg and Mazumdar rank correlation tests (Begg & Mazumdar, 1994) were used to test for the presence of a potential publication bias. In cases where publication bias was evident, the Trim and Fill procedure (Duval & Tweedie, 2000) was applied to correct it.

In order to identify variables which could contribute to modulation of empathy, pre-specified subgroup analyses were performed with the unit of trial by merging the data according to the rTMS parameters, including effect ("excitatory" vs. "inhibitory"), stimulation paradigm ("online" vs. "offline"), study design ("randomised" vs. "non-randomised"), stimulation site and task of outcome measurement.

Meta-regression was employed to examine the impact of between-study variation on study effect sizes. The effect size from each trial was set as the dependent variable while age, gender, intensity of stimulation, total pulses per condition, and weighted number of pulses (i.e., total number of rTMS pulses multiplied by intensity) were selected as predictor variables. All the quantitative analyses were performed using Stata 13.1 (StataCorp, 2013).

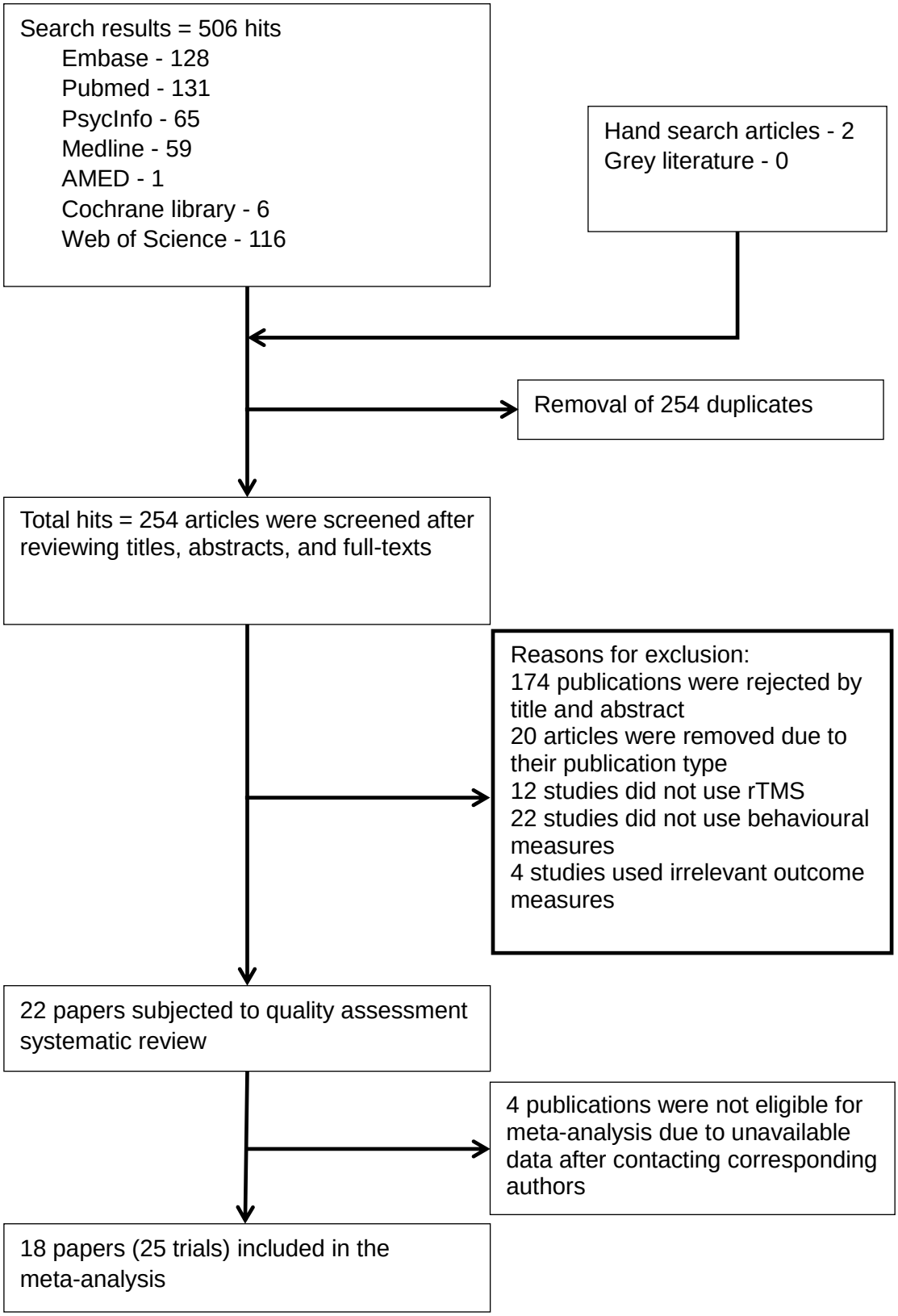


Figure 4-2 The process of study selection and search results

Table 4-2 Characteristics of included rTMS studies on empathy

Study (country)	Study design	participants number‡, Age(Mean± SD, range), male%, Diagnosis if not healthy volunteers	Tasks	Stimulation position	rTMS protocol (frequency, intensity, stimulation, paradigm, number of pulses per condition)	Sham method
Balconi & Bortolotti, 2012 (Italy)	UCR	18, (23.40± 2.60, 20-30), 44%	Facial expression recognition	mPFC	1Hz, 120% rMT, online, 400 pulses	Vertex stimulation & unknown sham method at FCz
Balconi & Bortolotti, 2013 (Italy)	CCR	19, (23.13± 2.11, 20-30), 47%	Facial expression recognition	dorsal mPFC	1Hz, 120% rMT, online, 400 pulses	Vertex stimulation & unknown sham method at mPFC
Balconi, Bortolotti, & Gonzaga, 2011 (Italy)	UCR	20, (23.73± 2.08, 20-30), 45%	Facial expression recognition	mPFC	1Hz, 120% rMT, online, 200 pulses	Vertex stimulation & unknown sham method at mPFC
Balconi & Canavesio, 2013 (Italy)	UCR	16, (23.11± 1.93, 20-28), 38%	Facial expression recognition	mPFC	10Hz, 120% rMT, online, 2500 pulses	Vertex stimulation & tilt (45 degree) coil at mPFC
Balconi & Canavesio, 2016 (Italy)	CCR	46, (26.77± 0.17, NA), 57%	Facial expression recognition	left DLPFC	1Hz, 120% rMT, online, 400 pulses	Vertex stimulation & tilt (45 degree) coil at left DLPFC
Balconi, Crivelli, & Bortolotti, 2010[c] (Italy)	UCR	18, (23.46± 2.65, NA), NA	Facial expression recognition	ACC	1Hz, 120% rMT, online, 400 pulses	Vertex stimulation & unknown sham method at FCz
Bolognini et al., 2013 (Italy)	CCR	Exp1: 18, (22.6± 3.5, NA), 11% Exp2: 18, (24.5±3.8, NA), 17%	Affective go/no-go task	Exp1: right S1 Exp2: left S1	1Hz, 110% rMT, offline, 600 pulses	Exp1:left DLPFC stimulation & no stimulation Exp2: right DLPFC stimulation & no stimulation
Costa et al., 2008 (Italy)	RCR†	11, (22.5± 3.0, NA), 45%	Short stories: false belief/faux pas/control	left TPJ right TPJ left DLPFC right DLPFC	1Hz, 90% rMT, offline, 900 pulses	unknown sham method

Enticott et al., 2014 (Australia)	RCT	28(active: 15, sham: 13), (32.32±11.80, 18-59), 82%, ASD	IRI RMET, Frith-Happé-animations	bilateral dorsal mPFC	5 Hz, 100% rMT, offline, 900 pulses	Sham coil
Giardina et al., 2011 (Italy)	RCR†	14, (22±3, NA), 21%	Social interaction scenarios requiring either hostile or non-hostile intentionality attributions	left TPJ right TPJ	1Hz, 90% rMT, offline, 600 pulses	Occipital cortex stimulation
Hoekert et al., 2010[c] (Netherlands)	CCR	9, (21.8± 2.6, 18-26), 40%[a]	Emotional language task	left IFG, right IFG	5Hz, 90% rMT, online, 576 pulses	right IFG stimulation Sham coil
Kalbe et al., 2010 (Germany)	RCR†	28, (24.0± 2.7, NA), 100%	RMET, Yoni task	right DLPFC	1Hz, 100% rMT, offline, 900 pulses	Vertex stimulation
Keuken et al., 2011 (USA)	RCT†	37 (active: 18, control: 19), (20.4± 2.0, 18-29), 100%	Modified RMET, Attribution of belief and intentions; reasoning about physical causations (modified from Brunet et al., 2000)	left IFG	1Hz, 45% MSO, offline, 300 pulses	Vertex stimulation
Krall et al., 2016 (Germany)	CCR	24, (27.7± 4.5, 18 – 40), 54%	False belief task	right TPJ	cTBS, 30% MSO, offline, 600 pulses	Vertex stimulation
Krause et al., 2012 (Australia)	UCR	16, (26.42± 3.82, 18 – 40), 38%	Yoni task RMET	bilateral dorsal mPFC	1 Hz, 100% rMT, offline, 900 pulses	Sham coil
Lev-Ran et al., 2012[c] (Israel)	RCR†	13, (24.73± 2.89, NA), 62%	Yoni task	ventral mPFC	1Hz, 100% rMT, offline, 400 pulses	Superior temporal region stimulation
Michael et al., 2014 (Denmark)	CCR	20, (23.5, 18–40), 60%	Action-understanding task	The hand and lip area in the left M1	cTBS, 70% rMT, offline, 300 pulses	Either stimulation site as control
Pobric and Hamilton, 2006 (UK)	CCR	exp1:9, (NA, 21-35), 64%[b] exp2:9, (NA, 21-35), 64%[b]	Action- understanding task	left IFG	5Hz, 110% rMT, online, 240 pulses	left occipital cortex stimulation, Vertex stimulation, & no stimulation

Schuwerk et al., 2014 (Germany)	CCR	17, (22.2± 2.3, NA), 35%	False belief task requiring the computation of another's and one's own belief	posterior mPFC	1Hz, 100% rMT, offline, 2000 pulses	Tilt (90 degree) coil at posterior mPFC
Silani et al., 2013 (Switzerland)	CCT	45 (active: 22 control: 23), (NA, NA), 0%	Judgments of pleasantness of self-or other-experienced visuo-tactile stimulation	right SMG	1Hz, 110% rMT, offline, 900 pulses	Vertex stimulation
Uddin et al., 2006[c] (USA)	CCR	8, (26.6, NA), 25%	self–other facial discrimination task	right IPL	1Hz, 100% rMT, offline, 1200	Left IPL stimulation
Young et al., 2010 (USA)	CCR	Exp1: 8, (NA, 18-30), 38% Exp2: 12, (NA, 18-30), 42%	Moral scenarios manipulating protagonists' beliefs and action outcomes	right TPJ	Exp1: 1Hz, 70% MSO, offline, 1500 pulses Exp.2: 10Hz, 60% MSO, online, 120 pulses	5 cm posterior to the right TPJ stimulation

ACC, anterior cingulate cortex; ASD, autistic spectrum disorder; CCR, counterbalanced crossover design; CCT, clinical controlled trial; cTBS, continuous theta burst stimulation; DLPFC, dorsolateral prefrontal cortex; Exp: experiment; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; IRI, Interpersonal Reactivity Index; M1, primary motor cortex; mPFC, medial prefrontal cortex; MSO, maximum of stimulator output; NA, not available; RCR, randomised crossover design; RCT, randomised controlled trial; RMET, Reading the Mind in the Eye Test; rMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; S1, primary somatosensory area; SMG, Supramarginal *gyrus;* TPJ, temporoparietal junction; UCR, crossover design with unknown allocation

† no randomisation method reported

‡ presented as number of participants included in final analysis and the number of participants in subgroups in the parenthesis

[a] presented as the original sex ratio

[b] presented as the sex ratio of participants in the whole study

[c] not included for meta-analysis

4.4 RESULTS

4.4.1 Study characteristics

Table 4-2 summaries study characteristics. In summary, 22 studies involving 466 participants (82% males; mean age: 24.45 years; range: 18-59 years) were included in the review. For studies recruiting participants from clinical populations, there was only one study (Enticott et al., 2014), recruiting patients with ASD as participants. Sixteen of the included studies were conducted in Europe, three in North America (Keuken et al., 2011; Uddin et al., 2006; Young et al., 2010), two in Australia (Enticott et al., 2014; Krause et al., 2012) and one in Israel (Lev-Ran et al., 2012). The most common study design employed was non-randomised crossover (*n* = 15), allocating the sequence of intervention conditions with counterbalancing (*n* = 10) or unspecified (*n* = 5) method. Of the six studies randomly allocating participants, two (Enticott et al., 2014; Keuken et al., 2011) were parallel randomised controlled trials and the other four (Costa et al., 2008; Giardina, Caltagirone, & Oliveri, 2011; Kalbe et al., 2010; Lev-Ran et al., 2012) were randomised crossover trials. The remaining one between-subject study (Silani, Lamm, Ruff, & Singer, 2013) did not mention the method of participant allocation.

Various tasks were used to assess empathy, including facial expression recognition tasks with materials derived from Ekman and Friesen (1976), the RMET or its modified version, the Yoni task, scenarios using video clips assessing individuals' capability of social judgement or action-understanding, the false belief task and the faux pas task. With regard to published self-report instruments, only one study (Enticott et al., 2014) selected a self-report

measure, the IRI, as the empathy measure. The number of pulses within each experimental session ranged from 120 to 3000. The majority of the reviewed studies (*n* = 15) set the intensity of the pulses to 100% or more of RMT, while other four studies used subthreshold intensity (Costa et al., 2008; Giardina et al., 2011; Hoekert et al., 2010; Michael et al., 2014). The remaining three studies (Keuken et al., 2011; Krall et al., 2016; Young et al., 2010) selected MSO as the index of intensity. The DLPFC, mPFC (ventral or dorsal portion), TPJ, and IFG were targeted as the main sites for stimulation. The most common control condition was vertex stimulation (*n* = 11). Five studies did not report the detail of their sham protocol.

4.4.2 Quality assessment

Of the twenty-two studies included, only one study (Enticott et al., 2014) attracted a rating of “strong”, nineteen studies were rated as “moderate”, and two studies as “weak” (Appendix 8). Poor rating on selection bias was the most common reason for not reaching the “strong” quality threshold. The two weak ratings were due to vulnerability to confounders (Silani et al., 2013) and poor description of the reliability and validity of the outcome measures used (Michael et al., 2014). For rTMS reproducibility, most of the reviewed studies (*n* = 16) provided all necessary parameters, but two studies (Balconi et al., 2010; Silani et al., 2013) failed to provide information in relation to the type of coil utilised and four studies (Balconi & Bortolotti, 2012; Balconi, Bortolotti, & Gonzaga, 2011; Costa et al., 2008; Pobric & Hamilton, 2006) lacked comprehensive information about the duration of the intervention. Only three studies described adverse effects relating to the administration of rTMS, with

one study indicating no adverse effects observed (Young et al., 2010) and the other two studies reporting minor post-rTMS side effects (Enticott et al., 2014) and one syncope event (Kalbe et al., 2010).

4.4.3 Meta-analysis

4.4.3.1 Effects of rTMS on empathy in clinical populations

Since there was only one trial (Enticott et al., 2014) involving participants with a mental disorder it was not possible to conduct a meta-analysis to examine the rTMS effect on empathy in clinical populations. This study (Enticott et al., 2014) showed that deep high frequency rTMS applied bilaterally to the dorsal mPFC in patients with ASD did not have a statistically significant facilitatory effects on empathy (g = -0.22; 95% CI, -1.55 to -0.01, p = 0.016), cognitive empathy (g = -0.32; 95% CI, -1.07 to 0.44, p = 0.41), or affective empathy (g = 0.08; 95% CI, -0.66 to 0.82, p = 0.21).

4.4.3.2 Effects of rTMS on empathy in healthy volunteers

Twenty-four trials extracted from reports of 17 studies were included for the meta-analysis of the effects of rTMS on empathy. This revealed a significant small overall effect size (g = 0.29; 95% CI, 0.10 to 0.48, p = 0.003) as plotted in Figure 4-3. A moderate level of heterogeneity was observed across the studies (Q_{23} = 39.22, p = .019; I^2 = 41.4%). Separate meta-analyses were conducted for trials involving cognitive empathy with its two components; cognitive and affective ToM. However, it was not possible to conduct a meta-analysis on the effects of rTMS on affective empathy due to lack of studies in the field.

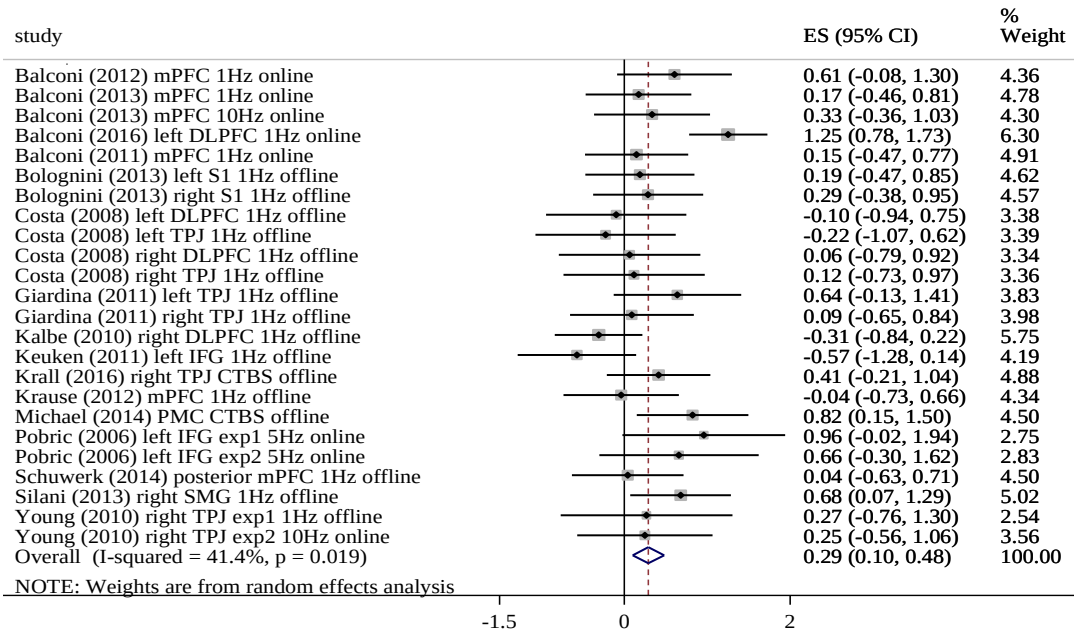


Figure 4-3 Statistical summary and forest plot of effect sizes for empathy

Abbreviations: CTBS, continuous theta burst stimulation; DLPFC, dorsolateral prefrontal cortex; ES, effect size; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex; PMC, primary motor cortex; S1, primary somatosensory area; SMG, supramarginal gyrus; TPJ, temporoparietal junction

4.4.3.3 Effects of rTMS on cognitive ToM

The meta-analysis of findings from 16 trials on the effects of rTMS on cognitive ToM showed a non-significant mean effect (g = 0.12, 95% CI, -0.15 to 0.40, p = .39; see also Figure 4-4). The trim and fill procedure applied suggested an estimated mean effect size of -0.13 after imputing five missing trials (Appendix 9). A moderate heterogeneity was found across trials (Q_{16} = 30.64, p = .01; I^2 = 51.0%). The funnel plot was asymmetrical by visual inspection (Figure 4-5), but neither the Begg's test (z = 0.95, p = .34) nor the Egger's test (intercept$_{16}$ = 2.42, t = 1.18, 2-tailed p = .26) suggested publication bias.

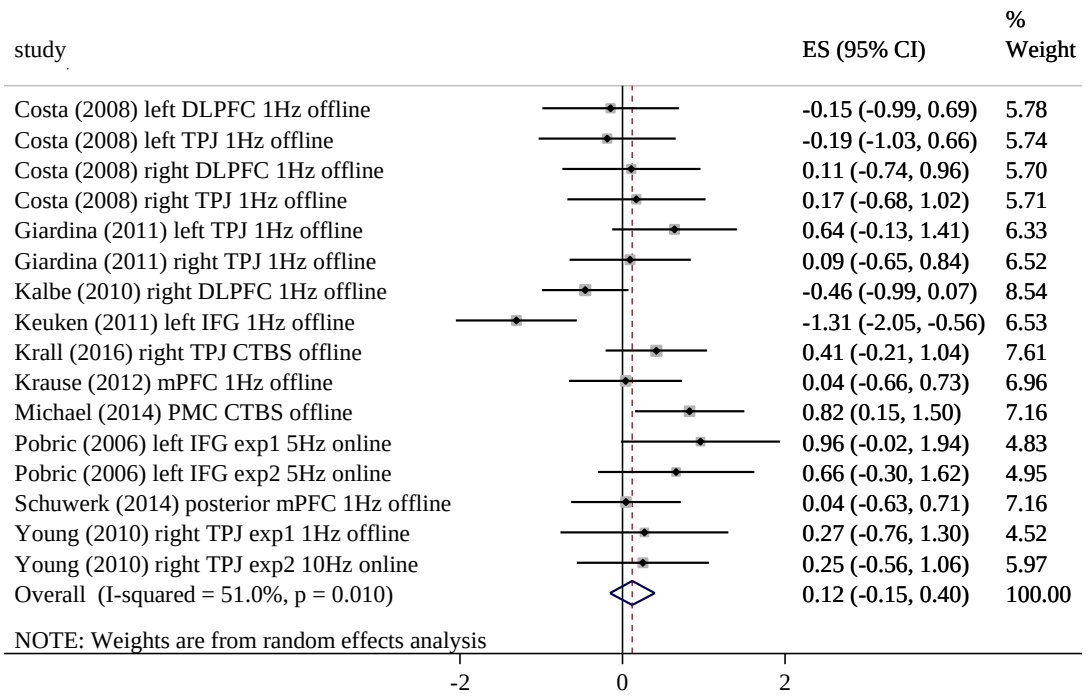


Figure 4-4 Statistical summary and forest plot of effect sizes for cognitive ToM

Abbreviations: CTBS, continuous theta burst stimulation; DLPFC, dorsolateral prefrontal cortex; ES, effect size; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex; PMC, primary motor cortex; TPJ, temporoparietal junction

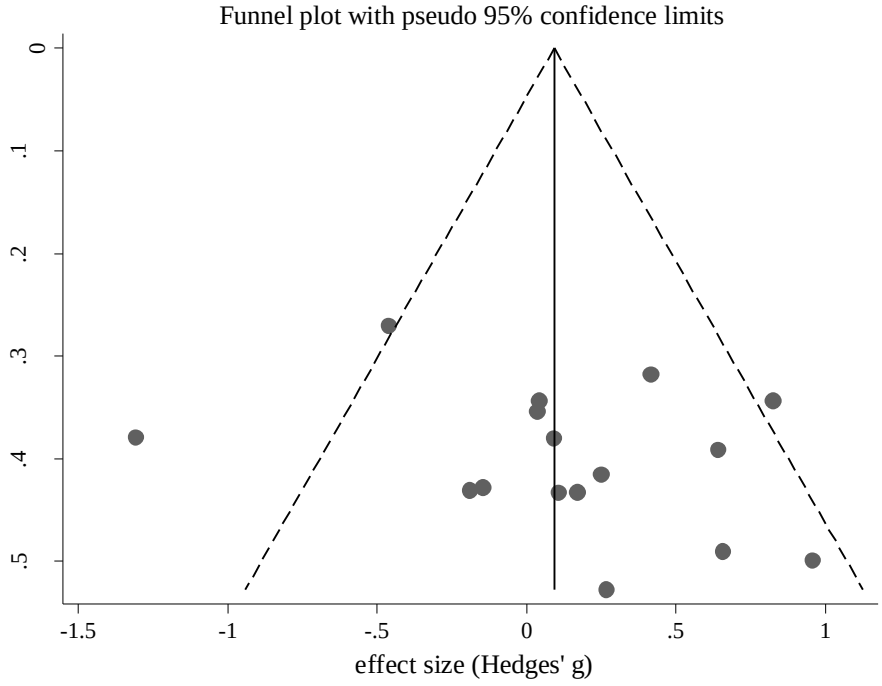


Figure 4-5 Funnel plot of the cognitive ToM trials in the meta-analysis

The subgroup analyses (Table 4-3) revealed a non-significant mean effect for inhibitory rTMS (g = 0.03, 95% CI, -0.27 to 0.33, p = .83) but a significant one for excitatory rTMS (g = 0.58, 95% CI, 0.05 to 1.10, p = .03). For the stimulation paradigm, since all trials with offline paradigms applied inhibitory rTMS and all trials with online paradigms applied excitatory rTMS, the results of the subgroup analysis were the same (offline: g = 0.03, 95% CI, -0.27 to 0.33, p = .83; online: g = 0.58, 95% CI, 0.05 to 1.10, p = .03). Moreover, the subgroup analysis for study designs revealed a non-significant mean effect size for trials with randomised design (g = -0.16, 95% CI, -0.56 to 0.25, p = .45) but a significant one for trials with non-randomised design (g = 0.40, 95% CI, 0.13 to 0.67, p = .004). Furthermore, the subgroup analysis for stimulation sites revealed non-significant mean effect sizes for all stimulation sites, including TPJ (g = 0.26, 95% CI, -0.04 to 0.56, p = .09), DLPFC (including IFG) (g = -0.09, 95% CI, -0.71 to 0.53, p = .79) and mPFC (g = 0.04, 95% CI, -0.44 to 0.52, p = .87). Finally, the subgroup analysis for the nature of outcome measure tasks revealed non-significant mean effect sizes for false-belief tasks (g = 0.10, 95% CI, -0.21 to 0.41, p = .51) and intention attribution tasks (g = -0.10, 95% CI, -0.57 to 0.37, p = .69) but a significant large mean effect size for action-understanding tasks (g = 0.82, 95% CI, 0.34 to 1.30, p = .001).

The meta-regression analysis across trials showed that none of between-study variables significantly predicted the effects of rTMS (mean age of participants: β = 0.08, p = .55; gender ratio: β = -1.01, p = .11; intensity of stimulation: β = -0.03, p = .26; number of pulses per condition: β = -0.005, p = .45; weighted number of pulses: β = 0.005, p = .48).

Table 4-3 Subgroup analyses

	Pooled effect size			Between-study heterogeneity		
	k	Effect size (Hedges' *g*)	95% CI	*Q* test	I^2	*p* value
Cognitive ToM						
Total	16	0.12	-0.15-0.40	30.64	51.0%	0.010
Effect of stimulation						
Inhibitory	13	0.03	-0.27-0.33	25.66	53.2%	0.012
Excitatory	3	0.58*	0.05-1.10	1.23	0.0%	0.539
Stimulation paradigm						
Online	3	0.58*	0.05-1.10	1.23	0.0%	0.539
Off-line	13	0.03	-0.27-0.33	25.66	53.2%	0.012
Study design						
Randomised	8	-0.16	-0.56-0.25	15.83	55.8%	0.027
Non-randomised	8	0.40*	0.13-0.67	5.40	0.0%	0.611
Stimulation site						
TPJ	7	0.26	-0.04-0.56	2.50	0.0%	0.869
DLPFC (including IFG)	6	-0.09	-0.71-0.53	18.34	72.7%	0.003
mPFC	2	0.04	-0.44-0.52	0.00	0.0%	0.992
Type of used task						
False-belief	6	0.10	-0.21-0.41	1.81	0.0%	0.875
Intention attribution	7	-0.10	-0.57-0.37	16.87	64.4%	0.010
Action understanding	3	0.82*	0.34-1.30	0.18	0.0%	0.912
Affective ToM						
Total	15	0.26*	0.02-0.50	25.98	46.1%	0.026
Effect of stimulation						
Inhibitory	14	0.25	-0.00-0.51	25.97	49.9%	0.017
Excitatory	1	0.33	-0.36-1.03	-	-	-
Stimulation paradigm						
Online	5	0.52*	0.05-1.00	11.95	66.5%	0.018
Off-line	10	0.10	-0.12-0.32	6.08	0.0%	0.732
Study design						
Randomised	6	-0.06	-0.35-0.50	0.91	0.0%	0.970
Non-randomised	9	0.43*	0.12-0.73	16.71	52.1%	0.033
Stimulation site						
TPJ	2	-0.14	-0.74-0.46	0.26	0.0%	0.611
DLPFC (including IFG)	5	0.28	-0.35-0.91	19.03	79.0%	0.001
mPFC	5	0.22	-0.07-0.52	2.11	0.0%	0.716
Type of used task						
emotion recognition	8	0.32	-0.06-0.69	20.66	66.1%	0.004
faux-pas recognition	4	-0.08	-0.50-0.35	0.35	0.0%	0.950

CI, confidence interval; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex; ToM, Theory of Mind; TPJ, temporoparietal junction
* $p < .05$

4.4.3.4 Effects of rTMS on affective ToM

The meta-analysis of results from 15 trials on the effects of rTMS on affective ToM showed a significant small mean effect (g = 0.26, 95% CI, 0.02 to 0.50, p = .03) with a moderate heterogeneity (Q_{14} = 25.98, p = .03; I^2 = 46.1%; see also Figure 4-6). The funnel plot (Figure 4-7) and the Egger's test (intercept$_{17}$ = -4.39, t = -2.55, 2-tailed p = .02) showed evidence of publication bias However, the Begg's test (z = 1.48, p = .14) and the trim and fill procedure did not show evidence of publication bias (Appendix 9).

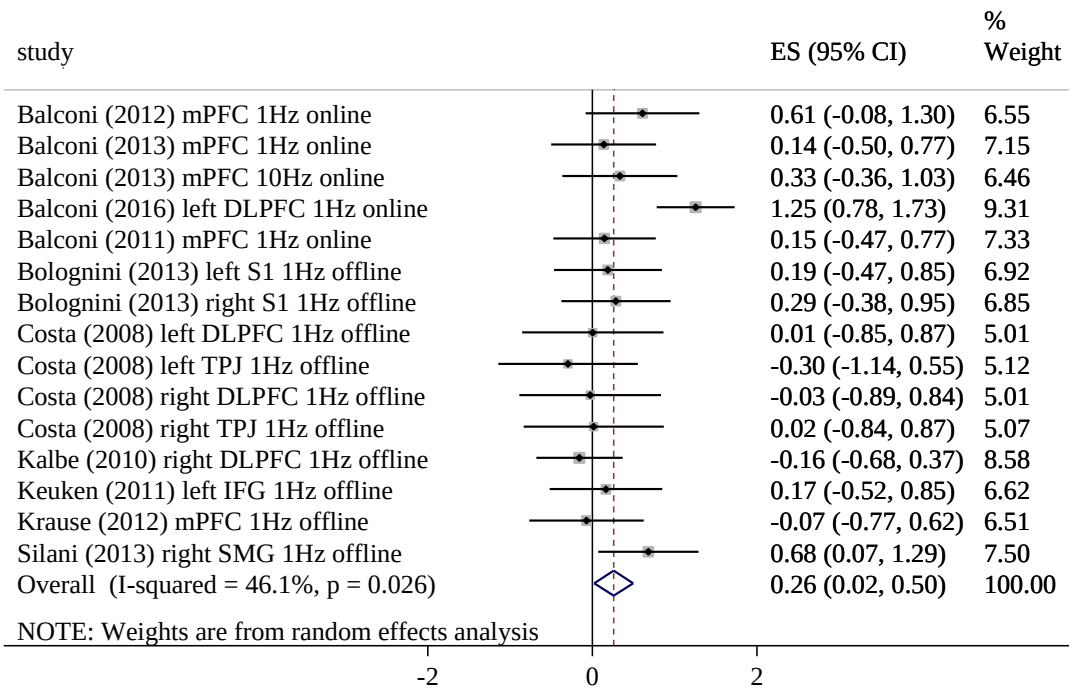


Figure 4-6 Statistical summary and forest plot of effect sizes for affective ToM

Abbreviations: DLPFC, dorsolateral prefrontal cortex; ES, effect size; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex; PMC, primary motor cortex; S1, primary somatosensory area; SMG, Supramarginal gyrus; TBS, theta burst stimulation; TPJ, temporoparietal junction

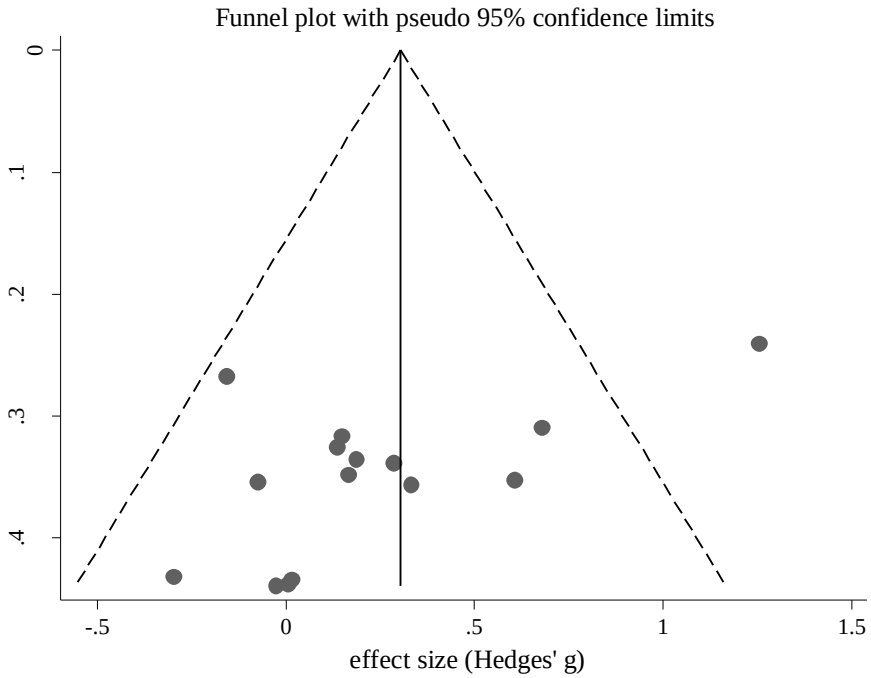


Figure 4-7 Funnel plot of the affective ToM trials in the meta-analysis

Further subgroup analyses (Table 4-3) showed that the mean effect size of inhibitory rTMS trials failed to reach statistical significance (*g* = 0.25, 95% CI, -0.00 to 0.51, *p* = .052). It was not possible to calculate the mean effect size for excitatory rTMS since there was only one trial (Balconi & Canavesio, 2013) in this subgroup which showed a positive effect (*g* = 0.33). For stimulation paradigms, trials with "offline" paradigms revealed a non-significant mean effect (*g* = 0.10, 95% CI, -0.12 to 0.32, *p* = .35) while trials with "online" paradigm showed a significant moderate effect (*g* = 0.52, 95% CI, 0.05 to 1.00, *p* = .03). The subgroup analysis for study design revealed a non-significant mean effect size for trials with randomised design (*g* = -0.06, 95% CI, -0.36 to 0.24, *p* = .71) but a significant one for trials with non-randomised design (*g* = 0.43, 95% CI, 0.123 to 0.73, *p* = .006). Regarding the sites of stimulation, all three locations revealed non-significant mean effect sizes (TPJ: *g* = -0.14,

95% CI, -0.74 to 0.46, p = .65; DLPFC [including IFG]: g = 0.28, 95% CI, -0.35 to 0.91, p = .39; mPFC: g = 0.22, 95% CI, -0.07 to 0.52, p = .14). For type of measurement, the mean effect sizes for trials using emotion recognition tasks (g = 0.32, 95% CI, -0.06 to 0.69, p = .10) and faux-pas recognition tasks (g = -0.08, 95% CI, -0.50 to 0.35, p = .73) were not significant.

The meta-regression analysis across trials showed that none of between-study variables significantly predicted the effects of rTMS (mean age of participants: β = 0.07, p = .44; gender ratio: β = -0.68, p = .22; intensity of stimulation: β = 0.15, p = .07; number of pulses per condition: β = 0.02, p = .11; weighted number of pulses: β = -0.02, p = .11).

4.5 DISCUSSION

This study aimed to examine the literature on the effects of rTMS on empathy and, where relevant, to determine which intervention parameters were associated with stronger effects. Our findings show that rTMS has a significant but small overall effect on empathy in healthy participants and that this effect varied according to empathy domains, cognitive or affective ToM. It has not been possible to draw valid conclusions regarding the effect of rTMS on empathy in clinical population as there was only one study conducted in the field.

The meta-analysis of rTMS studies relating to cognitive ToM revealed a non-significant effect size indicating that rTMS may not be effective in modulating cognitive ToM. Moreover, the results suggested that there might be five unpublished trials investigating this issue with negative findings. In contrast, a significant effect size was found on the meta-analysis of rTMS studies for affective ToM though the magnitude of effect was small. These findings of dissimilar effects of rTMS support the idea of examining subcomponents of empathy separately as they are associated with distinct brain regions (Dvash & Shamay-Tsoory, 2014).

Our subgroup analyses further identified parameters associated with a positive effect of rTMS, including excitatory vs. inhibitory rTMS and online vs. offline paradigms. However, these finding should be interpreted with caution due to the relatively small number of trials, particularly for excitatory rTMS. Although previous studies (e.g., Robertson et al., 2003) suggest that the duration of the rTMS after-effect only persists for half of the stimulation time,

physiological evidence indicates that the rTMS after-effect decays gradually with time (Eisenegger et al., 2008). Nevertheless, given that completion of conventional tasks measuring empathy is time-consuming, it is less likely to detect significant rTMS effect on empathy from experiments with offline paradigm.

Surprisingly, the subgroup analysis by stimulation site did not reveal statistically significant mean effects across different brain regions pertaining to specific empathetic components. The literature suggests differential roles of specific brain regions: The dorsal part of mPFC and TPJ (particularly the right side) for cognitive ToM (e.g., Denny, Kober, Wager, & Ochsner, 2012) and the ventral part of mPFC and IFG for affective ToM (Dal Monte et al., 2014; Sebastian et al., 2012). It would thus be expected to find significant effects if rTMS is administered to these regions, but not to other regions. However, we found no significant effect applying rTMS to TPJ for cognitive ToM or IFG for affective ToM and only one included trial (Keuken et al., 2011) explored affective ToM targeting at these crucial regions (e.g., IFG), a firm conclusion cannot be drawn at this stage.

It is worth noting here that the issue of spatial resolution is an inherent limitation of TMS research. The issue may be further compromised when non-imaging guided techniques are utilised to localise the stimulation sites. With this in mind, and since a considerable number of studies included in this review (Balconi & Bortolotti, 2012; Balconi et al., 2010; Krause et al., 2012; Schuwerk, Schecklmann, et al., 2014) did not utilise imaging guided techniques, we have categorised the studies according to the effects of TMS

on relatively large regions of the brain rather than smaller ones while performing subgroup analyses. Nevertheless, the results need to be interpreted with caution.

Meta-regression revealed no differential effects in relation to participant characteristics (age, gender) or stimulation parameters (intensity, number of pulses, weighted number of pulses). This may be due to the low heterogeneity detected in relation to participants' age and gender ratio. Contrary to the findings of other meta-analytic studies (e.g., Chou, Hickey, Sundman, Song, & Chen, 2015), rTMS parameters did not contribute significantly to effect sizes. A number of explanations exist as to why these findings were not replicated in this review. First, the number of studies included in this review was slightly higher than 10, the minimum number required to attain sufficient statistical power (Borenstein, Hedges, Higgins, & Rothstein, 2009c). Second, the impact of the rTMS parameters may only be evident when rTMS is applied to the brain region corresponding to the task measured. Third, empathy is a multifaceted construct involving a network of brain regions, and since the effects of TMS are dose-dependent, a larger number of sessions and pulses per session may be required to modulate empathy.

Future research should examine a number of pertinent issues. For example, some of the included studies (Balconi & Bortolotti, 2013; Balconi & Canavesio, 2016) suggested that baseline level of empathy can moderate the inhibitory effect of low frequency rTMS on facial emotional recognition. Interestingly, they found people with higher levels of empathy performed better under control conditions than those with lower levels of empathy when the activity of

the dorsal mPFC was inhibited. However, for the effect of facilitatory rTMS for enhancing empathetic ability, the role of baseline empathy level has not yet been investigated which is obviously a crucial issue for rTMS in clinical application. In addition, as speculated in a number of included studies, the behavioural tasks selected might not be appropriate for outcome measures due to their low sensitivity to detect rTMS-induced effects (e.g., Enticott et al., 2014; Keuken et al., 2011; Krause et al., 2012; Lev-Ran et al., 2012; Schuwerk, Schecklmann, et al., 2014). Gender related variables are also expected to be taken into account in future studies. Although the meta-regression revealed that sex ratio did not play a role in between-study heterogeneity resulting in the rTMS effects on both cognitive and affective ToM, the sex differences in empathy should not be overlooked. Quantitatively, females have significantly higher cognitive and affective empathy than males (Reniers et al., 2011). Qualitatively, males and females tend to respond differently to stimuli from different sex characters and of different emotional dimensions (Kynast & Schroeter, 2018). Finally, it might be too simplistic to expect that increased excitability contributes to behavioural improvement and decreased excitability to a deterioration as others have also suggested (Sandrini et al., 2011).

4.5.1 Strengths and limitations

A major strength of this study is that some of the studies included were relatively well designed with low dropouts rates and high reproducibility of rTMS protocols. However, the study suffered a number of limitations in relation to selection bias, reflected by restricted participants' age range,

recruitment resources and reporting adverse of effects which is essential in TMS studies (Rossi et al., 2009). Further, the subgroup analysis of study design showed that more significant effects were found in non-randomised than randomised trials. This raises the question whether the results of the current study may be vulnerable to some methodological limitations. However, since a majority of included studies were rated as equivalently moderate in quality assessment, the source of heterogeneity is less likely from allocation bias and needs further investigation. While the research on rTMS application into alteration of empathy is still in its infancy, this systematic review with meta-analysis applied a broad range of search terms to enrol eligible studies with variant outcome measures and different rTMS protocols. We included both randomised and non-randomised trials as a considerable number of studies in this field used non-randomised design. Multiple databases were thoroughly searched to minimise potential publication bias. However, a number of studies could not be included in the meta-analysis due to not reporting effect sizes, outcome measures not matching our inclusion criteria and the presence of possible publication bias. The majority of included studies applied empathy tasks providing multiple outcomes, such as accuracy and reaction time. We dealt with these multiple outcomes by averaging the effect sizes though this may have underestimated the size of effect. The number of studies included in the meta-analysis is relatively small, and this in conjunction with considerable levels of heterogeneity across the studies may have affected the power of the study. A caveat to generalise the current findings to females should be taken with care since the participants in the included studies were predominant males. Finally, only one study involving

interventions in a clinical population was included in the review and no meta-analytic data could therefore be provided for clinical samples. One possible reason may be that clinical trials tend to focus on therapeutic effects on overall symptom reduction; therefore, empathy would not be considered as a primary outcome. Another possibility may be that some studies used neurophysiological measurements to index empathy. These outcome measurements are out of the scope of the current systematic review since they are less validated with relatively low specificity to the empathetic process (Neumann et al., 2015). This highlights the urgent need to conduct clinical trials in the field. Moreover, these neurophysiological empathy measurements require further research to confirm their validity and reliability.

4.6 CONCLUSION

The present review with meta-analysis demonstrated that rTMS has a discernible contribution to the alteration in different components of empathy although the effect sizes may not be as favourable as expected. The most encouraging finding for clinical implications is the effect of excitatory rTMS on enhancing *affective ToM*. Therefore, this review may help researchers having an interest in exploring rTMS impacts on empathy tailor their rTMS protocols to maximise its effect. Future studies in the field can potentially examine the effects of excitatory rTMS in clinical populations with impaired empathetic capabilities, such as those with ASD, psychopathy and schizophrenia. However, we do not currently know whether the same effects will be observed in these populations. rTMS parameters may have to be refined further to maximise the effects on crucial brain regions and there is a need to develop ecologically validated and sensitive empathy tasks for rTMS experiments.

4.7 ACKNOWLEDGEMENTS

This research received no specific grant from any funding agency, commercial or not-for-profit sectors**.**

CHAPTER 5 : THE EFFECTS OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ON IMPULSIVITY IN HEALTHY ADULTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

This chapter is presented in the format of a published paper as outlined in 'Remarks on Presentation of Thesis in Alternative Format' namely Yang, C.-C., Völlm, B., & Khalifa, N. (2018). The effects of rTMS on impulsivity in normal adults: a systematic review and meta-analysis. *Neuropsychology Review*. doi: 10.1007/s11065-018-9376-6

Authors

Cheng-Chang Yang[1]*, Birgit Völlm[1,2], Najat Khalifa[1,2]

[1]Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, UK

[2]Nottinghamshire Healthcare NHS Foundation Trust, UK

***Author for correspondence**

Contact information:

Institute of Mental Health

University of Nottingham Innovations Park

Triumph Road

Nottingham, NG7 2TU

UK

Cheng-Chang Yang Email: cheng-chang.yang@nottingham.ac.uk

Birgit Völlm Email: birgit.vollm@nottingham.ac.uk

Najat Khalifa Email: najat.khalifa@nottingham.ac.uk

5.1 ABSTRACT

Background: Impulsivity is a multi-dimensional construct that is regarded as a symptom of many psychiatric disorders. Harm resulting from impulsive behaviour can be substantial for the individuals concerned, people around them and the society they live in. Therefore, the importance of developing therapeutic interventions to target impulsivity is paramount.

Aims and methods: We conducted a systematic review and meta-analysis of the literature from AMED, Embase, Medline, and PsycINFO databases on the use of repetitive transcranial magnetic stimulation (rTMS) in healthy adults to modulate different subdomains (motor, temporal and reflection) of impulsivity.

Results: The results indicated that rTMS has distinct effects on different impulsivity subdomains. It has a significant, albeit small, effect on modulating motor impulsivity (g = 0.30, 95% CI, 0.17 to 0.43, p < .001) and a moderate effect on temporal impulsivity (g = 0.59, 95% CI, 0.32 to 0.86, p < .001). Subgroup analyses (e.g., excitatory vs. inhibitory rTMS, conventional rTMS vs. theta burst stimulation, analyses by stimulation sites, and type of outcome measure used) identified key parameters associated with the effects of rTMS on motor and temporal impulsivity. Age, sex, stimulation intensity and the number of pulses were not significant moderators for effects of rTMS on motor impulsivity. Due to lack of sufficient data to inform a meta-analysis, it has not been possible to assess the effects of rTMS on reflection impulsivity.

Conclusions: The present findings provide preliminary evidence that rTMS can be used to modulate motor and temporal impulsivity in healthy individuals.

Further studies are required to extend the use of rTMS to modulate impulsivity in those at most risk of engaging in harmful behaviour as a result of impulsivity, such as patients with offending histories and those with a history of self-harming behaviour.

Key words:

Impulsivity; TMS; theta burst stimulation; brain stimulation; response inhibition; delay discounting

5.2 INTRODUCTION

Impulsivity is an important behavioural aspect of our daily life. It encompasses such actions as making premature decisions, favouring immediate over delayed reward, and failure to inhibit prepotent motor responses. Impulsivity is a multi-dimensional concept (Caswell et al., 2016; Evenden, 1999b) for which three different facets have been identified based on recent laboratory findings, including motor, temporal and reflection impulsivity. Motor impulsivity, also known as response inhibition, reflects the inability to inhibit a prepotent behavioural response. Delay-discounting (also referred to as temporal impulsivity) reflects failure to delay gratification. Reflection or cognitive impulsivity refers to the tendency to make premature decisions without sampling enough information or disadvantageous decisions which favour risky options (Verdejo-Garcia et al., 2008).

Several brain areas have been implicated in impulsivity (Fineberg et al. 2014). A fronto-subcortical network encompassing the right inferior frontal gyrus (rIFG) and basal ganglia (Aron & Poldrack, 2005; Chambers et al., 2009; Juan & Muggleton, 2012; Wilbertz et al., 2014) has been implicated in motor impulsivity, whereas a fronto-limbic network encompassing ventromedial prefrontal cortex (vmPFC), anterior cingulate cortices (ACC) and basal ganglia is thought to play an important role in temporal impulsivity (Peters & Buchel, 2011). In contrast, the neurobiological underpinning of reflection impulsivity appears to have received less attention in the literature.

Impulsivity plays a prominent role in psychopathology (Cyders, 2013) and has been regarded as a symptom of several psychiatric disorders, such as

attention deficit hyperactivity disorder (Musser et al., 2013), schizophrenia (Matsuzawa et al., 2015), obsessive compulsive disorder (Endrass et al., 2010), impulse-control disorders, borderline personality disorder, antisocial personality disorder, bipolar affective disorder, and SUDs (American Psychiatric Association, 2013; Fineberg et al., 2014). Impulsivity may partly explain the high rates of suicide and offending behaviour associated with some of these disorders particularly borderline personality disorder (Brevet-Aeby et al., 2016). In addition, impulsivity in early life is regarded as a significant predictor of future physical health and delinquent behaviour (Moffitt et al., 2011). Furthermore, impulsivity has been included as a core criminogenic factor in classical criminology theories (Gottfredson (Gottfredson & Hirschi, 1990) and an important risk factor of violence among both healthy (Chamorro et al., 2012) and clinical populations (Bjørkly, 2013; Singh, Serper, Reinharth, & Fazel, 2011).

The literature reviewed above indicates that in some clinical populations, impulsivity may play a role in such behaviours as aggression, self-harm or suicidality and substance abuse and this in conjunction with other emotional and psychological factors, may cause significant distress for the individual concerned and people around them. Given such consequences, the importance of developing interventions to target impulsive behaviour is paramount. While conventional psychological and pharmacological interventions have been used to target impulsivity within the rubric of wider dysfunctional behaviour (Tomko, Bountress, & Gray, 2016), there currently exist no specific interventions to target impulsivity.

Evidence is accumulating that Transcranial Magnetic Stimulation (TMS) can be used to modulate impulsivity. TMS is a non-invasive technique that has been used to modulate brain activity via brief, high-intensity magnetic pulses delivered through an electromagnetic coil placed on the surface of scalp over the brain area of interest. The stimulation pulses are generated by passing currents with a stimulator through the coil, producing a focal magnetic field which induces localised neuronal depolarization in the area beneath the coil (Wagner et al., 2007). Repetitive TMS (rTMS) refers to delivering multiple stimuli in trains instead of single-pulse stimulation over the target cortical region. The frequency of rTMS determines its effect on the neurons of the targeted brain regions. Low frequency rTMS of about 1 Hz, exerts an inhibitory function by reducing cortical excitability, whereas high frequency rTMS of about 5 Hz or more typically has a facilitatory effect, which tends to increase cortical excitability. Recently, a newer form of high-frequency rTMS protocol, namely theta burst stimulation (TBS) which exerts similar effects on brain activity but with lower magnetic intensity, has been utilised (Rossini et al., 2015; Thut & Pascual-Leone, 2010). TBS entails delivering pulses in bursts of three stimuli at 50 Hz with an inter-burst interval of 200 ms. Intermittent TBS (iTBS) enhances cortical excitability whereas continuous TBS (cTBS) has the opposite effect (Huang et al., 2005).

The utility of TMS in modulating brain activity has been demonstrated in the field of neuroscience (Luber & Lisanby, 2014). Additionally, over the past two decades, rTMS has widely been used to treat a variety of neurological and psychiatric disorders (Wassermann & Zimmermann, 2012), including depression (Sabesan et al., 2015), obsessive-compulsive disorder

(Mantovani, Simpson, Fallon, Rossi, & Lisanby, 2010), migraine, and Parkinson's disease (Benninger et al., 2012). It has also been used to modulate impulsivity with some promising results (Brevet-Aeby et al., 2016). Existing reviews have paid attention to the excitatory or inhibitory effect of rTMS on various dimensions of impulsivity, but to our knowledge, no meta-analysis has been conducted to comprehensively assess the efficacy of rTMS in the neuromodulation of impulsivity. There is a dearth of literature on the use of rTMS to modulate impulsivity in clinical populations, and the extant literature in the field is not sufficiently large to inform a meta-analysis. Therefore, studies involving healthy participants are potentially relevant and can help elucidate the effects of rTMS on specific domains of impulsivity and provide comparison data for groups diagnosed with specific disorders. This is supported by the view that symptoms of mental disorders are displayed on a continuum along normality, and the difference between the two is one of degree (Holroyd & Umemoto, 2016). In support of this view, Zisner and Beauchaine (2016) found that normal variations in impulsive tendencies are reflected in core aspects of personality while variations in trait impulsivity confer vulnerability to clinical psychopathology.

With this in mind, we aimed to conduct a systematic review and meta-analysis of prospective empirical studies on the effects of rTMS on impulsivity in healthy adults. Specifically, we aimed to determine which rTMS parameters or brain regions are associated with prominent effects on specific subdomains of impulsivity. The main advantage that this study confers over previous reviews in that is has systematically examined the effects of TMS on domains of impulsivity using meta-analytic technique. This has the added advantage of

providing precise estimates of the efficacy of TMS in modulating impulsivity and identifying and measuring sources of heterogeneity among studies. This line of enquiry helps inform the design of future studies to better understand the neurobiology of such behaviour to guide future interventions.

5.3 METHODS

We followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (Liberati et al., 2009a; Moher et al., 2009) in the reporting of our findings. The predetermined criteria, in terms of population, interventions, comparators, outcomes and study designs (PICOS), were followed to identify potentially eligible studies for the systematic review and meta-analyses.

5.3.1 Eligibility Criteria

Empirical studies were included in the review if they (1) involved healthy adult participants, (2) used rTMS as an active intervention, (3) had a comparison group or control condition, and (4) used at least one behavioural task to measure impulsivity. Studies involving children or people with neuropsychiatric disorders were excluded. The definitions of impulsivity and its subdomains were in accordance with previous literature (Caswell et al., 2015; Verdejo-Garcia et al., 2008). The behavioural tasks measuring impulsivity included, but were not limited to, the following tasks. Tasks measuring motor impulsivity included the Stop Signal Task (SST; Logan, 1994), the Go-No-Go task (GNG; Conners, Epstein, Angold, & Klaric, 2003), and the Stroop Colour and Word Test (SCWT; Stroop, 1935) and their variant versions. Tasks measuring temporal impulsivity included the Delay Discounting Task (Kirby, 2009). The Information Sampling Task (Clark et al., 2006) and tasks involving risky or disadvantageous decisions, such as the Ballon Analogue Risk Task (Lejuez et al., 2002) and the Iowa Gambling Task

(Bechara et al., 1994), were included to index reflection impulsivity. No restrictions were imposed in respect of publication date or language.

5.3.2 Information Sources and Search

The literature search was performed on four electronic databases (AMED, Embase, Medline, PsycINFO) until 17th February 2017. ”Transcranial magnetic stimulation”, ”TMS“, "theta burst stimulation" or "TBS" combined with “impulsiv*”, "self-regulation", "inhibitory control", "impulse control", "delay discounting", "response inhibition", "information sampling", "stop signal", "temporal discounting", "stroop", "inhibition", "go-no-go" were searched as keywords. The first author (CCY) performed the search and the search terms were confirmed after discussion with the other two authors (NK and BV). Filters regarding the age of participants (adult) and publication type were added where applicable. No language restriction was set. The full search strings are shown in Appendix 10. References of candidate citations were searched manually for potentially eligible studies missed by the electronic searches.

5.3.3 Study Selection

The articles identified via the search strategy were initially screened by titles and abstracts by the first author (CCY) to identify potentially eligible studies as defined by the PICOS criteria. The full texts of the potentially eligible articles were then reviewed in detail by the same author. In cases where eligibility for inclusion was unclear, the other two authors (NK and BV) independently reviewed the articles, and the final decision on inclusion was reached through consensus.

5.3.4 Data Collection Process and Data Items

Data extraction was performed by the first author (CCY) in discussion with the other authors. The authors regularly discussed the data collection process to resolve disagreements and to ensure consistency. A standardised form (Appendix 1) was used to extract information concerning authors, study objectives, sample characteristics, inclusion and exclusion criteria, study design, experimental processes, rTMS protocols, outcome variables, and analytic strategy. In cases where the means and standard deviations of key outcome measures were only presented in the diagrams, these parameters were estimated from the available figures.

5.3.5 Risk of Bias in Individual Studies

The methodological quality and the risk of bias for each study were assessed using the Quality Assessment Tool for Quantitative Studies (National Collaborating Centre for Methods and Tools, 2008). This was in accordance with recommendations by the Cochrane Collaboration (Armstrong et al., 2011). The domains of assessment included selection bias, study design, confounders, blinding, data collection method, and withdrawals and dropouts. The quality assessments included supplementary information on adverse effects. This quality assessment allowed us to classify studies as having a low, moderate, or high quality. Study quality was assessed by a single reviewer with verification by a second reviewer (BV).

5.3.6 Summary Measures

The effect size was recorded as a positive value if the effect of active rTMS was in the predicted direction and a negative one if it was in the opposite direction. For example, post inhibitory rTMS performance would be expected to be worse than baseline. Moreover, in cases where a study entailed stimulation of multiple sites within the same study, stimulation at each site was regarded as a standalone trial for the purpose of effect size calculation. Each trial was used as the unit of analysis to obtain the effect size in the meta-analysis. Since some studies included more than one effect, this nesting of effects within studies violates assumptions of independence and may contribute to imprecise effect size calculations (Borenstein, Hedges, Higgins, & Rothstein, 2009d). To adjust for the correlation of effects within studies, a multi-level model analysis was conducted using the Generalized Linear Latent and Mixed Model (gllamm) in STATA (Rabe-Hesketh, Skrondal, & Pickles, 2002, 2005) for meta-analysis. For studies involving more than one control group or condition (e.g., one group receiving rTMS at a control site and another receiving sham stimulation), only the comparison between experimental and sham group (condition) was selected. The effect sizes, represented as unbiased Hedges ' *g* and 95% confidence intervals (CIs), were computed by dividing the pre- and post-stimulation differences between experimental (real stimulation) and control (sham stimulation) conditions by the pooled pre-stimulation standard deviation (Morris, 2008).

5.3.7 Synthesis of Results & Measures of Inconsistency

It is well established that measures of impulsivity subdomains correlate weakly, if at all, with each other (e.g., Caswell et al. 2015; Yang, Khalifa, & Völlm, 2018b) due to having distinct neurobiological underpinnings (Fineberg et al., 2014). Therefore, we aimed to conduct a series of meta-analyses with the random-effects model to assess the effect of rTMS by subdomains of impulsivity; namely motor, temporal and reflection impulsivity. The *Q,* I^2 and T^2 statistics (Higgins & Thompson, 2002; Higgins et al., 2003) were used to assess heterogeneity between studies. *Q* provides significance testing for heterogeneity (*p*-value ≤ .05) which is calculated as the weighted sum of squared deviations of each study's effect size from the overall mean effect size (Borenstein et al., 2009a). I^2 estimates the percentage of the variability in effect estimates that is due to heterogeneity rather than chance. An I^2 value of greater than 50% was deemed as indicative of moderate heterogeneity (Deeks et al., 2011). As I^2 is a measure of relative heterogeneity, T^2 is the variance of the true effect sizes, as an estimate of absolute heterogeneity. When T^2 increases, the observed variance increases or the variance within-studies decreases (Borenstein et al., 2007).

5.3.8 Risk of Bias - Publication Bias

Funnel plots (Egger & Smith, 1995), the Egger test (Egger, Smith, Schneider, & Minder, 1997), and Begg and Mazumdar rank correlation tests (Begg & Mazumdar, 1994) were used to test for the presence of a potential publication bias.

5.3.9 Additional Analyses

To identify variables contributing to alternation of impulsivity, pre-specified subgroup analyses were performed with the unit of trial by merging the data according to the rTMS parameters, including effects (“excitatory” vs. “inhibitory”), type of rTMS (“conventional rTMS” vs. “TBS”), stimulation sites, and tasks of outcome measurements. Meta-regression was employed to examine the impact of between-study variation on study effect sizes using mean age and male ratio of the participants, intensity of stimulation, and total number of pulses per condition as predictor variables. All quantitative analyses were performed using Stata 13.1 (StataCorp, 2013).

5.4 RESULTS

5.4.1 Study Selection

Of the 3423 citations originally identified, 28 publications met the study inclusion criteria and were included in the systematic review; however, one article (Upton, Cooper, Laycock, Croft, & Fitzgerald, 2010) was excluded from the meta-analyses due to inability to obtain the effect size (Figure 5-1).

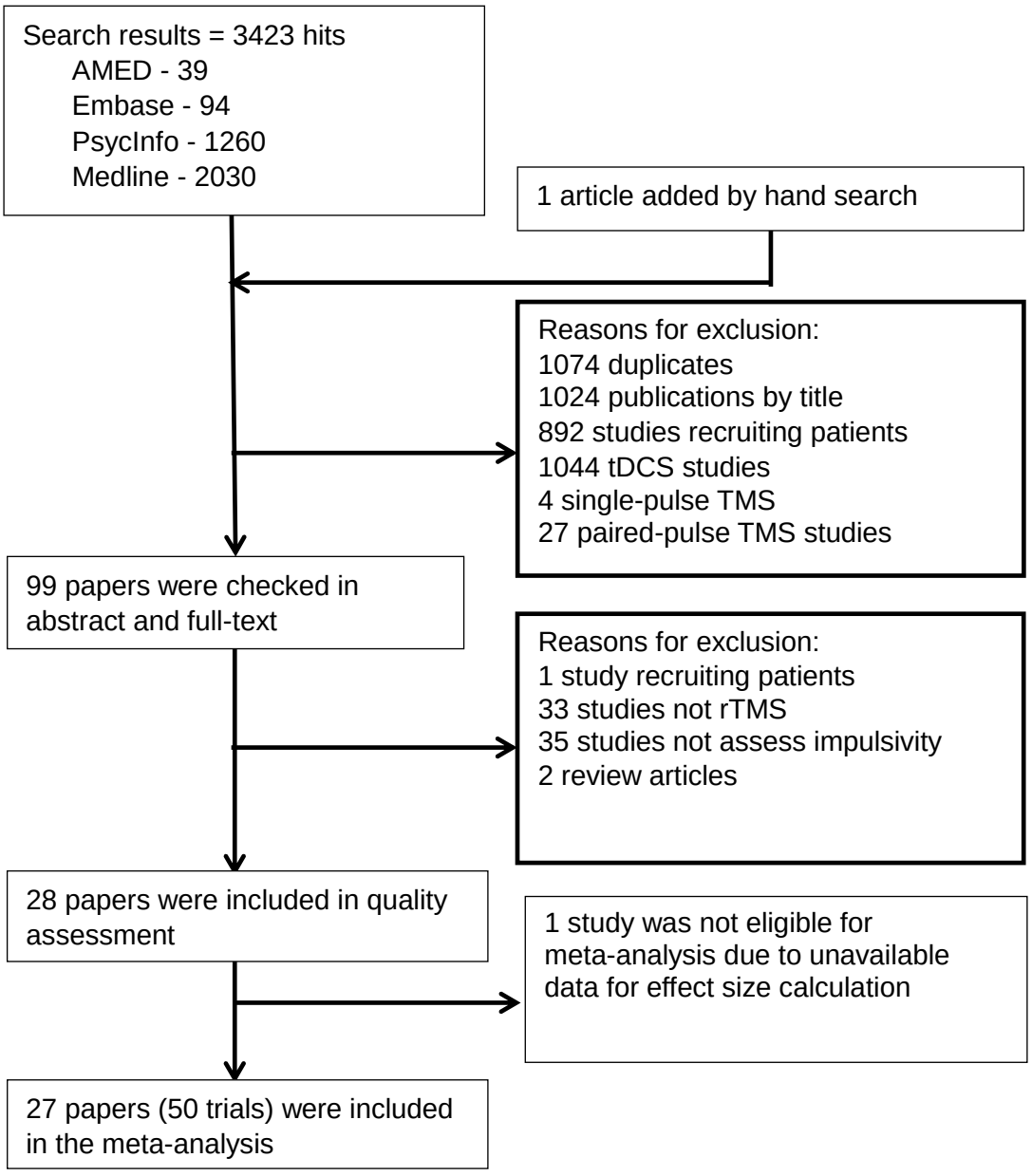


Figure 5-1 The process of study selection and search results

Table 5-1 Characteristics of eligible studies

Study/Country	study design	age of participants (mean± SD; range)	N[c], sex ratio (M/F)	target area	rTMS protocol (frequency, intensity, paradigm, number of pulses)	sham method	tasks	outcome measure
Motor impulsivity								
Bermpohl et al., (2005)/ Brazil	CCRT	38.3± 13.9	11, 5/6	RDLPFC LDLPFC	1Hz, 60%MSO (104-187%rMT, mean 151%rMT), off-line, 600	OC stimulation	affective GNG	false alarm rates
Chambers et al., (2006)/ Australia	CCRT	18-27	16, 8/8	rIFG right MFG right AG	1Hz, 92%dMT, off-line, 900	Coil oriented away from the scalp	SST	SSRT
Chambers et al., (2007)/ Australia	CCRT	19-46	16, NA	rIFG, right dPM, lIFG, left dPM	1Hz, 92%rMT in average, off-line, 1200	coil oriented away from the scalp	SST	SSRT
Chen et al., (2009)/ Taiwan	CCRT	25.7; 21-35	7, 7/2	left pre-SMA	10Hz, 60%MSO, online, 960	Vertex stimulation	SST	SSRT
Dambacher et al., (2014)/ Netherlands	CCRT	27±7.27	11, NA	right SFG, right MFG, right AI, right pre-SMA	cTBS, 100%AMT, off-line, 600	sham coil	GNG SST	false alarm rates in GNG; false alarm rates in inhibition trials of SST
Esterman et al., (2015)/ USA	CCRT	20.4 ± 2.4; RFEF(19.43 ± 1.70); LFEF	14, (RFEF: 10/4, 14,	RFEF, LFEF	1Hz, 110%RMT, off-line, 480	coil oriented 180° away	GNG	commission error

		(21.50 ± 2.79)	LFEF: 5/9)			from the scalp		
Grossheinrich et al., (2009) / Germany	RCRT[b]	20-35	12, 5/7	LDLPFC	iTBS, 80% AMT, off-line, 600	imTBS	GNG	commission error
exp1:					cTBS, 80%AMT, off-line, 600,			
exp2:		22-38	12, 4/8	MPFC	iTBS, 80% AMT, off-line, 600	imTBS	GNG	commission error
					cTBS, 80%AMT, off-line, 600,			
Huang et al., (2004)/ Taiwan	RCRT[b]	27.0± 4.7; 20-37	24, 12/12	LDLPFC	5Hz, 100%RMT, offline, 1600	Tilt coil at 90°	GNG	percentage of shortening choice reaction time
Hwang et al., (2010)/ South Korea	RCRT[b]	23.53± 2.12	17, 17/0	LDLPFC	10Hz, 90%MT, off-line, 900	Tilt coil at 90°	Conners' CPT (GNG)	mean commission errors
Kim et al., (2012)/ South Korea	RCT[b]	63.13± 4.90	16, 0/16	LDLPFC	10Hz, 30%MSO, off-line, 780 (5 sessions, 3900 in total)	Tilt coil at 90°	modified Stroop	reaction time of incongruent condition
Lee et al., (2016) / Taiwan	CCRT	23±2	24, 18/6	right pre-SMA rIFG	cTBS, 40%MSO, off-line, 600	Tilt coil at 90°	conditional SST	SSRT
Leyman et al., (2009)/	RCRT[b]	21.1± 1.45; 19-24	18, 0/18	LDLPFC	10Hz, 110%RMT, off-line, 1560	Tilt coil at 90°	NAP	NAP scores
Belgium		24± 2.33; 20-30	22, 0/22	RDLPFC	10Hz, 110RMT, off-line, 1560	Tilt coil at 90°	NAP	NAP scores
Lowe et al., (2014)/	CCRT	21.10±1.86	21, 0/21	LDLPFC	cTBS, 80%RMT,	Tilt coil at 90°	Stroop	interference

Canada					off-line, 600		GNG	time
							SST	d' sensitivity proportion of incorrect responses on stop trials
Muggleton et al., (2010)/ Taiwan exp1	RCRT[b]	25.7; 21-35	9, 7/2	rFEF	10Hz, 65%MSO, online, 960	sham coil	SST	SSRT
exp2		22.9; 20-27	9, 5/4	rFEF	10Hz, 65%MSO, online, 960	no stimulation	modified SST	SSRT
Obeso et al., (2013)/ Spain	CCRT	35.40±7.7; 24-44	16, 7/9	rIFG	cTBS, 80%AMT, off-line, 600	Tilt coil at 90° at M1	modified SST	SSRT
Upton et al., (2010)[a]/ Australia	CCRT	26± 3.4; 18-39	14, NA	RDLPFC LDLPFC	1Hz, 110%RMT, off-line, 900	Tilt coil at 90°	SST	NA
Vanderhasselt et al., (2006)/ Belgium	CCRT	23± 4.4; 18-60	28, 0/28	LDLPFC	10Hz, 110%MT, off-line, 1560	Tilt coil at 90°	computerised Stroop	reaction time of incongruent condition
Vanderhasselt et al., (2007)/ Belgium	CCRT	24± 2.6; 18-25	20, 0/20	LDLPFC	10Hz, 110%MT, off-line, 1560	Tilt coil at 90°	computerised Stroop	reaction time of incongruent condition (high expectancy)
Verbruggen et al., (2010)/ UK	CCRT	25.9; 20-38	18, 9/9	rIFG rIFJ right pre-SMA	cTBS, 70% distance-adjusted MT, off-line, unknown	coil oriented away from the scalp	SST	SSRT
Wagner et al., (2006)/ Switzerland	RCRT[b]	22.3±2.1; 19-26	17, 17/0	LDLPFC	20Hz, 100%RMT, off-line, 1600	Tilt coil at 90°	Stroop	interference time

Watanabe et al., (2015)/ Japan	CCRT	28-44	10, NA	right pre-SMA	QPS, 90%AMT, off-line, 1440	Sham coil	SST	SSRT
Zandbelt et al., (2013)/ Neitherlands	CCRT	24.1; 20-38	24, 12/12	rIFG SMA	1 Hz,(special), 90% RMT, for 6 Hz and 110%RMT, for 1Hz, off-line, 600 6Hz,(pulses), 600 1Hz,(pulses)	Sham coil at right superior parietal lobe	stop-signal anticipation task	SSRT
Temporal impulsivity								
Cho et al., (2010)/ Canada	CCRT	22.4±4.3; 18-29	7, 3/4	RDLPFC	iTBS, 80%AMT, off-line, 600 cTBS, 80%AMT, off-line, 600	Tilt coil at 90°	computerised DDT	k-value
Cho et al., (2012)/ Canada	CCRT	22.6±2.7; 18-27	8, 4/4	RDLPFC	cTBS, 80%AMT, off-line, 600	Tilt coil at 90°	computerised DDT	k-value
Cho et al., (2015)/ Canada	CCRT	22.1±2.9; 18-27	24, 13/11	MPFC	10Hz, 80%AMT, off-line, 150	vertex stimulation	computerised DDT	k-value
Figner et al., (2010)/ USA/Switzerland	RCT[b]	19-33	52, 52/0	LDLPFC RDLPFC	1Hz, 54%MSO, off-line, 900	Sham coil	choice task	preference reversals
Sheffer et al., (2013)/ USA	CCRT	41.3±10.4; 19-55	66, 40/26	LDLPFC	20Hz, 110%MT, off-line, 900 10 Hz, 110%MT, off-line, 900	sham coil	DDT	Ln(k-value)
Reflection impulsivity								
Knoch et al.,	RCT[b]	23.8; 21-31	27, 27/0	RDLPFC	1Hz, 100%MT,	not reported	Risk Task	total points

(2006)/ Switzerland		LDLPFC	off-line, 900	earned

[a] not included in meta-analysis; [b] no randomisation method reported; [c] number of participants start of study

AG, angular gyrus; AI, anterior insula; AMT, active motor threshold; CCRT, counterbalanced crossover trial; cTBS, continuous theta burst ;stimulation; DDT, delayed discounting task; dMT, distance-adjusted motor threshold; dPM, dorsal premotor cortex; LFEF, left frontal eye field; GNG, Go/No-Go; imTBS, intermediate theta burst stimulation; iTBS, intermittent theta burst stimulation; LDLPFC, left dorsolateral prefrontal cortex; lIFG, left inferior frontal gyrus; M1, primary motor cortex; MFG, middle frontal gyrus; MPFC, medial prefrontal cortex; MSO, maximum stimulator output; MT, motor threshold; NA, not available; OC, occipital cortex; RCRT, randomised crossover trial; RCT, randomised controlled trial; RDLPFC, right dorsolateral prefrontal cortex; rFEF, right frontal eye field; rIFG, right inferior frontal gyrus; rIFJ, right inferior frontal junction; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SFG, superior frontal gyrus; SMA, supplementary motor area; SSRT, stop signal reaction time; SST, Stop-signal task; Stroop, Stroop interference colour task, TBS, theta burst stimulation

5.4.2 Study Characteristics

Characteristics of selected studies categorised by the subtypes of impulsivity are summarised in Table 5-1.

In summary, 28 studies involving a total of 599 participants (51.6% male; mean age: 30.16 years; range: 18-70 years) were included in the quantitative synthesis. Eleven of the included studies were conducted in Europe, seven in East Asia, six in North America, three in Australia, and one in Brazil.

The most common study design employed was a counterbalanced crossover design (19 studies), followed by randomised crossover (6 studies) and randomised controlled parallel-group (3 studies) designs. The majority of studies selected focused on motor impulsivity (22 studies) while five studies (Cho et al., 2010; Cho et al., 2015; Cho et al., 2012; Figner et al., 2010; Sheffer et al., 2013) focused on temporal impulsivity and only one study (Knoch et al., 2006) on reflection impulsivity. Various tasks were used to assess impulsivity. For motor impulsivity, the SST and it variants were used in twelve studies, GNG in six studies, SCWT in five studies, and the Negative Affective Priming task in one study (Leyman, De Raedt, Vanderhasselt, & Baeken, 2009). Five different computerised delay-discounting tasks were used in the studies exploring temporal impulsivity and one risk-taking task (Rogers et al., 1999) was selected to index reflection impulsivity in one study (Knoch et al., 2006). All studies delivered a single rTMS session per condition, except for one study (Kim et al., 2012) which applied five rTMS sessions over five consecutive days. The number of pulses within each experimental

session ranged from 150 (Cho et al., 2015) to 1600 (Huang, Su, Shan, & Wei, 2004).

Regarding the stimulation sites, the dorsolateral prefrontal cortex (DLPFC) was the most commonly targeted area; the right DLPFC (RDLPFC) was selected in six studies and the left DLPFC (LDLPFC) in fourteen studies. The rIFG (6 studies) and pre-supplementary motor area (pre-SMA; 5 studies) were targeted in several studies. The most common control condition (17 studies) entailed tilting the coil to divert the magnetic pulses away from the scalp. Six studies (Dambacher et al., 2014; Figner et al., 2010; Muggleton, Chen, Tzeng, Hung, & Juan, 2010; Sheffer et al., 2013; Watanabe et al., 2015) used a sham coil, three (Bermpohl (Bermpohl et al., 2005; Chen, Muggleton, Tzeng, Hung, & Juan, 2009; Cho et al., 2015) used a control site stimulation, one (Grossheinrich et al., 2009) used another stimulation mode, and one study (Knoch et al., 2006) did not report details about the sham method.

5.4.3 Risk of Bias within Studies

All 28 included studies attracted a “moderate” quality rating (Appendix 11). This was largely due to poor ratings on selection bias. Only eleven studies reported on adverse effects relating to rTMS administration, of which eight studies found no significant adverse effects (Cho et al., 2012; Figner et al., 2010; Huang et al., 2004; Hwang et al., 2010; Knoch et al., 2006; Obeso et al., 2013; Verbruggen et al., 2010; Zandbelt, Bloemendaal, Hoogendam, Kahn, & Vink, 2013), and three studies (Dambacher et al., 2014; Grossheinrich et al., 2009; Wagner, Rihs, Mosimann, Fisch, & Schlaepfer, 2006) reported adverse events in seven participants whereas the other

seventeen studies did not provide any information regarding tolerability or adverse events (Appendix 11).

5.4.4 Synthesis of Results

Separate meta-analyses were conducted for studies involving the subdomains of impulsivity as described below.

5.4.4.1 Effects of rTMS on Motor Impulsivity

The meta-analysis of 41 effect sizes from 21 studies on the effects of rTMS on motor impulsivity showed a positive and significant mean effect size (g = 0.30, 95% CI, 0.17 to 0.43, p < .001; see also Figure 5-2). No significant heterogeneity was found across trials (Q_{40} = 53.91, p = .070; I^2 = 25.8%; T^2 = 0.047). The results were further confirmed using multi-level modelling analysis to adjust for potential bias resulting from within-studies correlation of multiple effects (g = 0.29, 95% CI, 0.15 to 0.43, p < .001). The between-studies (T^2 = 0.026) and between-trials (T^2 = 0.008) variances were all very small. No publication bias was indexed by the funnel plot (Figure 5-3), the Begg's test (z = 1.20, p = .23), or the Egger's test (intercept$_{41}$ = 1.188, t = 1.64, 2-tailed p = .109).

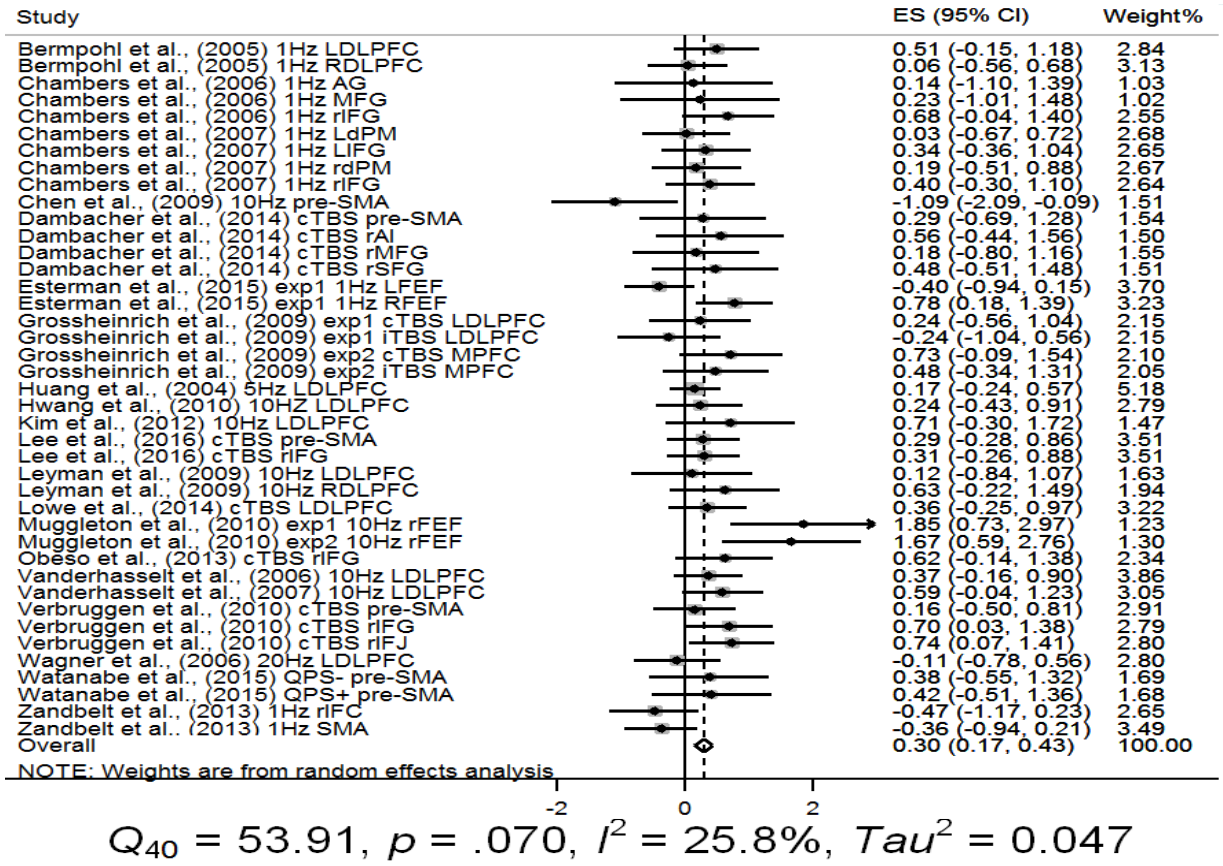


Figure 5-2 Statistical summary and forest plot of effect sizes for motor impulsivity

Abbreviations: AG, angular gyrus; rAI, right anterior insula; cTBS, continuous theta burst ;stimulation; ES, effect size; iTBS, intermittent theta burst stimulation; LDLPFC, left dorsolateral prefrontal cortex; ldPM, left dorsal premotor cortex; LFEF, left frontal eye field; lIFG, left inferior frontal gyrus; MFG, middle frontal gyrus; MPFC, medial prefrontal cortex; QPS, Quadro-pulse stimulation; RDLPFC, right dorsolateral prefrontal cortex; rdPM, right dorsal premotor cortex; rFEF, right frontal eye field; rIFG, right inferior frontal gyrus; rIFJ, right inferior frontal junction; rSFG, right superior frontal gyrus; SMA, supplementary motor area

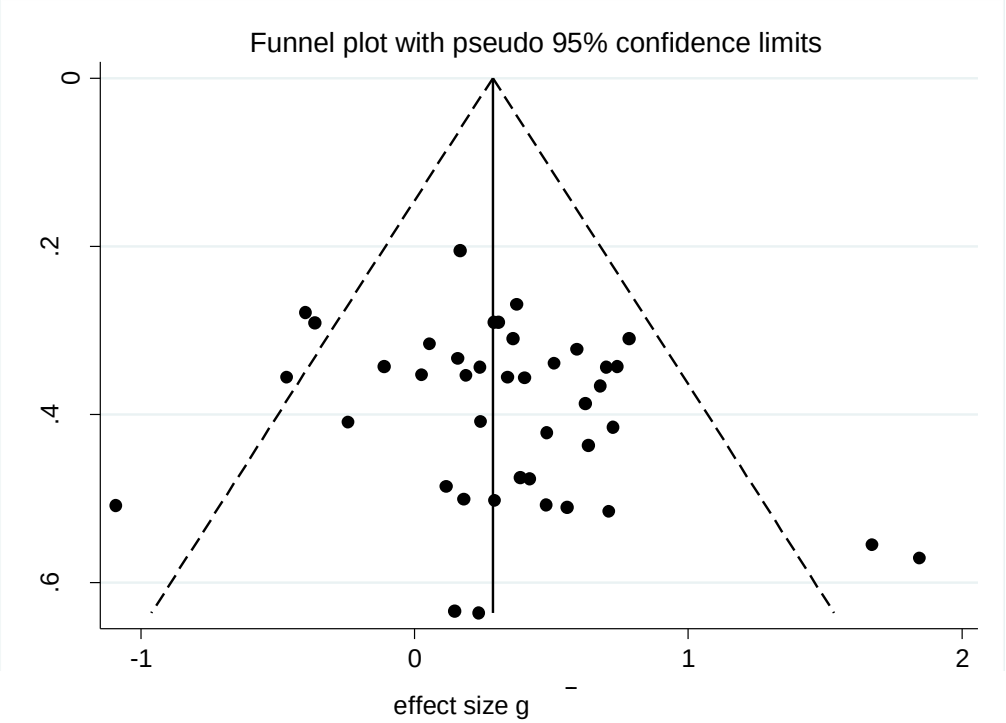


Figure 5-3 Funnel plot of the motor impulsivity trials in the meta-analysis

5.4.4.2 Additional Analyses

The subgroup analyses (Table 5-2) revealed positive and significant mean effects for both inhibitory (g = 0.27, 95% CI, 0.13 to 0.41, p < .001) and excitatory rTMS (g = 0.36, 95% CI, 0.06 to 0.65, p = .018), and the magnitude of effect sizes did not significantly differ between inhibitory and excitatory rTMS (β = 0.051, p = .730). Moreover, subgroup analysis by rTMS type revealed significant mean effect sizes for both conventional rTMS (g = 0.26, 95% CI, 0.07 to 0.45, p = .009) and TBS (g = 0.39, 95% CI, 0.20 to 0.58, p < .001), with no significant difference between the magnitude of these effects (β = -0.056, p = .694). Subgroup analysis by stimulation site revealed significant mean effect sizes only for the LDLPFC (g = 0.26, 95% CI, 0.07 to 0.46, p = .007), rIFG (g = 0.42, 95% CI, 0.11 to 0.73, p = .008), medial prefrontal cortex (MPFC; g = 0.60, 95% CI, -0.16 to 1.36, p = .040), and right

frontal eye field (rFEF; g = 1.30, 95% CI, 0.58 to 2.03, p < .001), while the mean effect sizes for RDLPFC (g = 0.24, 95% CI, -0.18 to 0.66, p = .267), SMA (g = -0.09, 95% CI, -0.47 to 0.28, p = .626) and right Pre-SMA (g = 0.29, 95% CI, -0.05 to 0.62, p = .098) were non-significant. Only the magnitude of effect sizes from rFEF significantly differed from those in other locations (β = 1.291, p < .001). Trials targeting other sites were excluded from the subgroup analysis if the number of effect sizes was less than two. Further subgroup analyses were performed to examine the effects of inhibitory and excitatory rTMS at LDLPFC and rIFG, brain areas that have been consistently implicated in impulsivity. The inhibitory rTMS at LDLPFC yielded an insignificant effect (g = 0.38, 95% CI, -0.01 to 0.78, p = .055). In contrast with this, excitatory rTMS at LDLPFC revealed a small but significant effect (g = 0.23, 95% CI, 0.00 to 0.45, p = .047). However, there was no significant difference between the magnitude of these effects (β = -0.158, p = .508). It has not been possible to conduct similar subgroup analysis in relation to the effects of TMS of the rIFG due to lack of sufficient data. Finally, the subgroup analysis for type of outcome measure used revealed significant mean effect sizes for GNG (g = 0.24, 95% CI, 0.05 to 0.42, p = .012), SST (g = 0.32, 95% CI, 0.10 to 0.55, p = .005) and SCWT tasks (g = 0.35, 95% CI, 0.02 to 0.68, p = .036). However, SST (β = 0.086, p = .826), SCWT (β = 0.041, p = .924), and GNG (β = -0.142, p = .721) were not significantly more sensitive to detect changes than other measurements, combined.

The meta-regression analysis across trials showed that none of the between-study variables significantly predicted the effects of rTMS (mean age of participants: β = 0.008, p = .509; male ratio: β = -0.300, p = .444; intensity

of stimulation: β = -0.004, p = .229; number of pulses per condition: β = 0.000, p = .525).

5.4.4.3 Effects of rTMS on Temporal Impulsivity

The meta-analysis of seven effect sizes from five studies on the effects of rTMS on temporal impulsivity showed a significant medium mean effect (g = 0.59, 95% CI, 0.32 to 0.85, p < .001) without significant heterogeneity (Q_6 = 6.38, p = .382; I^2 = 6.0%; T^2 = 0.008; see also Figure 5-4). The results were confirmed using the multi-level model analysis after adjusting for the nesting of multiple effects within studies (g = 0.59, 95% CI, 0.31 to 0.87, p < .001) where the between-studies (T^2 < 0.001) and between-trials (T^2 = 0.017) variances were all very small. The funnel plot (Figure 5-5), the Egger's test (intercept$_7$ = -0.655, t = -0.54, 2-tailed p = .615), and the Begg's test (z = 0.00, p = 1.00) did not show evidence of publication bias.

5.4.4.4 Additional Analyses

The subgroup analyses (Table 5-2) revealed significant mean effects for both inhibitory (g = 0.71, 95% CI, 0.21 to 1.21, p = .005) and excitatory rTMS (g = 0.54, 95% CI, 0.16 to 0.92, p = .006). Moreover, the subgroup analysis by rTMS type revealed a significant mean effect size for conventional rTMS (g = 0.65, 95% CI, 0.28 to 1.03, p = .001) but not for TBS (g = 0.33, 95% CI, -0.31 to 0.97, p = .315). Furthermore, the subgroup analysis by stimulation sites revealed a significant mean effect size for the LDLPFC (g = 0.76, 95% CI, 0.29 to 1.22, p = .002) but a non-significant mean effect size for the RDLPFC (g = 0.33, 95% CI, -0.31 to 0.97, p = .315). The meta-regression analysis and

further comparison of the subgroup analysis were not conducted because there were fewer than ten effects in the meta-analysis (Deeks et al., 2011).

5.4.4.5 Effects of rTMS on Reflection Impulsivity

The only study (Knoch et al., 2006) conducted in the field consisted of two effect sizes (1 Hz rTMS at LDLPFC: *g* = -0.24, 95% CI, -1.42 to 0.95; 1 Hz rTMS at RDLPFC: *g* = 0.95, 95% CI, -0.21 to 2.12); therefore, no further analysis was conducted.

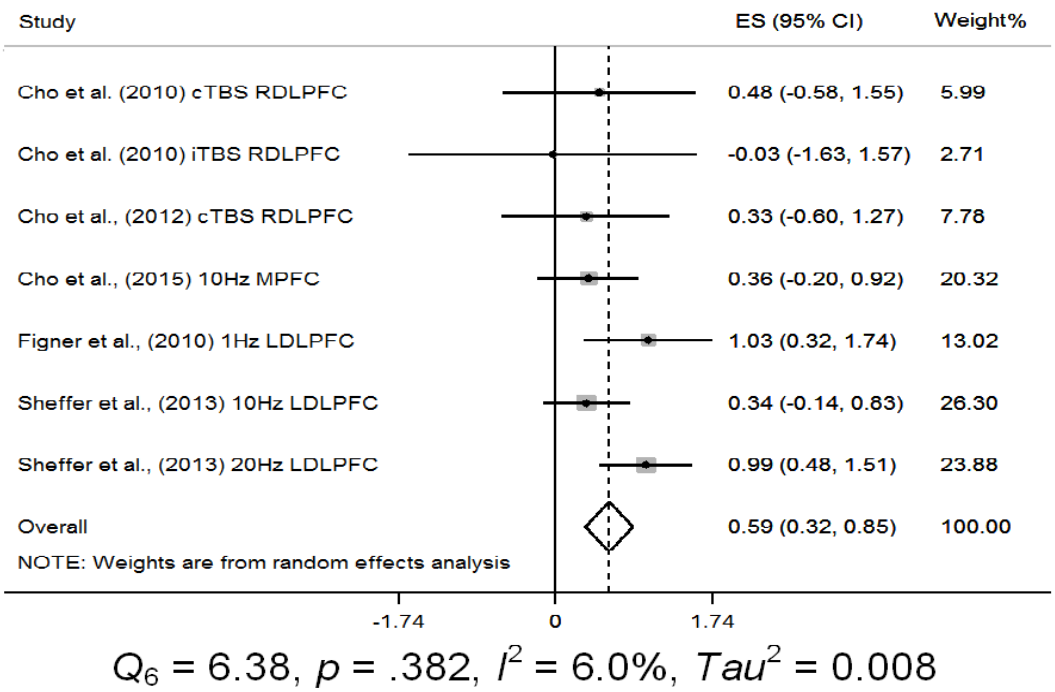


Figure 5-4 Statistical summary and forest plot of effect sizes for temporal impulsivity

Abbreviations: cTBS, continuous theta burst ;stimulation; ES, effect size; iTBS, intermittent theta burst stimulation; LDLPFC, left dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; RDLPFC, right dorsolateral prefrontal cortex

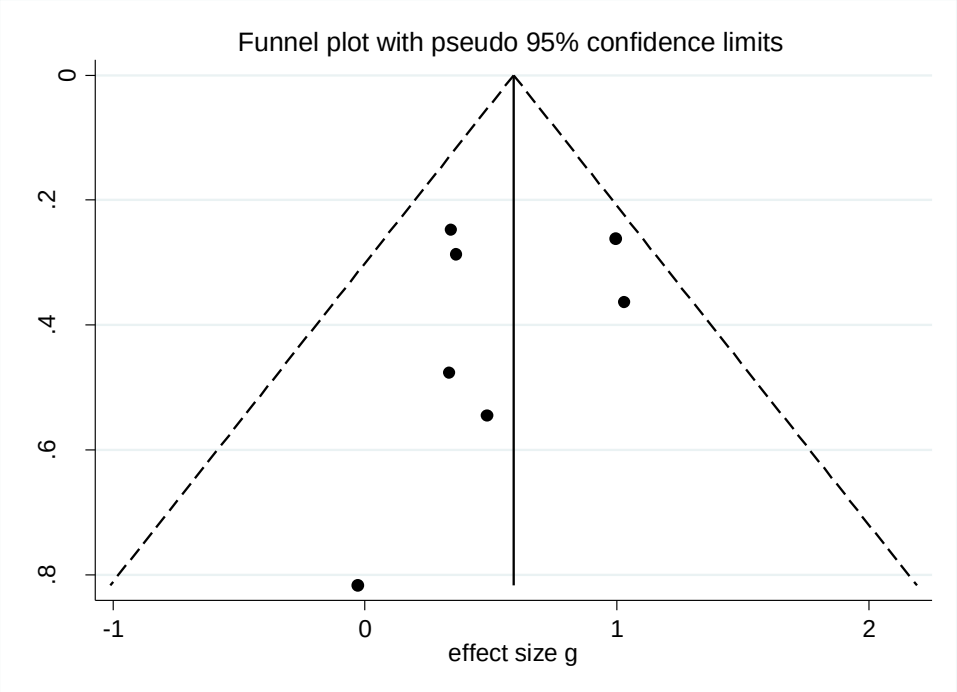


Figure 5-5 Funnel plot of the temporal impulsivity trials in the meta-analysis

Table 5-2 Subgroup analyses

	Pooled effect size			Between-study heterogeneity		
	k	Effect size (Hedges' *g*)	95% CI	*Q* test	I^2	*p* value
Motor impulsivity						
Total	41	0.30***	0.17-0.43	53.91	25.8%	0.070
Effect of stimulation						
Inhibitory	27	0.27***	0.13-0.41	26.75	2.8%	0.423
Excitatory	14	0.36*	0.06-0.65	27.04	51.9%	0.012
rTMS type						
Conventional rTMS	26	0.26**	0.07-0.45	45.59	45.2%	0.007
TBS	15	0.39***	0.20-0.58	6.49	0.0%	0.952
Stimulation site						
LDLPFC	11	0.26**	0.07-0.46	5.62	0.0%	0.846
rIFG	7	0.42**	0.11-0.73	8.69	31.0%	0.192
rFEF	3	1.30***	0.58-2.03	3.77	46.9%	0.152
mPFC	2	0.61*	0.03-1.19	0.10	0.0%	0.755
RDLPFC	4	0.24	-0.18-0.66	1.17	0.0%	0.761
SMA	3	-0.09	-0.47-0.28	0.17	0.0%	0.683
right Pre-SMA	5	0.29	-0.05-0.62	0.27	0.0%	0.991
Stimulation effect x site						
Inhibitory at LDLPFC	3	0.38	-0.01-0.78	0.27	0.0%	0.875
Excitatory at LDLPFC	8	0.23*	0.00-0.45	4.88	0.0%	0.675
Type of the task used						
GNG	14	0.24*	0.05-0.42	13.13	1.0%	0.438
SST	21	0.32**	0.10-0.55	36.70	45.5%	0.013
Stroop	4	0.35*	0.02-0.68	2.87	0.0%	0.412
Temporal impulsivity						
Total	7	0.59***	0.32-0.85	6.38	6.0%	0.382
Effect of stimulation						
Inhibitory	3	0.71**	0.21-1.21	1.57	0.0%	0.457
Excitatory	4	0.54**	0.16-0.92	4.52	33.6%	0.211
rTMS type						
Conventional rTMS	4	0.65**	0.28-1.03	5.37	44.1%	0.147
TBS	3	0.33	-0.31-0.97	0.27	0.0%	0.872
Stimulation site						
LDLPFC	3	0.76**	0.29-1.22	4.15	51.8%	0.126
RDLPFC	3	0.33	-0.31-0.97	0.27	0.0%	0.872

CI, confidence interval; GNG, Go/No-Go; LDLPFC, left dorsolateral prefrontal cortex; mPFC, medial prefrontal cortex; RDLPFC, right dorsolateral prefrontal cortex; rFEF, right frontal eye field; rIFG, right inferior frontal gyrus; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area; SST, Stop-signal task; Stroop, Stroop interference colour task, TBS, theta burst stimulation; * $p < .05$, ** $p < .01$, *** $p < .001$

5.5 DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis focusing on the evidence for the effectiveness of rTMS on impulsivity and its subdomains. Our results are broadly compatible with the suggestion (e.g., Zaman, 2014) that rTMS is an efficient tool for modulating impulsivity. Overall, the current evidence is sufficiently robust to determine the effect of rTMS on motor impulsivity in healthy participants. Our current positive finding of rTMS on temporal impulsivity might be updated with accumulating literature considering only a limited number of studies in this field. Moreover, a dearth of research on reflection impulsivity was noted and all reviewed studies focused on short-term effect. The findings of differential effects for rTMS on subdomains of impulsivity support the idea that these subdomains are heterogeneous in nature (Bari & Robbins, 2013).

The meta-analysis of rTMS studies relating to motor impulsivity revealed a small but positive and significant effect size, which is consistent with previous review literature (Juan & Muggleton, 2012). A non-significant level of heterogeneity indicated that the variability in effect sizes was relatively small. The subgroup analyses identified the key parameters associated with a positive effect for rTMS on impulsivity. These revealed a number of important findings as follows. Both inhibitory and excitatory rTMS yielded significant though small effects indicating that either protocol can be used to modulate impulsivity (Brevet-Aeby et al., 2016). Although both conventional rTMS and TBS yielded similar effects on motor impulsivity, a significant heterogeneity of the effects in conventional rTMS was noted. This supports the idea that TBS is associated with more consistent magnitude and directions of after-effects

compared to those found following conventional rTMS (Thut & Pascual-Leone, 2010). Subgroup analysis by the stimulation sites revealed significant effects on certain brain areas including the LDLPFC, rIFG, rFEF and MPFC. A recent review (Brevet-Aeby et al., 2016) has favoured the rIFG as a potential site for stimulation when using rTMS to modulate impulsivity and the functional activation of the rIFG has been consistently linked to response inhibition (Bari & Robbins, 2013). It is notable that no studies to date have examined the effects of excitatory rTMS on the rIFG, an important area for future studies to explore. As the right pre-SMA has been commonly identified in the network connecting the IFG and subthalamic nucleus involved in response inhibition, it is noteworthy that only a non-significant effect was found on the right pre-SMA stimulation. One possible explanation is that the pre-SMA may not play the same role as rIFG during the process of response inhibition and the conventional SST outcome measures may not directly link to the activation level of the pre-SMA (Cai, Cannistraci, Gore, & Leung, 2014). Other studies identified the rFEF as a potential site for stimulation (Hung et al. 2011).

It is notable that this study entailed the use of visual stimuli, indicating that the rFEF may have a specific role in the top-down control of visual attention. The role of rFEF in controlling motor impulsivity, as indexed by use of non-visual stimuli, is yet to be established. While the DLPFC is regarded as a crucial region implicated in executive control of response inhibition (Bari & Robbins, 2013) and reward-anticipation (Ehrlich et al., 2015), only the stimulation of the LDLPFC was found to have a significant effect on motor impulsivity. It may be too simplistic to deduce that brain stimulation at LDLPFC alone led to changes in motor impulsivity (Loftus, Yalcin, Baughman, Vanman, & Hagger,

2015). One possible explanation for this is that in healthy participants, the finding may be attributable to changes in the interhemispheric balance of activation across the DLPFC. Another possible explanation is that, contrary to conventional views, LDLPFC may play a more important role in motor impulsivity than RDLPFC. For example, reduced LDLPFC activation has been associated with poor response control in obese populations (Brooks, Cedernaes, & Schiöth, 2013). In addition, findings from recent structural neuroimaging studies (e.g., Cho et al., 2013; Tu, Kuan, Li, & Su, 2017) suggest that only the grey matter volume in LDLPFC but not RDLPFC correlates with self-report measures of impulsivity. The third possible explanation is that the rTMS modulation effect on DLPFC may be only reflected by the tasks measuring proactive rather than reactive motor inhibition (Brevet-Aeby et al., 2016). Moreover, neuroimaging studies (e.g., Floden, Vallesi, & Stuss, 2011) have shown that the degree of activation in the LDLPFC correlates with proactive motor inhibition performance. In conclusion, given that both excitatory and inhibitory rTMS exhibit similar effects at LDLPFC in motor impulsivity, LDLPFC is suggested to be a prioritised target for neurostimulation in relation to motor impulsivity.

Subgroup analysis by types of outcome measures used revealed insignificant differences between the magnitude of effects on three key tasks (i.e., GNG, SST, SCWT) indicating their similar utility in assessing motor impulsivity in future studies. Moreover, only the effect sizes from SST yielded a small to moderate level of heterogeneity. The source of variability might be from the different versions of SST used among studies. Furthermore, given that SST is regarded as a measure of reactive motor control (Verbruggen & Logan, 2008)

and GNG and SCWT as measures of proactive motor control (Aron, 2011; Smittenaar et al., 2015), future studies should select appropriate outcome measures according to their objectives.

The results of the meta-regression revealed no differential effects in relation to participant characteristics, such as mean age and sex ratio, or stimulation parameters, in terms of intensity and number of pulses. Some commentators (e.g., Thompson & Higgins, 2002) have argued that using mean age or sex ratio within trials may not be appropriate since the information is averaged and may not reflect the true relationship between the parameters of interest. Caution is required when using the same parameters from conventional rTMS and TBS as covariates in the regression analysis because these paradigms deliver magnetic pulses in different ways. Another possibility is that such relationship may be manifested when a sufficient number of sessions or pulses per session reached since the effects of TMS are dose-dependent. Therefore, to test these hypotheses, future research in this field recruiting a variety of age groups with multiple rTMS sessions is warranted.

The meta-analysis of the effects of rTMS on temporal impulsivity, involving seven effect sizes from five studies identified a positive and significant medium effect size. Subgroup analyses revealed positive and significant medium effects for both inhibitory and excitatory rTMS. They also identified the LDLPFC, but not RDLPFC, as a crucial stimulation site for modulation of temporal impulsivity. The finding regarding laterality needs to be interpreted with caution due to the limited number of studies included, although functional neuroimaging studies (e.g., Ballard & Knutson, 2009) have found positive

associations between the activation of the LDLPFC and temporal impulsivity. Future studies concerning motor impulsivity and temporal impulsivity may therefore consider selecting the LDLPFC as the brain regions of interest.

We were not able to perform a meta-analysis of the effects of rTMS on reflection impulsivity due to the dearth of studies in the field. Although there are a considerable number of transcranial Direct Current Stimulation (tDCS) studies aiming at the neuromodulation effect on reflection impulsivity with inconsistent findings (Brevet-Aeby et al., 2016), the innate limitation of tDCS with low spatial resolution and poor localisation restricts its utility and using rTMS studies to explore the issue is still preferred.

5.5.1 Strengths and Limitations

A major advantage of this review over previous reviews is that it involved conducting a meta-analysis to quantify the effects of rTMS on modulating impulsivity, in terms of the effects on subdomains of impulsivity. The studies included in this review were of moderate quality and this can be regarded as a relative strength given that the field is still in its infancy. Compared to the composition of samples of the included studies in the previous chapter, the sample in the current systematic review were more representative with larger sample size, relatively balanced sex ratio, higher mean age and a broader range of age. This may be because the included studies in the systematic review were more community-based and less emotional involvement which may affect the willingness of participation distinctively on participants of both sexes and different age groups. However, the studies included in the review suffered several limitations in relation to selection bias, small sample sizes,

heterogeneity of designs and outcome measures used, and lack of information on the adverse effects of rTMS. It is notable that studies included in this review attracted poor ratings in relation to selection bias. This is likely due to selection of well-educated young adult participants, such as university students, which limits the generalisability of the findings to other populations. Another major limitation of this study is that is does not examine the impact of rTMS on impulsivity in clinical populations. This was due to lack of sufficient studies in the field. Nevertheless, studies involving healthy controls are relevant and can provide invaluable information in regard to the effects of rTMS on domains of impulsivity. Moreover, there is a relative dearth of studies involving the use of excitatory rTMS paradigms and those involving temporal and reflection impulsivity. Furthermore, whilst the study applied a rigorous search strategy, it is still possible that it failed to capture all relevant studies due to variations in the conceptualisation of impulsivity across studies. Finally, whilst meta-analytic reviews have inherent advantages, it still holds that pooling data through meta-analysis can cause problems such as non-linear correlations (Greco, Zangrillo, Biondi-Zoccai, & Landoni, 2013).

In addition to addressing the limitations highlighted above, future research should define impulsivity consistently and use a range of outcome measures to better define the differential effects of rTMS on subdomains of impulsivity. It should consider using multiple stimulation sessions as opposed to a single session. It should also consider combining rTMS with neuroimaging techniques to assess the differences between the effects of conventional TMS and connectivity guided TMS in modulating impulsivity to help guide future interventions. Whilst TMS is a relatively easy to administer brain stimulation

technique, ethical concerns may arise in relation to its use in the context of impulsivity, particularly in relation to safety issues such as seizures and issues surrounding stigmatisation. Therefore, it is important that participants are well informed of the implications of taking part and carefully selected to ensure their safety (Najib & Horvath, 2014; Rossi et al., 2009).

5.6 CONCLUSIONS

In conclusion, this meta-analysis provides preliminary evidence that rTMS can be used to modulate impulsivity in healthy individuals, particularly motor impulsivity and temporal impulsivity. Further studies are required to extend the use of rTMS to modulate impulsivity to those who experience most harm from impulsive behaviour such as people with a history of offending or self-harming. Applying excitatory rTMS to clinical populations and tailoring parameters of the rTMS, such as the intensity, location, and stimulation mode (conventional rTMS or TBS), implementation of ecologically validated instruments assessing impulsivity are also strongly recommended.

5.7 ACKNOWLEDGEMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that they have no conflict of interest.

CHAPTER 6 : EXCITATORY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION APPLIED TO THE RIGHT INFERIOR FRONTAL GYRUS HAS NO EFFECT ON MOTOR OR REFLECTION IMPULSIVITY IN HEALTHY ADULTS

This chapter is presented in the format of a published paper as outlined in 'Remarks on Presentation of Thesis in Alternative Format' namely Yang, C.-C., Khalifa, N., & Völlm, B. (2018). Excitatory repetitive transcranial magnetic stimulation applied to the right inferior frontal gyrus has no effect on motor or cognitive impulsivity in healthy adults. *Behavioural Brain Research*.*347*, 1-7. doi: 10.1016/j.bbr.2018.02.047

Authors

Cheng-Chang Yang[1]*, Najat Khalifa[1, 2] & Birgit Völlm[1, 2]

[1] Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, UK

[2] Nottinghamshire Healthcare NHS Foundation Trust, UK

***Author for correspondence**

Contact information:

Institute of Mental Health

University of Nottingham Innovation Park

Triumph Road

Nottingham, NG7 2TU
UK

Cheng-Chang Yang Email: cheng-chang.yang@nottingham.ac.uk
Najat Khalifa Email: najat.khalifa@nottingham.ac.uk
Birgit Völlm Email: birgit.vollm@nottingham.ac.uk

6.1 ABSTRACT

Background: Impulsivity is a multi-faceted concept. It is a crucial feature of many neuropsychiatric disorders. Three subtypes of impulsivity have been identified: motor, temporal, and cognitive impulsivity (referred to as reflection impulsivity). Existing evidence suggests that the right inferior frontal gyrus (rIFG) plays a crucial role in impulsivity, and such a role has been elucidated using inhibitory repetitive transcranial magnetic stimulation (rTMS). There is a dearth of studies using excitatory rTMS at the rIFG, an important gap in the literature this study aimed to address.

Methods: Twenty healthy male adults completed a single-blind sham-controlled randomised crossover study aimed at assessing the efficacy of rTMS in the neuromodulation of impulsivity. This involved delivering 10-Hz excitatory rTMS to the rIFG at the intensity of 100% motor threshold with 900 pulses per session. Trait impulsivity was measured at baseline using the Barrett Impulsiveness Scale and UPPS-P Impulsiveness Scale. The Stop Signal Task (SST) and Information Sampling Task (IST), administered before and after rTMS sessions, were used as behavioural measures of impulsivity.

Results: No significant changes on any measures from either SST or IST after active rTMS at the rIFG compared to the sham-controlled condition were found.

Conclusions: Excitatory rTMS applied to the rIFG did not have a statistically significant effect on response inhibition and reflection impulsivity. Further research is required before drawing firm conclusions. This may involve a

larger sample of highly impulsive individuals, a different stimulation site or a different TMS modality such as theta burst stimulation.

Keywords: transcranial magnetic stimulation; impulsivity; inferior frontal gyrus; response inhibition; stop signal task; information sampling task

6.2 INTRODUCTION

The term impulsivity is a heterogeneous term encompassing a range of behaviours such as making premature decisions, favouring immediate over delayed and larger rewards and failure to inhibit motor responses (Caswell et al., 2015). Besides playing a prominent role in psychopathology (Cyders, 2013), impulsivity is a core feature of many psychiatric disorders such as attention deficit hyperactivity disorder (ADHD; Musser et al., 2013), schizophrenia (Matsuzawa et al., 2015), obsessive compulsive disorder (Endrass et al., 2010), impulse-control disorders, borderline personality disorder, antisocial personality disorder, bipolar affective disorder, and SUDs (American Psychiatric Association, 2013; Fineberg et al., 2014).

There is a general consensus among researchers that impulsivity is a multi-faceted concept (Evenden, 1999b; Grant & Kim, 2014), encompassing: motor impulsivity (MI), the inability to suppress a behavioural response (also referred to as inhibitory control or response inhibition); temporal impulsivity (TI; also referred to as delay-discounting), the failure to delay gratification; and reflection/cognitive impulsivity (RI), the tendency to make premature decisions without sampling enough information or to favour a more risky option resulting in disadvantageous decision-making (Caswell et al., 2016; Verdejo-Garcia et al., 2008). In contrast with TI and RI, MI has received more attention in the scientific literature. Recent evidence (Aron, 2011) suggests that MI is underpinned by two processes; reactive (the ability to stop an ongoing response when instructed by a stop signal) and proactive (the ability to suppress a response in anticipation of a no-go signal) control mechanisms.

Traditionally, self-report inventories have been employed to measure trait impulsivity (Evenden, 1999b). However, given that self-report measures assessing individuals' traits may lack sensitivity to detect changes over time in clinical trials despite the presence of proper psychometric properties (Fok & Henry, 2015), recent research has focused more on using laboratory paradigms, or behavioural measures, to index performance-based impulsive responses. Self-report and behavioural measures of impulsivity correlate weakly with each other, or not at all, due to their distinct neurobiological underpinnings (Caswell et al., 2015) indicating that they are not analogous.

In this study we focused on MI and RI. MI is a common feature of all externalising disorders (conduct disorder, antisocial personality disorder, SUDs, ADHD), and one that has been implicated in some of the most serious consequences of impulsivity such as aggression, self-harm and suicidality (Castellanos-Ryan & Séguin, 2015). The stop-signal task (SST) is currently one of the most commonly used paradigms to measure MI, by generating an important index, stop signal reaction time (SSRT), to estimate the reactive inhibitory control (Verbruggen & Logan, 2008). There is no consensus among researchers as to what measure can be used to index proactive inhibitory control (Elchlepp, Lavric, Chambers, & Verbruggen, 2016). Whilst some researchers have proposed that proactive inhibitory control equates to response slowing (Verbruggen & Logan, 2009; Wierenga et al., 2014), others have argued that proactive inhibitory control represents anticipatory regulation of response activation or motor excitability (Aron, 2011; Stuphorn & Emeric, 2012).

Several brain areas have been implicated in MI (Fineberg et al., 2014) and it is thought to result from dysfunction in a cognitive control mechanism involving the right inferior frontal gyrus (rIFG), right dorsolateral prefrontal cortex, anterior cingulate cortex, premotor cortex and limbic structures (Castellanos-Ryan & Séguin, 2015). The rIFG has been implicated in MI and it is a crucial region belonging to a fronto-subcortical network connecting the cortical areas and basal ganglia (Aron, Robbins, & Poldrack, 2014; Chambers et al., 2009; Wilbertz et al., 2014). While different facets of impulsivity have distinct neurobiological underpinnings, they link back to the core definition of impulsivity, namely a tendency to act without thinking through the consequences of one's actions (Hamilton et al., 2015). This brings to the core construct of RI which overlaps significantly with decision-making and MI. Such overlap may explain why some people, particularly those with personality disorder, habitually make disadvantageous choices in their personal lives, with varying degree of consequences for self or others (Beszterczey, Nestor, Shirai, & Harding, 2013). Therefore, a measure of RI, namely the Information Sampling Task (IST; Clark et al., 2006) was included in this study..

Transcranial magnetic stimulation (TMS), a non-invasive brain stimulation technique, that induces changes in cortical excitability via a brief, high-intensity magnetic pulses delivered through the scalp, has been widely used to modulate impulsivity (Juan & Muggleton, 2012). Repetitive TMS (rTMS), a specific form of TMS delivering multiple stimuli in trains, has been broadly used in practice because its effect (excitatory vs. inhibitory) can be determined by the frequency of pulses delivered. Low-frequency (about 1 Hz) rTMS exhibits an inhibitory effect by reducing cortical excitability, while

high-frequency (about 5 Hz or more) rTMS typically has an excitatory effect by increasing cortical excitability (Wassermann & Zimmermann, 2012).

Studies using inhibitory rTMS over the rIFG have found detrimental effects on inhibitory control (Chambers et al., 2007; Chambers et al., 2006; Lee et al., 2016; Verbruggen et al., 2010; Zandbelt, Bloemendaal, Hoogendam, et al., 2013), lending further support to the critical role of the rIFG in MI. Meanwhile, the role of rIFG in other subtypes of impulsivity, especially RI, has been examined in recent studies. For example, stronger functional connectivity between the rIFG and the anterior insula has been noted in risk-seeking individuals compared to risk-averse individuals during performing risk preference tasks (Cox et al., 2010). Hyperactivity in rIFG has been found in risk-averse participants while selecting less risky options (Christopoulos et al., 2009). Further, another functional imaging study also found increased activity over the ventral portion of lateral prefrontal cortex, including the rIFG, during risk-taking tasks (Cohen et al., 2013).

While rTMS has been used to elucidate the role the rIFG in impulse control (Brevet-Aeby et al., 2016; Juan & Muggleton, 2012), firm conclusions regarding its mechanism of action in relation to MI or RI cannot be drawn from the available literature owing to methodological limitations and limited knowledge of the neurobiological underpinnings of MI and RI (Brevet-Aeby et al., 2016). Several issues merit further scientific enquiry. Firstly, to our knowledge, research in this field has focused on using inhibitory rTMS applied over the area corresponding to the rIFG; there is a dearth of research on the effects of excitatory rTMS on the rIFG. Although some neuromodulation

studies employing anodal transcranial direct current stimulation (tDCS) of the rIFG found beneficial effects on MI (Cai et al., 2016; Castro-Meneses, Johnson, & Sowman, 2016; Ditye, Jacobson, Walsh, & Lavidor, 2012; Jacobson, Javitt, & Lavidor, 2011), a major limitation of tDCS is that it is of a relatively low spatial resolution, making it difficult to draw firm conclusions about the effect of the excitatory brain stimulation techniques in modulating impulsivity (de Berker, Bikson, & Bestmann, 2013). Secondly, rTMS studies have mainly examined the effects on reactive inhibitory control, the effects on proactive inhibitory control and the role of rIFG in proactive inhibitory control are relatively under researched (Meyer & Bucci, 2016; Zandbelt, Bloemendaal, Hoogendam, et al., 2013). Thirdly, the effect of rTMS applied at rIFG on RI has not been comprehensively explored. Further studies in the field are required since rIFG plays an important role in RI, which has been considered more clinically relevant (Caswell et al., 2015) compared to MI and TI. Finally, although trait impulsivity has persistently shown low to none association with laboratory-based impulsivity, the magnitude of the effects of rTMS on impulsivity may be affected by the impulsive tendencies of each individual. To be concluded, there is a need to conduct a study using excitatory rTMS on the rIFG to examine whether such a protocol may improve MI and RI, considering the levels of each participant's trait impulsivity.

The current study aims to examine the efficacy of excitatory rTMS applied to the rIFG in modulating different subtypes of impulsivity. Based on findings from existing literature in the field, we hypothesised that (i) excitatory rTMS will enhance MI (both reactive inhibitory control and proactive inhibitory control) and RI; (ii) there will be no significant correlations between self-report

and behavioural measures of impulsivity in relation to and MI and RI; and (iii) scores on self-report impulsivity will affect the magnitude of the post-rTMS changes in laboratory-based impulsivity.

6.3 MATERIAL AND METHODS

6.3.1 Study design and participants

A single-blind randomised cross-over sham controlled study design was employed in this study. Initially, 36 male volunteers aged from 18 to 30 years were recruited via advertisement on bulletin boards in the campus of University of Nottingham. They were then contacted and screened with the rTMS screening questionnaire (Rossi et al., 2009); those with a history of severe psychiatric disorders, alcohol and substance abuse, and drug dependence were excluded according to participants' self-report. Thirty-one eligible candidates were invited to take part in the study; however, seven of them were unable to attend due to other commitments, three participants dropped out after the first session without giving a reason, and another withdrew from the study without giving a reason. This was after completion of the impulsivity questionnaires and prior to receiving rTMS. The data for those 4 participants who did not complete the study were excluded from the analysis. The final sample consisted of 20 healthy male participants (mean age = 21.80 years, SD = 1.85 years; range: 18 – 25 years).

Most researchers rely on previous studies or personal experience to determine the sample size in TMS studies (Héroux, Taylor, & Gandevia, 2015). Since no previous studies used excitatory rTMS over the rIFG to modulate impulsivity, we followed the suggestion in common practise of using a medium effect size to determine the sample size. To determine the minimum sample size required to reach sufficient statistical power, a priori power analysis for repeated measures ANOVA was performed using the

software G*Power 3.1.5 (Faul, Erdfelder, Lang, & Buchner, 2007). Essential parameters were set as follows: a medium effect size (f = 0.25) of the within-between interaction effect, significance level (α = .05), power (1 – β = .80), the number of groups = 2, and the correlation among repeated measures as the default value (r = .5); a minimum number of 34 participants was estimated for a randomised parallel design study. Since only half of the sample is required for a randomised crossover design (Brown, 1980), we argue that the current study was sufficiently powered to detect differences in effects between active TMS and sham.

All study participants, except for one, were right-handed. All participants were students from University of Nottingham and had normal or corrected-to-normal visual acuity. The study was approved by the Research Ethics Committee of the University of Nottingham Medical School (G18102012 IMH rTMS) and written informed consent was obtained from all participants before commencing the study.

6.3.2 Procedures

After confirming eligibility, consenting participants were asked to complete two self-report measures of impulsivity, namely the the Barratt Impulsiveness Scale, Version 11 (BIS-11; Patton et al., 1995; See Appendix 12) and UPPS-P Impulsive Behaviour Scale (UPPS-P; Lynam et al., 2006; See Appendix 13). Participants were then asked to complete the IST and SST before and after the rTMS session. A second rTMS session was conducted at least 5 days later to minimise the carry-over effect from the first rTMS session. The procedure in the second session was identical to the first one, but without

repeating the administration of the BIS and UPPS-P. Participants were randomly allocated to receive either active rTMS or sham such that one session involved the administration of active rTMS, while the other involved the administration of sham rTMS. Half of the participants received active rTMS for their first session. The orders of the active or sham stimulation condition and the two computerised tasks administered were randomised within and across participants according to the random number table. Participants were blind to the stimulation condition. Once the order of the two computerised tasks was confirmed, they would be performed with the same sequence on the 4 occasions. The IST and SST tasks were administered on a Motion Computing J3500 tablet PC with Intel Pentium i5 processor (1.07 GHz), 2 GB RAM, Windows 7 Professional 32-bit operating system, fitted with an 11.2-inch touch screen monitor and a press pad as appropriate. The volume of sound was set at 50% of the device maximum output. After completing the full sessions of the study, participants were debriefed, and asked to guess whether they received the active or sham stimulation. All participants received monetary compensation (20 pounds) for their time. All evaluations, questionnaires and tasks were administered according to a comprehensive manual of operation instructions in a standardised manner.

6.3.3 Materials

6.3.3.1 rTMS

A transcranial magnetic stimulator (Magstim Rapid 2) and a 70-mm standard figure-of-eight shaped air-cooled coil were used for rTMS. Individual resting motor threshold (RMT) was defined as the lowest intensity inducing visible

movement of the right abductor pollicis brevis in 5 of 10 consecutive trials through a priori single-pulse TMS experiment with a hand-held coil. The intensity of rTMS in the main experiment was set at 100% of RMT. The mean RMT across participants was 53.10± 8.64% (range: 36- 67%) maximum stimulator output. The 45 trains of 10-Hz rTMS stimulation session consisted of 900 pulses in total with a 2-sec duration of each train and a 10-sec interval between each train. The centre of the coil producing the maximum magnetic field was positioned perpendicularly to the rIFG. In sham stimulation, a sham coil was placed on the rIFG with the same protocol applied. The sham rTMS coil was identical to the active coil in appearance, operation, and sound properties without magnetic pulse delivery. The accurate stimulation site was confirmed using the localisation method proposed by Gough, Nobre and Devlin (Gough et al., 2005) for targeting the posterior rIFG: 4.5 cm posterior to the right canthus along the canthus-tragus line and 6 cm perpendicularly superior to the line. The rIFG localisation technique has been identified by using frameless stereotaxy in a group of volunteers with structural MRI scans used by other recent rTMS studies (Waldowski et al., 2012).

6.3.3.2 Self-report measures of impulsivity

UPPS-P is a multifaceted scale measuring five dimensions of impulsivity: sensation-seeking, lack of premeditation, lack of perseverance, negative urgency, and positive urgency. The overall scale, as well as its components, has been validated for use in clinical and healthy populations (Cyders, 2013; Cyders et al., 2007; Whiteside & Lynam, 2001).

BIS-11 is a 30-item inventory encompassing three subscales: motor (acting out without thinking), attentional (making-up one's mind quickly), and non-planning (not planning ahead) impulsivity. The internal consistency coefficients for the BIS-11 total score are considerably good, ranging from 0.79 to 0.83 for variant populations of young adults, clinical samples, and criminal populations (Patton et al., 1995).

6.3.3.3 Performance-based (behavioural) measures of impulsivity

The SST and IST, two computerised neuropsychological tasks from the Cambridge Computerised Neuropsychological Battery (CANTAB; Cambridge Cognition, 2016), were used to index impulsivity. The CANTAB has been used to assess cognition in over 800 research institutions and validated by over 1,500 peer-reviewed publications (Cambridge Cognition, 2015; Fray, Robbins, & Sahakian, 1996). CANTAB tasks are administered via a computer with a touch screen and a press pad for some specific tasks. The normative data of CANTAB tasks consists of a large-scaled UK population across almost the whole lifespan (4-90 years) collected from various studies with satisfactory levels of reliability and validity (Strauss, Sherman, & Spreen, 2006).

SST, the task to assess MI, is a classic stop signal response inhibition test that measures an individual’s ability to inhibit a prepotent response (Logan, 1994). Participants received initial training to use the press pad, and were instructed to rapidly press the left hand button with their left index finger for arrows pointing to the left and the right hand button with their right index finger for arrows pointing to the right. Afterwards, participants were given a practice

session of 16 trials showing a circle appearing on the screen with an arrow pointing either to the right or left of the screen (go signal). The direction of the arrow changed randomly after a 500ms delay. In the formal experimental session, a beeping sound (auditory stop signal) is randomly delivered by the computer at a short delay after the presentation of the arrows in 25% of the trials; participants are instructed to withhold their response if they hear the beep but keep pressing the button corresponding to the particular arrow if the beep is not present. The task consists of five blocks with 64 trials in each block and the time of completing SST is estimated around 15 minutes. In between two blocks, the participant is presented with a feedback screen which indicates the speed of pressing. The participant is encouraged to press faster while advised that the stopping after a beep is as important.

The difficulty of the task is changed by manipulating the delay time of the stop signal (stop signal delay, SSD) such that the sooner the stop signal occurs after the onset of the go signal, the easier it becomes for the participants to inhibit their responses. Four interleaved step-case functions were used, starting at 100, 200, 400, and 500ms to make it difficult for the participant to predict the onset of the stop signal. The test was calibrated such that the difficulty of the next trial was increased following a successful withhold response by increasing the SSD by 50ms. Conversely, failure to inhibiting a response decreased the difficulty of the next trial by reducing the SSD by 50ms.

SSRT is the primary outcome measure for reactive inhibitory control. It is defined as the mean reaction time on go trials minus the mean SSD at which

the participant was able to successfully withhold a response on 50% of the trials. Based on this definition, longer SSRT corresponds to poorer response inhibition. The index of proactive inhibitory control was defined as “post-error slowing” measured as the mean increment of go reaction times in the trial following an unsuccessful stop.

IST is a measure of RI. It examines the tendency to gather and evaluate information before making a decision. The task entails presenting a grid of 25 closed boxes on the computer screen. The boxes can be opened by touching the screen to reveal an underlying colour from two specific colours displayed at the bottom of the screen. Participants are then requested to decide, on each trial, which one of the two colours is predominant by sampling information from opening boxes. Participants are instructed to open as many boxes as they wish before making a decision. The decision is confirmed by touching a coloured square at the bottom of the screen.

The task comprises of two conditions each consisting of 10 trials; the fixed win (FW) and the decreasing win (DW). In the FW condition, participants can win 100 points for a correct response regardless of the number of boxes opened. In the DW condition, and in order to introduce a conflict between level of certainty and the points available to win, the number of points that can be earned from 250 decreases by 10 with each box opened. A penalty of 100 points is given for every incorrect response in both conditions. Participants received clear instructions about the rules of the task before each condition and asked to perform a practice trial. The level of certainty (i.e., the probability

of making the correct decision given the information sampled; termed Pcorrect) is the primary outcome measure.

Since there are some debates (Axelsen, Jepsen, & Bak, 2017; Bennett, Oldham, et al., 2017; Bennett, Yücel, & Murawski, 2017) about the traditional *algorism* of Pcorrect proposing that the original Pcorrect overestimates the real level of RI, this study used the Pcorrect algorism recently proposed by Bennett et al., (Bennett, Oldham, et al., 2017) and also recommended by Clark and Robbins (Clark & Robbins, 2017), the inventors of the IST. Higher Pcorrect values denote a lower tendency of RI and higher cognitive control. Other key measures for this task were selected as secondary outcomes, including the number of correct decisions, total points earned and the mean number of boxes opened. The number of sampling errors was expected to be inversely related to the number of boxes opened (DeVito et al., 2009). The time of completing the whole IST is about 15 minutes according to the manual.

6.3.4 Statistical analysis

Data analysis was carried out using SPSS v22.0. Continuous data were checked for normality using Shapiro-Wilk statistics before conducting further statistical analyses. Data obtained from SST and IST were analysed separately as follows. Outliers were detected using the rule of 1.5 interquartile range and skewed data were statistically transformed for the fitness of assumptions for analysis of variance (ANOVA). For adjusting positive skewness, square-root or logarithm transformation was used. For reducing negative skewness, a reflected transformation was employed. Independent

t-test was applied to examine possible variations between individuals in the group receiving active or sham rTMS as the first session. In cases where the data violated the assumptions of ANOVA but were not appropriate for transformation, non-parametric tests (Friedman's test and Wilcoxon signed rank test) were used. Separate 2 X 2 repeated measures ANOVAs with stimulation (rTMS vs sham) and session (pre-rTMS vs post-rTMS) as within-subject factors were used to compare the change of each outcome variable during rTMS between active and sham conditions. The Spearman's rank correlation coefficient (r_S) was calculated to determine the correlations between self-report and behavioural measures of impulsivity measures. To determine the influence of self-reported impulsivity, the total scores BIS-11 and UPPS-P were selected as covariates in repeated measures analysis of covariance (ANCOVA). A *P* value of < .05 was considered as statistically significant.

6.4 RESULTS

6.4.1 Overview

The participants' baseline performance on trait impulsivity measures is presented in Table 6-1. Compared to the BIS-11 total and subscale scores of 393 young male adults in Stanford et al., (2009), the impulsivity level of participants in the current study were within normal range (t_{411} = 0.235 – 1.622, p = .106 – .814, d = 0.054 – 0.372). With regard to the subscale scores of UPPS-P, the participants did not have differently mean scores on all subscales compared to those of 447 male colleges students in Cyders (2013) (t_{465} = 0.702 – 1.623, p = .105 – .483, d = 0.160 – 0.371). The manipulation of single blind sham-controlled design was successful since the rate (65%) of correct identification of the active rTMS condition did not significantly differ from chance (χ^2 [1, N = 20] = 0.921, p = .337). All participants tolerated rTMS well and completed the study. Only short-lived adverse events were reported including mild local pain (n = 3), mild headache (n = 2), and muscle twitching around the right eye (n = 5). Analysis indicated that the effect of the presentation order (SST first, IST FW condition first, and IST DW condition first) was not significant (all p > .05) for all outcome variables; therefore, we did not take this factor into account in subsequent analyses (Table 6-2).

Table 6-1 Baseline performance on self-report measures of impulsivity

measurements	mean± SD	range	Normative data[b]
BIS-11 Total	62.30± 10.68	(41 - 81)	62.80± 9.20
Motor	23.70± 5.10	(13 - 32)	22.40± 3.40
Attentional	16.10± 3.11	(12 - 23)	16.80± 3.90
Non-planning	22.50± 4.45	(15 - 33)	23.60± 4.50
UPPS-P Total[a]	2.23± 0.31	(1.68 – 2.86)	
Negative Urgency[a]	2.19± 0.47	(1.58 – 3.33)	2.32± 0.57
Lack of Premeditation[a]	2.07± 0.34	(1.45 – 2.64)	2.00± 0.44
Lack of Perservance[a]	1.77± 0.41	(1.20 – 2.80)	1.85± 0.42
Sensation Seeking[a]	2.96± 0.56	(1.58 – 3.75)	3.15± 0.51
Positive Urgency[a]	2.11± 0.45	(1.43 – 3.00)	1.97± 0.59

[a] The Mean is the average response across items in each scale
[b] The normative data (males only) are from the following studies: BIS-11: Stanford et al., (2009), n =393; UPPS-P: Cyders et al., (2013), n =447
BIS-11, Barratt Impulsiveness Scale, Version 11; UPPS-P, UPPS-P Impulsiveness Scale

6.4.2 SST

In relation to go trials, there was no difference among conditions (pre-active, post-active, pre-sham, and post-sham) for either accuracy (χ^2 [3, N = 20] = 2.591, p = .459) or mean correct reaction time (χ^2 [3, N = 20] = 3.424, p = .331). The proactive inhibitory control index values were square-root transformed and the repeated measures ANOVA for the proactive inhibitory control index did not reveal significant main effects for stimulation type (F [1,19] = 0.167, p = 0.687, η^2 = .009) and interaction (F [1,19] = 0.011, p = 0.92, η^2 = .001), but for the timing (F [1,19] = 4.710, p = 0.043, η^2 = .199).

Regarding stop trials, there was also no difference among conditions for the proportion of successful stops (χ^2 [3, N = 20] = 0.897, p = .826), SSD (χ^2 [3, N = 20] = 0.377, p = .945), and failed to stop reaction time (χ^2 [3, N = 20] = 1.620, p = .655). SSRT values were log transformed; the repeated measures

ANOVA for the SSRT did not reveal significant main effects for stimulation type (F [1,19] = 0.221, p = 0.643, η^2 = .012), timing (F [1,19] = 0.054, p = 0.819, η^2 = .003) and interaction (F [1,19] = 0.107, p = 0.747, η^2 = .006).

Practice effect was evident in SST with a significant shortening of pre-rTMS SSRT (t[19] = 2.23, p = .038, d = 0.50) and the proactive inhibitory control index (t[19] = 4.08, p = .001, d = 0.91) in the second session compared to those in the first session, regardless of whether active or sham stimulation was delivered in the first session.

6.4.3 IST

Analyses of FW trials revealed no statistically significant differences among conditions for correct decision (χ^2 [3, N = 20] = 1.215, p = .749) and points earned (χ^2 [3, N = 20] = 1.215, p = .749). ANOVA for the Pcorrect in FW conditions did not reveal significant main effects for stimulation (F [1,19] = 0.597, p = 0.449, η^2 = .030), time (F [1,19] = 0.033, p = 0.858, η^2 = .002), nor for the interaction (F [1,19] = 0.005, p = 0.942, η^2 = .000). The repeated measures ANOVA for the number of boxes opened in FW conditions revealed a significant effect for interaction (F [1,19] = 7.104, p = 0.015, η^2 = .272) but not main effects for stimulation (F [1,19] = 0.012, p = 0.913, η^2 = .001) and time (F [1,19] = 0.075, p = 0.787, η^2 = .004). Post-hoc analyses of the interaction using one-way ANOVA did not reveal any significant difference in any of the comparisons (p > 0.05). In DW, there was no difference among conditions for correct decision (χ^2 [3, N = 20] = 1.870, p = .600). The repeated measures ANOVA for the Pcorrect in DW conditions did not reveal significant main effects for stimulation (F [1,19] = 0.818, p = 0.377, η^2 = .041), time (F

[1,19] = 0.943, p = 0.344, η^2 = .047), nor for the interaction (F [1,19] = 0.89, p = 0.769, η^2 = .005). The repeated measures ANOVA for the number of boxes opened in DW conditions did not reveal significant main effects for stimulation (F [1,19] = 0.613, p = 0.443, η^2 = .031), time (F [1,19] = 0.711, p = 0.409, η^2 = .036), nor for the interaction (F [1,19] = 1.701, p = 0.208, η^2 = .082). No practice effect was found in relation to IST (Pcorrect in FW: t[19] = 0.59, p = .57; Pcorrect in DW: t[19] = 0.61, p = .55).

6.4.4 Correlations between tasks

Table 6-3 presents the intercorrelations between baseline measures of self-report and performance-based impulsivity. Significant correlations were found between the total scores of UPPS-P and BIS-11 (r_S = .66, p = .002) and some of their subscales. However, with respect to performance-based impulsivity, only the Pcorrect in the FW condition was correlated with self-report impulsivity. No significant associations were found between the Pcorrect in the FW and DW conditions. Moreover, there was no significant correlation between the primary measures of the SST and IST.

6.4.5 Self-report impulsivity as covariates

Total scores of BIS-11 and UPPS-P were selected as covariates into the ANCOVA to analyse the effects of self-report impulsivity on their performance-based counterparts. No significant effects on the post-stimulation changes among behavioural measures was found regardless of using the total scores of either BIS-11 or UPPS-P as covariates (all p > .05).

Table 6-2 Performances on impulsivity tasks across conditions

Tasks	Pre-Sham	Post-Sham	Pre-Active	Post-Active
SST-go trials				
Success rate (%)	99.15± 0.90	98.71±1.77	99.11±1.17	98.48±2.26
RT (msec)	402.65± 143.21	395.43± 167.18	423.48± 175.15	416.75± 214.37
PI (msec)	65.46± 37.39	53.73± 26.15	68.78± 35.67	60.62± 41.65
SST-stop trials				
Success rate (%)	48.75± 0.07	48.00± 0.08	49.94± 0.12	49.31± 0.11
SSD (msec)	263.00± 134.43	252.96± 147.50	287.36± 176.59	274.24± 190.49
SSRT (msec)	139.65± 24.07	142.47± 43.53	136.11± 34.15	142.51± 51.59
Failed RT (msec)	354.16± 102.97	346.48± 108.01	360.84± 98.41	365.98± 169.06
IST-FW				
Correct decision	9.25± 1.07	9.10± 1.25	9.20± 0.95	9.30± 1.17
Points earned	950.00± 213.99	910.00± 246.88	940.00± 190.29	960.00± 234.86
Boxes opened	17.68± 4.83	18.48± 4.23	18.41± 4.23	17.62± 4.85
P (correct) (%)	91.13± 7.75	91.78± 6.52	92.34± 6.93	91.78± 8.18
IST-DW				
Correct decision	8.40± 1.35	8.60± 1.14	8.30± 1.34	8.60± 1.05
Points earned	1125.00± 272.00	1154.50± 224.58	1062.50± 221.38	1161.00± 176.04
Boxes opened	10.20± 3.45	10.70± 3.57	10.88± 3.36	10.74± 3.25
P (correct) (%)	83.79± 5.83	84.70± 5.01	83.43± 6.15	83.88± 5.47

Data are presented as Mean± SD

DW, decreased win condition; FW, fixed win condition; IST, Information Sampling Task; PI, index of proactive inhibitory control; RT, reaction time; SSD, stop signal delay; SSRT, stop-signal reaction time; SST, Stop-Signal Task

Table 6-3 Correlation matrix for the baseline impulsivity

Spearman's rho Correlation Coefficient	1	2	3	4	5	6	7	8	9	10	11	12	13
BIS-11													
1 attentional													
2 motor	.30												
3 non-planning	.46*	.78**											
4 total score	.61**	.90**	.91**										
UPPS-P													
5 NU	-.13	.55*	.46*	.44*									
6 PM	-.01	.78**	.60**	.62**	.46*								
7 PE	.06	.29	.47*	.33	.21	.40							
8 SS	-.10	.39	.08	.21	.31	.29	-.11						
9 PU	.52*	.54*	.60**	.66**	.62**	.36	.18	.32					
10 total score	.12	.75***	.60**	.66**	.76***	.69**	.37	.62**	.78***				
11 IST PFW	-.64**	-.40	-.65**	-.61**	-.18	-.15	-.26	-.10	-.57**	-.43			
12 IST PDW	-.09	-.07	-.34	-.23	-.37	.15	-.01	-.11	-.38	-.22	.34		
13 SST SSRT	-.24	-.05	-.03	-.11	-.10	.00	-.26	-.01	-.14	-.17	.27	-.25	
14 SST PI	.06	-.14	-.03	-.14	-.25	-.19	-.20	.18	-.09	-.07	-.10	.09	-.03

BIS-11, Barratt Impulsiveness Scale, Version 11; IST, Information Sampling Task; NU, Negative Urgency Subscale; PDW, Pcorrect in the decreased win condition; PE, Lack of Perseverance Subscale; PFW, Pcorrect in the fixed win condition; PI, index of proactive inhibitory control; PM, Lack of Premeditation Subscale; PU, Positive Urgency Subscale; SS; Sensation-Seeking Subscale; SSRT, stop-signal reaction time; SST, Stop-Signal Task; UPPS-P, UPPS-P Impulsivity Behavioural Scale

indicates significant correlation ($p < .05$, ** $p < .01$, *** $p < .001$)

6.5 DISCUSSION

The present study aimed to examine the effects of excitatory rTMS at the rIFG on MI and RI. Contrary to our prediction, there were no post-excitatory rTMS changes in any of the performance-based impulsivity tasks. Findings from existing neuroimaging research (Aron, 2007; Levy & Wagner, 2011) suggested that the rIFG is highly involved in MI, especially the reactive inhibitory control. Significant modifications in SSRT result from inhibitory rTMS (Chambers et al., 2007; Chambers et al., 2006) and anodal tDCS studies (Cai et al., 2016; Castro-Meneses et al., 2016; Ditye et al., 2012; Jacobson et al., 2011) also support this view. Our findings regarding reactive inhibitory control seem to contradict the existing evidence. A notable exception is a recent study (Dambacher et al., 2015) utilising bilateral tDCS to IFG to modulate impulsivity, which also revealed null results on reactive inhibitory control.

These findings add to the controversy surrounding the role of rIFG in proactive inhibitory control. Some commentators (Li et al., 2008) argued that rIFG is involved in proactive inhibitory control as indexed by post-error slowing while others (Zandbelt, Bloemendaal, Neggers, Kahn, & Vink, 2013) found that stimulation of the rIFG produced no tangible effects on proactive inhibitory control.

With regard to RI, contrary to existing evidence which implicates the rIFG in risk evaluation (Christopoulos et al., 2009; Cohen et al., 2013), our findings suggest that excitatory rTMS had no significant impact on RI as measured using the IST. One potential explanation is that IST taps into decision making

based on evaluation of information gathered rather than risky decision-making. Therefore, some authors (Fineberg et al., 2014) regard disadvantageous decision-making as a subtype of impulsivity which is distinct from RI. Since no other studies examined the use of rTMS at the rIFG to modify RI (Brevet-Aeby et al., 2016), further studies are required to ascertain the role of rIFG in RI.

A number of other explanations exist to interpret our findings. First, it is possible that the rTMS protocol used in the current study was not sufficiently strong to induce functional changes at the rIFG. However, this is unlikely to be the main reason since previous studies (Hwang et al., 2010; Sibon et al., 2007) using similar protocols reliably demonstrated neuromodulatory effects at prefrontal and striatal brain regions. Second, it is possible that the post rTMS effects were not sustained for long enough to be detected by the post-rTMS examination. Once again, this is unlikely to be a major factor since the three-way repeated measures ANOVA did not find main effects or interaction from the order of the task presentation. Further, according to Thut and Pascual-Leone (Thut & Pascual-Leone, 2010), the after effect induced by high frequency rTMS could last for up to 30 minutes, which is longer than the time required to complete the two tasks in our study. Third, it is possible that the rIFG was not properly targeted and stimulated due to our localisation method. The precision of targeted stimulation using neuro-navigation techniques is superior to the traditional landmark method (Ruohonen & Karhu, 2010). Considering that the rIFG localisation method we used (Gough et al., 2005)has been verified (Waldowski et al., 2012) and TMS studies remain working without imaging assistance (Sack, 2010), it is still highly possible that the rIFG was correctly targetted. Finally, another argument is that the

participants recruited were over-controlled to allow the detection of post rTMS changes and some ceiling effects could be assumed from their task performances. For example, this might be true since our participants were from a well-educated university sample. However, repeating the analyses after exclusion of the three highly-controlled participants with extremely low scores on the BIS-11 (Stanford et al., 2009), yielded similar results. Put together, given dearth of similar studies in the field, our findings should be regarded as evidence of absence rather than absence of evidence (de Graaf & Sack, 2011).

Contrary to predictions, our results did not reveal significant associations between Pcorrect in FW and DW and between the proactive inhibitory control index and SSRT. Previous studies (Caswell et al., 2015) employing IST have found stable correlations between Pcorrect in FW and in DW conditions using the traditional algorism proposed by Clark et al. (2006). This may reflect the uniqueness of new Pcorrect since the decision processes in FW and DW are underpinned by different levels of uncertainty (Clark et al., 2006) and the findings of weak or nil correlation between these two measures should be expected. Moreover, it is unexpectedly to find significant correlations between Pcorrect in FW and some scores (attentional, non-planning and total score of the BIS-11 as well as the Positive Urgency of the UPPS-P) of self-report measures. However, it should be less surprising to obtain the positive correlations given that the FW condition is not designed to introduce high uncertainty to encourage the participant to generate impulsive responding (Clark et al., 2006). Since there is no conflict between reinforcement and

certainty in the condition, the participant can make his decisions according to his usual behavioural repertoire (i.e., traits of impulsivity).

Although the non-association between the reactive inhibitory control and proactive inhibitory control further supports the view of dual mechanisms of inhibitory control (Stuphorn & Emeric, 2012), other studies (Cai et al., 2016) have found a positive relationship between proactive inhibitory control and reactive inhibitory control using other indicators of proactive inhibitory control. As there is no unitary index of proactive inhibitory control (Elchlepp et al., 2016), future studies are encouraged to develop a universal agreed index to denote proactive inhibitory control.

Given that SST and IST are both included in the CANTAB, one may argue that the similarity or overlapping of the task components would affect the outcome in the current study although they measure different subdomains of impulsivity. However, this is less likely in the current study. Firstly, the order of task presentation was randomised controlled, and the effect of task presentation was not significant on performances of either IST or SST. Secondly, there were no significant correlations between the primary measures of the SST and IST. This is in accord with the suggestion of Clark et al., (2006) that response disinhibition (i.e., motor impulsivity) seems unlikely to account for poor IST performances, because box opening should become more prepotent than the decision response. Therefore, the effects of task relevance should not be crucial to interpret the findings in the current study.

The limitations of this study are numerous, including a relatively small sample size, use of the traditional method to localise stimulation site, as opposed to

using navigated rTMS, and the absence of neuroimaging or neurophysiological outcomes. Further, both sham and active rTMS first groups displayed evidence of practice effects on the SST (i.e., shorten SSRT in the second pre-rTMS assessment), and ceiling effects were generally noted from their task performances. Therefore, it is necessary to design tasks with adjustable difficulties to detect the post stimulation changes among a high-functioning adult sample. Moreover, the enrolment of young adult males with less impulsive tendencies further weakens the generalisability to other samples, such as female adults. The reason that only males were recruited in the study was for providing empirical evidence for future studies aiming at treating impulsivity of individuals with antisocial personality disorder or psychopath which may be predominantly male.

6.6 CONCLUSIONS

In summary, this study provides preliminary findings of non-significant effects from excitatory rTMS at the rIFG on impulsivity, although it contradicts findings from previous anodal tDCS studies. It will be worthy to modify the protocol with multiple sessions, more robust excitatory rTMS, like iTBS, or higher stimulation intensity to generate stronger effects to the rIFG. Recruitment of clinical populations with certain impaired impulse control is also merited. Study limitations are numerous and in hindsight, we accept that these could have been addressed at an earlier stage.

6.7 CONFLICT OF INTEREST

There is no conflict of interest.

6.8 ACKNOWLEDGEMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CHAPTER 7 : EFFECTS OF INTERMITTENT THETA BURST STIMULATION APPLIED TO THE LEFT DORSOLATERAL FRONTAL CORTEX ON EMPATHY AND IMPULSIVITY IN HEALTHY ADULT MALES

This chapter is presented in the format of a submitted manuscript as outlined in 'Remarks on Presentation of Thesis in Alternative Format' namely Yang, C.-C., Khalifa, N., Lankappa, S. & Völlm, B. (2018). Effects of intermittent theta burst stimulation applied to the left dorsolateral prefrontal cortex on empathy and impulsivity in healthy adult males. *Brain and Cognition* (under review).

Authors

Cheng-Chang Yang[1]*, Najat Khalifa[1, 2], Sudheer Lankappa[2] & Birgit Völlm[1, 2]

[1] Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, UK

[2] Nottinghamshire Healthcare NHS Foundation Trust, UK

***Author for correspondence**

Contact information:

Institute of Mental Health
University of Nottingham Innovation Park
Triumph Road

Nottingham, NG7 2TU
UK

Cheng-Chang Yang Email: cheng-chang.yang@nottingham.ac.uk

Najat Khalifa Email: najat.khalifa@nottingham.ac.uk

Sudheer Lankappa Email: Sudheer.Lankappa@nottshc.nhs.uk

Birgit Völlm Email: birgit.vollm@nottingham.ac.uk

7.1 ABSTRACT

Background: Impulsivity and empathy are both multi-dimensional with clinical relevance. Existing evidence suggests that the left dorsolateral frontal cortex (LDLPFC) plays a crucial role in impulsivity and empathy, and it has not been well-examined using excitatory repetitive transcranial magnetic stimulation (rTMS). We therefore aimed to use intermittent theta burst stimulation (iTBS) at the LDLPFC to address this important gap in the literature.

Methods: Twenty-three healthy male adults completed a single-blind sham-controlled randomised crossover study. The iTBS protocol delivered 1800 pulses to the LDLPFC at the intensity of 80% motor threshold in each condition. Trait impulsivity and empathy were measured at baseline using the Barrett Impulsiveness Scale and UPPS-P Impulsiveness Scale. The Reading the Mind in the Eyes Test (RMET), Information Sampling Task (IST), and Adjusting Amount Task (AAT) serving as behavioural measures of empathy, reflection impulsivity and temporal impulsivity respectively administered before and after iTBS sessions.

Results: No significant changes were found on any measures from RMET, IST, and AAT after iTBS at the LDLPFC compared to the sham stimulation.

Conclusions: Excitatory neuromodulation at the LDLPFC using iTBS did not reveal statistically significant effect on cognitive empathy and temporal and reflection impulsivity. Further research is required to amend the current protocol with multiple sessions in a large-scaled sample.

Keywords: transcranial magnetic stimulation; theta burst stimulation; impulsivity; empathy; dorsolateral prefrontal cortex; delayed discounting

7.2 INTRODUCTION

Violence has been recognised as a major public health issue worldwide (Krug, Mercy, Dahlberg, Zwi, & Lozano, 2002). Risk factors for violent behaviour have been investigated in the last few decades (Reidy et al., 2013) where low empathy (Jolliffe & Farrington, 2004; van Langen et al., 2014) and high impulsivity (Bjørkly, 2013; Chamorro et al., 2012) have persistently been identified in literature. Both of them are considered multi-dimensional consisting of heterogeneous components with specific neuroanatomical underpinnings (Dvash & Shamay-Tsoory, 2014; Fineberg et al., 2014).

Empathy refers to the abilities of human beings to detect and understand cognitive and emotional processes in others (Smith, 2006). Accumulating neuroscientific evidence (Dvash & Shamay-Tsoory, 2014) reveals that empathy encompasses two components, namely cognitive empathy (also referred to as Theory of Mind, ToM) and emotional (affective) empathy, although some debates regarding the two-component construct remain (e.g., Blair, 2005). Cognitive empathy is considered the ability to understand another's emotions and feelings while affective empathy is the ability to share another's emotional state, and to experience feelings of the other person (Dvash & Shamay-Tsoory, 2014; Reniers et al., 2011; Smith, 2006). For assessing empathic trait and behaviour, self-report questionnaires, such as the Questionnaire of Cognitive and Affective Empathy (QCAE; Reniers et al., 2011), are a common and convenient instrument over the decades. In contrast, recent neuroscientific studies in this field tend to apply behavioural or neurophysiological measures to index empathy. The Reading the Mind in the Eyes Test (RMET; Baron-Cohen et al., 2001) is one of the validated

behavioural tasks measuring cognitive empathy by requesting participants to identify the emotional or mental state of a person based on only an image of their eyes. On the other hand, investigating affective empathy in laboratory has often relied on the use of neurophysiological measurements, such as neuroimaging, facial electromyography or cardiovascular activity; however, this approach is still developing and pre-mature to elucidate empathy (Neumann & Westbury, 2011). Given that a variety of brain regions have been considered to engage in empathy (Hetu et al., 2012), anterior cingulate cortex (ACC), supplementary motor area, and bilateral anterior insula have been identified as being consistently activated in empathy in one meta-analytic neuroimaging study (Fan et al., 2011).

The concept of impulsivity encompasses a range of behaviours such as motor impulsivity, the inability to suppress a behavioural response; temporal impulsivity (also referred to as delay discounting), the failure to delay gratification with the preference for small but immediate rewards; and reflection impulsivity, the tendency to make premature decisions without sampling enough information or to favour a more risky option resulting in disadvantageous decision-making (Caswell et al., 2015; Caswell et al., 2016; Evenden, 1999b; Grant & Kim, 2014; Verdejo-Garcia et al., 2008). Traditionally, self-report inventories have been employed to measure trait impulsivity (Evenden, 1999b). The Barratt Impulsiveness Scale, Version 11 (BIS-11; Patton et al., 1995) and UPPS-P Impulsive Behaviour Scale (UPPS-P; Lynam et al., 2006) are two of the famous inventories with appropriate psychometric properties. In laboratory settings, motor impulsivity is commonly assessed using the Stop-Signal Task (Logan, 1994) or Stroop

Colour-Word Interference Test (Stroop, 1935). With regard to temporal impulsivity, the Monetary Choice Questionnaire (Kirby et al., 1999) and the Adjusting Amount Task (AAT; Du, Green, & Myerson, 2002; Frye, Galizio, Friedel, DeHart, & Odum, 2016) are utilised across studies. For reflection impulsivity, it is typically measured using information-sampling tasks such as the Information Sampling Task (IST; Cambridge Cognition, 2016; Clark et al., 2006) and the Iowa Gambling Task (Bechara et al., 1994) to index inadequate reflection and disadvantageous decision-making respectively. The dorsalateral prefrontal cortex (DLPFC), ventromedial prefrontal cortex (vmPFC) and ACC play an important role in all forms of impulsivity (Castellanos-Ryan & Séguin, 2015).

Given that impulsivity and empathy are found in a myriad of violent behaviour, they are assumed as compelling targets for intervention. However, results of current psychological and psychopharmacological treatments aiming at decreasing impulsivity (Tomko et al., 2016) and enhancing empathy (Day et al., 2010; Mann & Barnett, 2013) remain equivocal. It highlights the need for a novel intervention approach that directly targets their underlying neural dysfunction. Repetitive Transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that has been widely used to modulate brain activities (Wassermann & Zimmermann, 2012). Compared with conventional rTMS, a new form of rTMS, namely Theta Burst Stimulation (TBS; Huang et al., 2005) leads to comparable effects with higher tolerability but considerable shorter duration and lower intensity of stimulation (Bakker et al., 2015; Thut & Pascual-Leone, 2010) with intermittent TBS (iTBS) generating excitatory effects while continuous TBS (cTBS) exhibiting

inhibitory effects (Rossi et al., 2009). Recent systematic reviews have shown that rTMS may effectively modulate impulsivity (Brevet-Aeby et al., 2016; Yang, Völlm, & Khalifa, 2018) and empathy (Yang, Khalifa, & Völlm, 2018a) in healthy individuals; nevertheless, several issues require further investigations.

Firstly, as proposed in the previous reviews (Hetu et al., 2012; Schuwerk, Langguth, et al., 2014), effective stimulation protocols and behavioural outcome measurements sensitive to the rTMS-induced changes would be suggested. Secondly, for impulsivity, a majority of rTMS studies have tend to concentrate on motor impulsivity rather than on temporal and reflection impulsivity which are considered of higher clinical (Caswell et al., 2015; Caswell et al., 2016) and ecological relevance to daily life (Cho et al., 2010). Future rTMS studies should pay more attention to these two domains. Thirdly, some recent evidence in healthy samples has shown that the effects of neuromodulation on behavioural measures of empathy (e.g., Balconi & Bortolotti, 2013; Krause et al., 2012) and impulsivity (e.g., Cheng & Lee, 2016; Shen et al., 2016) are moderated by the individual's baseline trait. However, this associations have not been addressed in the previous reviews and not well explored among studies although self-report and behavioural measures of impulsivity correlate weakly with each other (Caswell et al., 2015; Yang, Khalifa, et al., 2018b). Lastly, as mentioned in the recent review articles (Hetu et al., 2012; Yang, Völlm, et al., 2018), a considerable number of research has been devoted to using inhibitory rTMS but less attention has been paid to employing excitatory rTMS, which is of more clinical implication. To be concluded, there is a need to conduct a study using a validated excitatory

rTMS protocol to examine its effects on empathy, temporal impulsivity and reflection impulsivity, considering the levels of healthy individuals' trait empathy and impulsivity at baseline.

With respect to outcome measure tasks, AAT and IST were selected for measuring temporal and reflection impulsivity respectively while RMET was used for measuring cognitive empathy. For the stimulation site, one recent meta-analytic article (Yang, Völlm, et al., 2018) suggest the left DLPFC (LDLPFC) might be a crucial region for modulating impulsivity. Moreover, neuroimaging evidence (Baron-Cohen et al., 1999; Carrington & Bailey, 2009) has identified the involvement of LDLPFC while performing cognitive empathy tasks. Furthermore, one recent iTBS study (Iwabuchi et al., 2017) found remarkable enhanced connectivity between LDLPFC and the anterior insula, another important region for empathy, after stimulating the LDLPFC. Therefore, LDLPFC was considered as the target region for modulating cognitive empathy and impulsivity in the current study.

The current study aims to examine the efficacy of iTBS applied to the LDLPFC in modulating empathy, temporal impulsivity and reflection impulsivity. Based on findings from existing literature in the field, we hypothesised that iTBS would effectively enhance cognitive empathy (measured by RMET) and the control of temporal (measured by AAT) and reflection impulsivity (measured by IST). We also hypothesised that the impact of iTBS on behavioural cognitive empathy and impulsivity measures would be moderated by self-reported empathy and impulsivity respectively.

7.3 MATERIAL AND METHODS

7.3.1 Participants and study design

A single-blind randomised cross-over sham controlled study design was employed in this study. Initially, 33 male volunteers aged from 18 to 30 years were recruited via advertisement on bulletin boards in the campus of University of Nottingham. They were then contacted and screened with the rTMS screening questionnaire (Rossi et al., 2011) and the BIS-11. Those with a history of severe psychiatric disorders, alcohol and substance abuse, and drug dependence were excluded based on the participants' self-report. Five of the candidates did not respond to further invitation without giving a reason, one decided to discontinue the study after seeing the TMS equipment in the laboratory, and another three respondents were excluded because of unusual response patterns (scored less than 52) in BIS-11. Individuals with a total score lower than 52 usually may either be extremely over-controlled or not genuinely respond to the items (Stanford et al., 2009). One participant was excluded due to experiencing suspected neurocardiogenic fainting for few seconds after receiving single-pulse TMS at the intensity of 34% maximum stimulator output (MSO) with less than 10 pulses for determination of his motor threshold. This participant had rapid full recovery of consciousness without any sequela when contacted one week later. Therefore, 23 participants (mean age = 23.57 years, *SD* = 2.95 years; range: 20 – 29 years) took part in and completed the whole study sessions. All study participants, except for one, were right-handed. All participants were students or staff from the University of Nottingham and had normal or corrected-to-normal visual acuity. The study protocols were approved by the Faculty of Medicine and

Health Sciences Research Ethics Committee of the University of Nottingham (C200317) and registered (ClinicalTrial.gov: NCT03200873). Written informed consent was obtained in all cases before commencing the study. Using G*Power 3.1.9.2, a repeated measures ANOVA sample size calculation was conducted based on the previous excitatory rTMS study at LDLPFC in temporal impulsivity (Sheffer et al., 2013). This indicated that a total of 40 participants were required for an effect size of d = 0.34 with 80% power at two-sided p = 0.05, the number of groups = 2, correlation among repeated measures = 0.6. The repeated measures correlation was set as 0.6 based on the result in Chapter 6, instead of the default value of 0.5. Accounting for a 5% dropout rate, a total of 42 people were needed to obtain desired power.

7.3.2 Procedures

The study procedure is shown in Figure 7-1. After confirming their eligibility, consenting participants were asked to complete UPPS-P and QCAE to measure their baseline impulsive and empathic traits. All participants then underwent two different stimulations (iTBS and sham) over the LDLPFC and conducted the computerised behavioural tasks (IST, AAT, and RMET) before and after the completion of TBS in each stimulation session. Stimulation conditions and the order of task administration were randomised across the participants using a random number table generated by Microsoft Excel. There was at least a 48-hour interval between each stimulation condition to minimise the carry-over effect from the prior stimulation. The procedure in the second session was identical to the first one, except for repeating the procedure of obtaining the RMT. Participants were randomly allocated to

receive either active iTBS or sham such that one session involved the administration of active iTBS, while the other involved the administration of sham rTMS. Half of the participants received active iTBS for their first session. For safety concerns, blood pressure, pulse rates, and oxygen saturation level were checked before and after the stimulation. Participants were blind to the stimulation condition until they finished the whole study. Once the order of the three computerised tasks was confirmed, they would be performed with the same sequence on the 4 occasions (i.e., pre- and post- sham iTBS; pre- and post-active iTBS). The IST was processed as one of the in the Cambridge Computerised Neuropsychological Battery (CANTAB; Cambridge Cognition, 2016), while the AAT and RMET were programmed and presented using the E-Prime 2.0 (Schneider, Eschman, & Zuccolotto, 2002). These computerised tasks were administered on a Motion Computing J3500 tablet PC with Intel Pentium i5 processor (1.07 GHz), 2 GB RAM, Windows 7 Professional 32-bit operating system, fitted with an 11.2-inch touch screen monitor and a press pad as appropriate. After completing the full sessions of the study, participants were debriefed, and asked to guess whether they received the active or sham stimulation. All participants received monetary compensation (20 pounds) for their time. All evaluations, questionnaires and tasks were administered according to a comprehensive manual of operation instructions in a standardised manner.

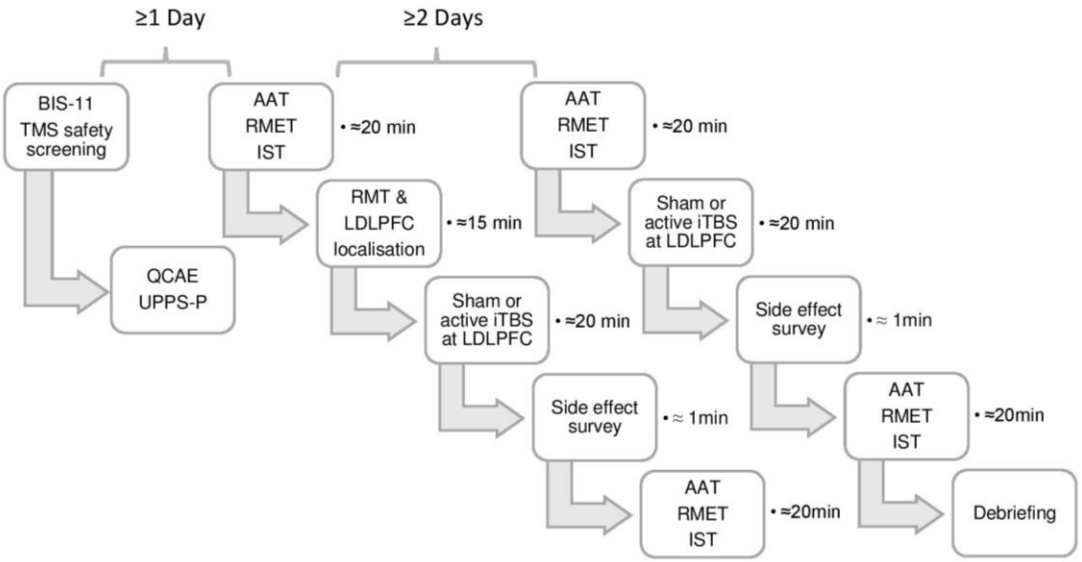


Figure 7-1 Study procedure

BIS-11 = Barratt Impulsiveness Scale, Version 11; IST = Information Sampling Task; iTBS = Intermittent theta burst stimulation; LDLPFC = Left dorsolateral prefrontal cortex; QCAE = Questionnaire of Cognitive and Affective Empathy; RMET = Reading the Mind in the Eyes Test; RMT = Rest motor threshold; TMS = Transcranial magnetic stimulation; UPPS-P = UPPS-P Impulsive Behaviour Scale

7.3.3 rTMS

A transcranial magnetic stimulator (Magstim Rapid 2) and a 70-mm standard figure-of-eight shaped air-cooled coil were used for rTMS. Individual resting motor threshold (RMT) was defined as the lowest intensity inducing visible movement of the right abductor pollicis brevis in 5 of 10 consecutive trials through a priori single-pulse TMS experiment with a hand-held coil. The mean RMT across participants was 57.04± 7.74% (range: 40 - 72%) MSO. Considering the efficiency and duration of stimulation, iTBS was selected as the form of high frequency rTMS with triplets of 50 Hz in a 5 Hz rhythm at 80% of the RMT. The iTBS protocol applied 3 runs of 600 pulses to the LDLPFC, with 20 2-second trains and an 8-second inter-train interval for each run of 190 seconds and five minute rest intervals between runs. This protocol has

been confirmed to effectively induce connectivity and metabolic changes over the LDLPFC (Iwabuchi et al., 2017). Previous neurophysiological studies found the after-effect of the iTBS protocol can last from around 30 (Huang et al., 2005; Katayama & Rothwell, 2007) to 60 mins (Gamboa, Antal, Moliadze, & Paulus, 2010). LDLPFC localisation method applied was the “5-cm method” for treating patients with depression proposed by Pascual-Leone et al. (1996): 5 cm anterior from the stimulating site obtaining RMT along a parasagittal line. For producing the maximum magnetic field to the target area, the centre of the coil plane was positioned tangentially to the scalp with the handle facing backwards at approximately 45° to the midline. In sham stimulation, a sham coil was placed on the LDLPFC with the same protocol applied. The sham coil was identical to the active coil in appearance and only sounds and vibrations were generated without magnetic pulse delivery during the session.

7.3.4 Self-report measures

7.3.4.1 UPPS-P

The UPPS-P is a multifaceted scale measuring five dimensions of impulsivity composed of 59 items, with 10-14 items per dimension: sensation-seeking (seeking out novel and thrilling experiences), lack of premeditation (acting without thinking), lack of perseverance (inability to remain focused on a task), negative urgency (acting rashly under extreme negative emotions), and positive urgency (acting rashly under extreme positive emotions). Each subscale has an internal consistency reliability greater than .80 (Cyders et al., 2007). The overall scale, as well as its components, has been validated for

use in clinical and healthy populations (Cyders, 2013; Cyders et al., 2007; Vanderveen & Cyders, 2014).

7.3.4.2 BIS-11

The BIS-11 is a 30-item inventory encompassing three subscales: motor (acting out without thinking), attentional (making quick decisions), and non-planning (a lack of forethought) impulsivity. The internal consistency coefficients for the BIS-11 total score are considerably good, ranging from 0.79 to 0.83 for variant populations of young adults, clinical samples, and criminal populations (Patton et al., 1995). The normal range of the BIS-11 total scores is considered between 52 and 71 (Stanford et al., 2009).

7.3.4.3 QCAE

The QCAE was developed based on previous widely used self-report measures of empathy with factor analyses to generate 31 items comprising five subscales to assess either cognitive or affective component of empathy (Reniers et al., 2011). The subscales of cognitive empathy are perspective taking and online simulation. Perspective taking measures the capability of the respondents to see things from others' perspectives, whereas online simulation assesses the level of effort that respondents attempt to understand and mentally represent another's emotional state. The subscales of affective empathy are emotion contagion, proximal responsivity, and peripheral responsivity. Emotion contagion is focused on the automatic mirroring of other's feelings. Proximal responsivity is a measure of the emotional responsiveness to the feelings of others who are emotionally or physically close. Peripheral responsivity assesses one's emotional responsiveness to

the moods of others in a detached social context, such as characters in a film or a novel. A 4-point Likert scale is utilised for the respondents to indicate the level of their agreement with each item's statement.

7.3.5 Behavioural measures

7.3.5.1 RMET

The RMET is widely considered a task measuring the affective component of cognitive empathy (i.e., affective ToM). It involves the presentation of 36 mono-coloured photographs of the eye region of males and females, flanked by four emotional terms with one target and three foils. The options are all complex mental states (e.g., shame, guilt, curiosity, desire) rather than simple emotions (e.g., happiness, anger). Participants were shown each photograph and asked to choose the word best describing the thinking or feeling of the person in the photograph by pressing the keyboard corresponding to the number of that word on the screen. The sequence of the items was randomised for preventing practice effects. Accuracy was recorded as the primary outcome. The RMET has possessed good validity (Baron-Cohen et al., 2001) and appropriate test-retest reliability (Fernández-Abascal, Cabello, Fernández-Berrocal, & Baron-Cohen, 2013).

7.3.5.2 AAT

AAT is a delay discounting task originally developed by Du et al. (2002) and recently programmed by Frye et al. (2016). Participants are presented with a series of paired-choices to indicate their preference of receiving a given quantity of money within a specific time duration. For example, participants

have to make a decision between "Get £10.00 now" or "Get £100.00 after a year". If the participant chooses the immediate alternative, then the amount of the immediate alternative in the following trial will decrease. Contrarily, if the participant chooses the greater but delayed reward, then the amount of the immediate alternative for the next trial will increase. In the current study, seven time durations (one week, two weeks, one month, six months, one year, five years, and 25 years) were set. Each time duration consisted of 10 trials to obtain the final indifference value. As proposed by the authors, indifference points can be reached with relatively few questions to minimise the time and boredom due to the adjusting nature of the task. The hyperbolic function of delayed discounting by Mazur (1987) were implemented: $V = A/(1+KD)$, where V is the value of the delayed outcome (i.e., the indifference value), A is the delayed reward, D is the length of the delay, and K expresses the steepness of the discount function. The outcome measure is the geometric mean of K for each participant. Based on this function, higher K-values are associated with preference for immediate small-size reward and lower K-values are expression of delayed large-size reward. Conventionally, considering the distribution of the K-values, the K-value was natural-log transformed as *Ln (K)* for the following analyses.

7.3.5.3 IST

The IST is a reflection impulsivity measure examining the tendency to gather and evaluate information before making a decision. The task entails presenting a grid of 25 closed boxes on the computer screen. The boxes can be opened by touching the screen to uncover an underlying colour from two

specific colours displayed at the bottom of the screen. Participants are then requested to decide, on each trial, which one of the two colours is predominant by sampling information from opening boxes. Participants are instructed to open as many boxes as they wish before making a decision. The decision is confirmed by touching a coloured square at the bottom of the screen.

The task comprises of two conditions each consisting of 10 trials; the fixed win (FW) and the decreasing win (DW). In the FW condition, participants can win 100 points for a correct response regardless of the number of boxes opened. In the DW condition, and in order to introduce a conflict between level of certainty and the points available to win, the number of points that can be earned from 250 decreases by 10 with each box opened. A penalty of 100 points is given for every incorrect response in both conditions. Participants received clear instructions about the rules of the task before each condition and asked to perform a practice trial. The level of certainty (i.e., the probability of making the correct decision given the information sampled; termed Pcorrect) is the primary outcome measure. Considering the existing drawbacks in the original algorism of Pcorrect (Axelsen et al., 2017; Bennett, Oldham, et al., 2017; Pokhvisneva, Léger, Meaney, & Silveira, 2018), the new algorism proposed by Bennett, Oldham, et al. (2017) was used to derive Pcorrect in the current study instead of the original one. Higher Pcorrect values denote a lower tendency of reflection impulsivity and higher cognitive control. Another key measure for this task (Clark & Robbins, 2017), the mean number of boxes opened was selected as the secondary outcome.

7.3.6 Statistical analysis

Data analysis was carried out using SPSS v24.0. Continuous data were checked for normality using Shapiro-Wilk statistics before conducting further statistical analyses. Data obtained from RMET, IST, and AAT were analysed separately as follows. Non-normalised distributed data were statistically processed or transformed for the fitness of assumptions for analysis of variance (ANOVA). Practice effect, defined as the difference between the pre-stimulation task performances at each session was examined using paired t-test. In cases where the data were not appropriate for transformation, non-parametric Wilcoxon signed rank test was used. Separate mixed design repeated measures ANOVAs with stimulation (iTBS vs sham) as the within-subject factor and the order of stimulation (sham first vs iTBS first) as the between-subject factor were used to compare the pre-post stimulation change of each outcome variable between the iTBS and sham conditions. The Spearman's rank correlation coefficient (r_s) was calculated to determine the correlations between self-report and behavioural measures of impulsivity measures. To determine the influence of self-reported impulsivity, the total scores or subscale scores of the QCAE, BIS-11 and UPPS-P were selected as covariates in repeated measures analysis of covariance (ANCOVA). A *P* value of < .05 was considered as statistically significant.

7.4 RESULTS

7.4.1 Overview

The participants' baseline performances on the trait impulsivity and empathy measures are presented in Table 7-1. Compared to the BIS-11 total and subscale scores of 393 young male adults in Stanford et al., (2009), the impulsivity level of participants in the current study were within normal range (t_{414} = 0.193 – 1.730, p = .084 – .847, d = 0.046 – 0.353). With regard to the subscale scores of UPPS-P, the mean scores on the Negative Urgency, Lack of Premeditation, and Lack of Perseverance subscales of the participants did not significantly differ from those of 447 male colleges students in Cyders (2013) (t_{468} = 0.431 – 0.668, p = .504 – .667, d = 0.092 – 0.143). However, the participants in the current study had higher mean scores on the Positive Urgency subscale (t_{468} = 2.812, p = .005, d = 0.601) and lower mean scores on the Sensation Seeking subscale (t_{468} = -2.843, p = .005, d = 0.608). With respect to scores on subscales of QCAE compared to the normative data of 302 male college students in Reniers et al., (2011), participants in the current study did not have different scores on all subscales (t_{302} = 0.053 – 1.906, p = .058 – .958, d = 0.012 – 0.413) with the exception of higher scores on the Online Simulation subscale (t_{302} = 1.986, p = .048, d = 0.431). The proportion (65.2%) of correct identification of the active rTMS condition did not significantly differ from chance (χ^2 [1, N = 23] = 2.13, p = .144). All the 23 participants tolerated iTBS well and completed the study. Short-lived headache (n = 2), eye pain (n = 1), local pain (n = 1) and ear discomfort (n = 1) were reported but only after receiving sham TMS. One participant reported mild euphoria after the session of active TMS. The completion time of

behavioural tasks was within the after-effect time window (20.41± 2.66 mins; range: 16 – 25.67 mins), and there was no significant difference between the completion time after active iTBS and sham iTBS (t_{22} = 0.654, p = .740, d = 0.158).

Table 7-2 presents the intercorrelations between baseline measures of self-report and performance-based impulsivity. Significant correlations were found between the total scores of UPPS-P and BIS-11 (r_s = .53, p = .010) and some of their subscales. The Pcorrect in the FW condition was negatively correlated with scores of attentional subscale (r_s = -.56, p = .006) of the BIS-11 and Negative Urgency subscale (r_s = -.47, p = .024) of UPPS-P. No significant associations were found between the Pcorrect in the FW and DW conditions. The *Ln (K)* of AAT was positively correlated with scores of Positive (r_s = .57, p = .004) and Negative Urgency (r_s = .60, p = .002) subscales and total score (r_s = .62, p = .002) of UPPS-P. Moreover, there was a significant negative correlation (r_s = -.64, p = .001) between the *Ln (K)* of AAT and the Pcorrect in the DW condition of IST.

Analysis indicated that the effects of the stimulation order (sham first vs iTBS first) were not significant (all p_s > .05) for all outcome variables; therefore, the order effect was no longer considered in the subsequent analyses and only paired-t tests were used for examine the pre-post stimulation difference between active and sham iTBS instead of repeated measure ANOVA. Table 7-3 exhibits the results presented in the following paragraphs.

Table 7-1 Baseline performance on trait impulsivity and empathy measures

measurements	mean± SD	range	Normative data[b]
BIS-11 Total	61.00± 6.60	(52 - 74)	62.80± 9.20
Motor	21.13± 3.79	(17 - 33)	22.40± 3.40
Attentional	16.96± 2.93	(12 - 23)	16.80± 3.90
Non-planning	22.91± 4.78	(17 - 36)	23.60± 4.50
UPPS-P Total[a]	2.27± 0.28	(1.78 – 2.76)	
Negative Urgency[a]	2.24± 0.50	(1.33 – 3.58)	2.32± 0.57
Lack of Premeditation[a]	1.96± 0.30	(1.55 – 2.55)	2.00± 0.44
Lack of Perseverance[a]	1.90± 0.41	(1.20 – 2.80)	1.85± 0.42
Sensation Seeking[a]	2.84± 0.51	(1.92 – 3.67)	3.15± 0.51
Positive Urgency[a]	2.32± 0.39	(1.71 – 3.00)	1.97± 0.59
QCAE			
Cognitive empathy	59.52± 5.90	(50 - 74)	56.12± 8.38
Perspective taking	31.13± 4.45	(23 - 40)	29.85± 5.03
Online simulation	28.39± 3.27	(23 - 35)	26.27± 5.03
Affective empathy	32.70± 5.55	(24 - 44)	32.27± 5.03
Emotion contagion	10.78± 2.43	(6 - 15)	10.64± 1.68
Proximal responsivity	11.17± 2.35	(6 - 16)	11.19± 1.68
Peripheral responsivity	10.74± 2.20	(8 - 15)	10.43± 1.68

[a] The Mean is the average response across items in each scale
[b] The normative data (males only) are from the following studies: BIS-11: Stanford et al., (2009), n =393; UPPS-P: Cyders et al., (2013), n =447; QCAE: Reniers et al., (2011), n =281
BIS-11, Barratt Impulsiveness Scale, Version 11; QCAE, Questionnaire of Cognitive and Affective Empathy; UPPS-P, UPPS-P Impulsiveness Scale

Table 7-2 Correlation matrix for the baseline impulsivity

Spearman's rho Correlation Coefficient	1	2	3	4	5	6	7	8	9	10	11	12
BIS-11												
1 attentional												
2 motor	-.21											
3 non-planning	-.02	.16										
4 total score	.44*	.42*	.76***									
UPPS-P												
5 NU	.65***	-.14	.38	.57**								
6 PM	-.04	.00	.44*	.28	.34							
7 PE	.24	-.30	.24	.19	.34	.45*						
8 SS	-.05	.11	.10	.07	.11	.08	-.23					
9 PU	.38	-.04	.51*	.53**	.77***	.51*	.32	.20				
10 total score	.44*	-.13	.50*	.53**	.82***	.63***	.54**	.39	.85***			
11 IST PFW	-.56**	.04	-.04	-.35	-.47*	-.08	.11	.28	-.25	-.16		
12 IST PDW	-.20	.21	.14	.12	-.29	.09	.41	-.16	-.10	-.11	.34	
13 AAT Ln(K)	.29	.00	.35	.39	.60**	.27	-.01	.33	.57**	.62**	-.10	-.64***

AAT, Adjusting Amount Task; BIS-11, Barratt Impulsiveness Scale, Version 11; IST, Information Sampling Task; Ln(K), natural logarithm value of K value; NU, Negative Urgency Subscale; PDW, Pcorrect in the decreased win condition; PE, Lack of Perseverance Subscale; PFW, Pcorrect in the fixed win condition; PI, index of proactive inhibitory control; PM, Lack of Premeditation Subscale; PU, Positive Urgency Subscale; SS; Sensation-Seeking Subscale; UPPS-P, UPPS-P Impulsivity Behavioural Scale

*indicates significant correlation (*p < .05, ** p <.01, *** p <.001)

7.4.2 RMET

Data from one participant was then excluded for the following analyses regarding RMET because the participant performed extremely poorly in accuracy among the four occasions. No significant practice effect was found in correct scores in RMET (t[21] = 2.01, p = .057 , d = 0.43). The pre-post difference scores of RMET were reciprocal transformed and the paired-t test did not reveal a significant main effect for stimulation type (t[21] = 0.42, p = .676 , d = 0.09). A repeated measures ANCOVA showed that after the inclusion of the total score of the QCAE as a covariate, the main effect of stimulation on pre-post RMET score was not significant (F[1, 20] = 2.52, p = .128, η^2 = .112). Considering that the score of the online simulation subscale was significantly associated with the baseline RMET performance (r = .509, p = .016), another ANCOVA was performed using the online simulation as a covariate, contributing to a non-significant result (F[1, 20] = 0.40, p = .533, η^2 = .020).

7.4.3 AAT

Practice effects were found in relation to the AAT regarding the *Ln (K)* (t[22] = 2.68, p = .014, d = 0.56). One extreme outlier in the pre-post difference score of *Ln (K)* was winsorised and the paired-t test did not reveal a significant difference on the change of the *Ln (K)* between the two stimulation conditions (t[22] = 0.78, p = .446 , d = 0.16). A repeated measures ANCOVA showed that when the total score of the UPPS-P was covaried out, the main effect of stimulation on pre-post *Ln (K)* was not significant (F[1, 21] = 0.26, p = .615, η^2 = .012). Another ANCOVA using the total score of the BIS-11 as a covariate

also revealed a non-significant result (F[1, 21] = 0.94, p = .345, η^2 = .043).

7.4.4 IST

No practice effect was found in relation to IST (Pcorrect in FW: t[22] = 1.40, p = .175, d = 0.29; Pcorrect in DW: t[22] = 0.61, p = .550; d = 0.13). The pre-post difference scores of Pcorrect in FW from active iTBS and sham did not differ significantly (t[22] = 0.36, p = .722 , d = 0.08). One extreme outlier in the pre-post difference score of Pcorrect in DW was winsorised and the paired-t test did not reveal a significant effect for stimulation type on Pcorrect in DW (t[22] = 1.04, p = .309 , d = 0.22). Repeated measures ANCOVAs showed that after the inclusion of the total score of the BIS-11 as a covariate, the main effects of stimulation were not significant on pre-post stimulation changes of Pcorrect in FW (F [1,21] = 0.01, p = 0.911, η^2 = .001) and in DW (F[1, 21] = 0.10, p = .757, η^2 = .005). Repeated measures ANCOVAs showed that when the total score of the UPPS-P was covaried out, the main effects of stimulation conditions were not significant on the Pcorrect in FW (F [1,21] = 0.08, p = 0.785, η^2 = .004) and in DW (F [1,21] = 0.01, p = 0.935, η^2 = .001). One extreme outlier in the pre-post difference score of the mean number of boxes opened in FW was winsorised and the paired-t test did not reveal a significant effect for stimulation type on the mean number of boxes opened in FW (t[22] = 0.07, p = .942 , d = 0.02). The pre-post difference scores of the number of boxes opened in DW from active iTBS and sham did not differ significantly (t[22] = -0.96, p = .348 , d = -0.20). Repeated measures ANCOVAs showed that after the inclusion of the total score of the BIS-11 as a covariate, the main effects of stimulation were not significant on pre-post stimulation changes of the mean number of boxes opened in FW (F [1,21] =

0.93, p = 0.345, η^2 = .042) and in DW (F[1, 21] = 0.11, p = .747, η^2 = .005). Repeated measures ANCOVAs showed that when the total score of the UPPS-P was covaried out, the main effects of stimulation conditions were not significant on the mean number of boxes opened in FW (F [1,21] = 0.05, p = 0.832, η^2 = .002) and in DW (F [1,21] = 1.81, p = 0.193, η^2 = .079).

Table 7-3 Performances on impulsivity tasks across conditions

Tasks	Pre-Sham	Post-Sham	Pre-iTBS	Post-iTBS
RMET				
Correct (%)	68.36± 12.22	71.01± 14.31	69.20± 13.55	71.50± 12.00
AAT				
Mean *Ln (K)*	-7.67± 2.87	-6.73± 3.01	-6.50± 2.77	-7.59± 3.14
IST-FW				
Pcorrect (%)	87.10± 7.89	85.31± 8.70	87.70± 7.07	86.67± 8.75
Boxes opened	14.28± 5.52	14.00± 5.22	14.57± 5.13	14.55± 4.75
IST-DW				
Pcorrect (%)	81.17± 5.51	80.12± 6.57	78.37± 9.06	79.65± 5.53
Boxes opened	8.60± 2.52	9.20± 2.64	8.58± 3.11	8.64± 2.79

Data are presented as Mean± SD
AAT, Adjusting Amount Task; DW, decreased win condition; FW, fixed win condition; IST, Information Sampling Task; iTBS, intermittent theta burst stimulation; RMET, Reading the Mind in the Eyes Test

7.5 DISCUSSION

To the best of our knowledge, the present study is the first to apply iTBS at the LDLPFC to investigate the excitatory neuromodulation effects on cognitive empathy, temporal impulsivity and reflection impulsivity in healthy adults. According to previous research with healthy volunteers (Balconi & Canavesio, 2014; Balconi & Canavesio, 2016; Sheffer et al., 2013), iTBS was expected to increase accuracy rates on the RMET, lower impulsive choice on the AAT, and to reduce the proportions of premature decisions on the IST. However, the current findings did not support this prediction.

Consistent with results in the previous chapter, the relationships between Pcorrect in the FW condition of the IST and self-report measures of impulsivity were further confirmed. Interestingly, the *Ln* (*K*) on the AAT negatively correlated with scores of total and urgency related subscales of the UPPS-P. This is in line with the suggestion that delay discounting is a trait-like tendency driven by past positive and negative experience and future expectations (Frye et al., 2016; Koffarnus, Jarmolowicz, Mueller, & Bickel, 2013; Odum, 2011). Although previous studies (e.g., Caswell et al., 2015) did not find the significant relationship between measures of behavioural temporal and reflection impulsivity, the *Ln* (*K*) on the AAT and Pcorrect in the DW condition of the IST revealed a remarkable association in the current study. Given that problems of temporal and reflection impulsivity have been evident in patients with some sorts of SUDs, such as alcohol use disorder (Banca et al., 2016), the association between the two subtypes of impulsivity and their overlapping neurosubstrates may require further investigations.

Before discussing the research main topics separately in the following sections, some issues should be addressed in advance. Firstly, it is convinced that the iTBS protocol used in the current study was sufficient with intensity and the number of pulses to induce functional changes at the LDLPFC based on Iwabuchi et al. (2017). Secondly, it is less possibly that the after-effects of iTBS vanished within the period of post-stimulation examination according to Thut and Pascual-Leone (2010). Thirdly, the negative findings among the outcome measures should not be overlooked only depending on the small sample size since the effect sizes between the active and sham stimulation obtained from all the outcome measures were extremely small. Therefore, given dearth of similar studies in the field, we suggest that our findings should be treated as evidence of absence rather than absence of evidence (de Graaf & Sack, 2011) although numerous limitations should be highlighted.

As the neuroimaging studies (e.g., Enzi, Amirie, & Brune, 2016) identified the involvement of the LDLPFC in the empathic process, in the current study, iTBS at the LDLPFC did not lead to significant improvement on cognitive empathy. This is also at odds with the findings of Rêgo et al. (2015) using bilateral tDCS at the DLPFC. Given that they found increased excitability in either side of DLPFC enhanced cognitive empathic responses in different domains, they suggest distinct roles for lateralised DLPFC activity in cognitive empathy. However, the role of LDLPFC in cognitive empathy may be more complicated. Möbius et al. (2017) applied one session of high frequency rTMS over the LDLPFC to healthy individuals and found a significant reduction of provoked mood compared to sham stimulation. It may represent that people become less empathic to negative emotional stimuli after LDLPFC activation

although Möbius et al. (2017) propose that it reflects improved emotion regulation. Balconi and Canavesio (2016) found a decrease empathic response only limited to positive facial stimuli after using low-frequency rTMS to interfere the activity at the LDLPFC. Therefore, the valence of emotion stimuli as materials of empathic responses should be taken into account in the future studies. Although the consideration of baseline individual differences is needed when assessing post-stimulation response to neuromodulation (Fitzgibbon et al., 2017), the baseline empathy trait did not play a role in modulating cognitive empathy in our study. Considering that baseline empathy trait only moderates empathic responses to positive facial stimuli after inhibitory rTMS (Balconi & Canavesio, 2016), such associations may not be found in our study using more complex and ambiguous stimuli. Finally, it is also possible that the LDLPFC chosen as the targeted site may not play a major role in the modulation of cognitive empathy. Using deep brain stimulation to the ACC may be a better option considering the convergent functional imaging evidence showing the involvement of the ACC in empathy (Fan et al., 2011). The current evidence regarding the impact of LDLPFC modulation on empathy may be circumstantial since it may result from the altered connectivity between LDLPFC and other crucial regions (such as anterior insula and ACC) in the empathic process after neuromodulation (Iwabuchi et al., 2017; Weber, Messing, Rao, Detre, & Thompson-Schill, 2014).

In line with the view of the DLPFC in temporal impulsivity, inhibitory low frequency rTMS at the LDLPFC increases delay discounting of monetary gains (Figner et al., 2010) while cTBS at the right DLPFC (Cho et al., 2010)

and excitatory high frequency rTMS at the LDLPFC (Sheffer et al., 2013) decrease delay discounting of monetary gains. Contrary to Sheffer et al. (2013), we did not observe significant decrease in tendency of temporal impulsivity following iTBS at the LDLPFC. One possibility of the inconsistent finding may be the participants' characteristics. Although the data regarding cigarette consumption in the participants did not obtain from in the current study, around half of the participants in Sheffer et al.'s study were smokers, who were more respondent to the neuromodulation revealing significantly higher decreased discounting rates compared to their non-smoking counterparts (Bickel, Yi, Kowal, & Gatchalian, 2008). Unsuprisingly, such controversality exists in the literature of neuromodulation at the LDLPFC in temporal impulsivity. For example, Hecht, Walsh, and Lavidor (2013) used bilateral transcranial Direct Current Stimulation (tDCS) to the DLPFC and found that left anodal with right cathodal tDCS increase the choices of immediate and smaller gains compared to the sham stimulation while results were not significant with right anodal and left cathodal tDCS. Contrary to Hecht et al., Nejati, Salehinejad, and Nitsche (2018) found that both left anodal with right cathodal and right anodal with left cathodal tDCS led to a significant decreased rate of delayed discounting compared to sham tDCS. These findings raise a question about the role of LDLPFC in temporal impulsivity. Although the recent meta-analytic study (Yang, Völlm, et al., 2018) suggests that LDLPFC may be the candidated region for modulating temporal impulsivity, it is based on a very limited number of studies. Moreover, there is aggregating evidence suggesting that the network recruiting the ventromedial prefrontal cortex is crucial to temporal impulsivity (Cho et al., 2015; Peters &

Buchel, 2011). Lastly, it may be that an individual's inclination to delay gratification is less likely to be altered by one-session neuromodulation. Some researchers (Frye et al., 2016; Koffarnus et al., 2013; Odum, 2011) argued that delayed discounting is a trait-like feature and less sensitive to intervention at least in normal individuals. This might be partially true in our study since their baseline *Ln* (*K*) on the AAT significantly correlated with the total scores of UPPS-P, the trait measure of impulsivity. However, unlike the finding in Shen et al. (2016) revealing that the effect of tDCS modulation at the LDLPFC was contingent on participants' baseline impulsivity, the trait impulsivity was not a remarkable moderator of the iTBS modulation effects in temporal impulsivity in the present study. Since the issue remains relatively less well-studied, future research is required to enrol the baseline or trait impulsivity as a potential factor affecting the neuromodulation effects in temporal impulsivity.

With regard to reflection impulsivity, contrary to our hypothesis, our findings suggest that iTBS at the LDLPFC had no significant impact on reflection impulsivity in healthy adults. Given that there is no excitatory rTMS at the LDLPFC focusing on reflection impulsivity, the current negative finding should be highlighted. A majority of neuromodulation studies for this issue used tDCS to alter normal individuals' reflection impulsivity; the results remain also equivocal. Some (Cheng & Lee, 2016) found that only left cathodal–right anodal stimulation at the DLPFC led to significantly reduced risk-taking, some (Fecteau et al., 2007; Nejati et al., 2018) found that using tDCS with either left anodal–right cathodal mode or the reverse montage significantly reduced risky attempts compared to sham stimulation whereas others (Minati,

Campanhã, Critchley, & Boggio, 2012; Ye et al., 2015) could not find any significant effect from bilateral tDCS over the DLPFC with the two montages (i.e., left cathodal–right anodal and left cathodal–right anodal). One potential explanation for the results in current study compared to those in the tDCS studies is that the IST used in our study as the outcome measure of reflection impulsivity taps into premature decision-making rather than risky decision-making, measured in most of the aforementioned tDCS studies. Although premature and risky decision-making are both categorised into a board term of reflection impulsivity (Verdejo-Garcia et al., 2008), some (Fineberg et al., 2014) regard risky decision-making as another subtype of impulsivity while others (Lejuez et al., 2002; Panwar et al., 2014) suggest that risk taking is a related but phenomenologically distinct process from impulsivity. From an neuroanatomical perspective, findings from one meta-analytic study reveal that the brain regions regarding decision-making under uncertainty and risk only partially overlapped (Krain, Wilson, Arbuckle, Castellanos, & Milham, 2006). The task-specific outcome of the impulsive decision-making corresponding to neuromodulation effects may require further investigation.

Several limitations should be addressed in this study. The small sample size reduces the reliability of the results. Given that a considerate ratio of participants (*n* =3; 42.9% of the dropouts) dropping out from the study were high impulsive, selection bias may be considered. This also reflects their impulsive trait: making decision without gathering enough information. The enrolment of young adult males further weakens the generalisability to females or older adults. The LDLPFC localisation method performed by

means of the traditional “5-cm rule” may be argued in the context that a growing body of evidence from neuro-navigation techniques (e.g., Bradfield, Reutens, Chen, & Wood, 2012; Herwig, Padberg, Unger, Spitzer, & Schönfeldt-Lecuona, 2001) has questioned its precision. Neuro-navigated rTMS with functional neuroimagings is favoured in the future studies (Rossini et al., 2015) although some (Sack, 2010) doubt the incremental utility of functional neuroimagings in TMS studies. Finally, the crucial information of cigarette consumption in the participants was missing since smokers prefer immediate reward compared to other healthy individuals without smoking history. This may potentially affect the results regarding AAT and the representativeness of the sample in the present study.

In summary, this study provides preliminary findings of no significant effects from iTBS at the LDLPFC on cognitive empathy and impulsivity, although it is not congruent with the findings from a limited number of previous neuromodulation studies. Future research should modify the protocol with multiple sessions and neuroimagings in a larger sample size population with empathy or impulsivity problems to determine the therapeutic potential of iTBS in clinical settings.

7.6 CONFLICT OF INTEREST

There is no conflict of interest.

7.7 ACKNOWLEDGEMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CHAPTER 8 : GENERAL DISCUSSION

As described in the introduction chapter of this thesis, impulsivity and low empathy are regarded as cardinal features of a several neuropsychiatric disorders (American Psychiatric Association, 2013; Fineberg et al., 2014) and main risk factors of violence (Bjørkly, 2013; Chamorro et al., 2012; Jolliffe & Farrington, 2004; van Langen et al., 2014). The therapeutic utility of rTMS in a diverse range of neuropsychiatric disorders have been reported consistently in the literature (Lefaucheur et al., 2014; Rossini et al., 2015; Wassermann & Zimmermann, 2012). In addition, there is some evidence to suggest that rTMS may be efficacious in modulating empathy and impulsivity (Hetu et al., 2012; Juan & Muggleton, 2012). However, the effects of rTMS on impulsivity and empathy in healthy individuals have not been reviewed systematically with meta-analytic methods. This thesis therefore conducted two systematic reviews with meta-analyses and two empirical rTMS studies aiming at further examining the role of rTMS in modulating both empathy and impulsivity. The general discussion of this thesis will summarise the results of the four studies presented in this thesis, discuss methodological issues, and highlight the strengths and limitations of this work. Furthermore, implications for future studies in relevant research field will be described.

8.1 OVERVIEW OF MAIN FINDINGS

The first study described in this thesis investigated the effects of rTMS on empathy in healthy adults. A systematic review with meta-analysis was conducted and 18 studies contributing to 24 effect sizes were included. Due to

the outcome measures defined in the PICOS being limited to behavioural measurements, no rTMS studies investigating affective empathy were included. The findings suggest an overall small effect favouring active rTMS over sham on cognitive empathy in healthy individuals. Differential effects across cognitive and affective ToM domains were evident. Meta-regression revealed no significant between-study heterogeneity in respect of sex ratio, mean age, number of pulses, and stimulation intensity. In conclusion, the study found that rTMS may have discernible effects on different components of cognitive empathy. The relative small number of excitatory rTMS studies was noted in the review, and further research employing excitatory rTMS to enhance empathy is required before extending research to clinical populations.

The second study in this thesis examined the effects of rTMS on impulsivity in healthy adults by conducting a systematic review and meta-analysis. The findings from 27 articles consisting of 50 effect sizes indicate that rTMS has distinct levels of effects on motor and temporal impulsivity subdomains. A small effect was found on modulating motor impulsivity while a moderate effect was found on temporal impulsivity. Due to lack of sufficient data, it was not possible to examine the effects of TMS on reflection impulsivity. Findings from subgroup analyses suggested several regions of interest for modulating motor impulsivity (e.g., LDLPFC, rIFG, and rFEF) and temporal impulsivity (LDLPFC). No specific parameters played a significant role in moderating the effects of rTMS on motor impulsivity. Additionally, sparse and limited literature in the field of cognitive and temporal impulsivity highlight the need to conduct further studies in the field.

The third study described in this thesis investigated the efficacy of excitatory rTMS applied at the rIFG in modulating impulsivity. It also examined the relationship between trait and behavioural measures of impulsivity. Specifically, this study assessed the impact of HF-rTMS on motor and reflection impulsivity, the two subdomains of impulsivity considered relevant to rIFG. Participants were randomly assigned using a single-blind crossover study design, and undertook two computerised tasks before and after rTMS in active stimulation and sham conditions. Contrary to our predictions, findings from this excitatory rTMS protocol revealed no significant effects on either motor or reflection impulsivity as indexed by performances on SST and IST tasks respectively. This was despite including baseline trait measures of impulsivity as covariates in the analyses. In accord with the extant literature, trait and behavioural measures of impulsivity were not significantly associated.

The final study described in this thesis applied iTBS at the LDLPFC to facilitate empathy and to reduce impulsivity in healthy adults. This study specifically investigated the effects of an iTBS protocol on cognitive empathy (assessed by RMET), temporal impulsivity (assessed by AAT) and reflection impulsivity (assessed by IST). Participants were randomly assigned in a single-blind crossover design and undertook three computerised tasks before and after iTBS in active stimulation and sham conditions. The findings suggest no significant effects for iTBS at LDLPFC on both cognitive empathy and impulsivity. The results remained insignificant after adding baseline trait measures of empathy and impulsivity as covariates to control the impact of pre-stimulation individual difference on the iTBS modulation.

The results of the two systematic reviews were used to inform the two empirical rTMS studies, although negative findings were unexpectedly obtained. However, given that there is a considerable number of 'file-drawer papers' (i.e., finished but unpublished studies) in this field (Héroux et al., 2015) demonstrating null modulating effects for TMS, it is not surprising that negative findings were obtained in the thesis. The only and minor finding which was in accord with our predictions was the absence of significant correlations between trait and behavioural measures of impulsivity.

There may be several possible explanations for this. Firstly, self-report instruments are vulnerable to demand characteristics and social desirability biases (van de Mortel, 2008), especially for negative personality traits like impulsivity. Secondly, impulsivity may directly influence the accuracy of questionnaires ratings since impulsive participants may not spend enough time on each item to give a correct response (Evren et al., 2014). Finally, introspective ratings require sufficient self-awareness on the part of the participant of their own impulsive tendencies (Verdejo-Garcia et al., 2008).

8.2 METHODOLOGICAL ISSUES

8.2.1 Systematic reviews with meta-analyses

The selection of outcome measurements in the meta-analyses needs further consideration. Given the multi-faceted nature of both impulsivity and empathy, inclusion of a variety of behavioural tasks may be necessary, particularly in cases where disagreements regarding the appropriateness of each task exist. For tasks measuring empathy, while inference of emotional facial expression is an essential component of cognitive empathy (Besel & Yuille, 2010), some

may criticise the inclusion of facial expression recognition tasks. However, if the RMET is viewed as a valid measurement of cognitive empathy, facial expression recognition tasks should not be excluded from cognitive empathy measurements given that they are similar in nature albeit with different levels of task difficulty and complexity. Similarly, the tasks measuring impulsivity included in the meta-analysis were based on suggestions from existing literature (e.g., Caswell et al., 2015; Verdejo-Garcia et al., 2008). Tasks designed to measure the same subdomain of impulsivity may indeed measure different components or processes underpinning impulsivity. For instance, in MI, SST is regarded as a measure of reactive motor control (Verbruggen & Logan, 2008) while GNG and SCWT are viewed as measures of proactive motor control (Aron, 2011; Smittenaar et al., 2015). However, this should not invalidate findings from the meta-analyses since such inter-task variations were to some extent addressed using subgroup analyses.

Another methodological concern is that of multiplicity, which arises when using multiple outcomes. It is not uncommon for studies using multiple instruments to measure their outcome variables based on the same participants. Several methods have been proposed to address this issue (e.g., Arends, Voko, & Stijnen, 2003; Borenstein et al., 2009d). In this thesis, a widely used method proposed by Borenstein et al. (2009d) was utilised. This entails averaging the effect sizes collected from different outcomes. Another issue related to the use of multiple outcomes from the same task under different intervention conditions. This has been observed frequently in TMS studies with a cross-over design where the same participants receive active stimulation at different brain regions on different time-points and complete the

same post-stimulation tasks. Theoretically, this approach would violate assumptions of independent data points and introduces errors into statistical inference if effect sizes were obtained from the same study (Borenstein et al., 2009b). In the second systematic review with meta-analysis, the multi-level meta-analysis was therefore used to avoid the "nesting" of multiple effects within single studies (Pastor & Lazowski, 2018) rather than the traditional method of selecting only one region of interest in one study.

8.2.2 Empirical rTMS studies

The method of determining a participant's RMT using visual observation has its own limitations, although it has been utilised in clinical trials for decades. This approach may not obtain an accurate RMT and may overestimate the RMT compared to using EMG (Rossi et al., 2009; Westin et al., 2014). However, this is not sufficient to invalidate our negative findings since RMT overestimation would only result in higher stimulation intensity, leading to more remarkable effects from active stimulation. Moreover, it is notable that participants in the two empirical studies did not exhibit prolonged or severe adverse events after active rTMS despite seemingly receiving slightly higher stimulation doses. Furthermore, existing evidence (Varnava, Stokes, & Chambers, 2011) suggests that the observation method is a reliable technique for obtaining RMT with certain advantages, in terms of convenience and saving time. Therefore, the use of observation method for RMT determination should not be undervalued.

Localisation of stimulation sites (rIFG, LDLPFC) without neuro-navigation can be regarded as a limitation. However, considering the cost implications of

neuro-navigation, using a validated landmark remains an acceptable and compromised alternative, given that it has been used extensively in clinical research (Bradfield et al., 2012). For targeting rIFG, a variety of landmark methods have been used. We used the method proposed by Gough et al. (2005) which is considered to be both convenient and relatively precise. This method has been validated by Waldowski et al. (2012) for use in patients with acute stroke with remarkable improvement in naming abilities. Similarly, most studies have applied the “5 cm rule” to define the DLPFC for its convenience (Johnson et al., 2013) although its precision has been questioned (Herwig et al., 2001). Some authors have argued that 6cm or 7cm anterior to the M1 might be a more accurate estimate for locating the DLFPC (Bradfield et al., 2012; Johnson et al., 2013). However, in order to reduce methodological variations and to correspond to the majority of clinical studies in this field, it was deemed appropriate to use the “5 cm rule”.

8.3 STRENGTHS AND LIMITATIONS

The present thesis provides further empirical evidence in relation to the use of rTMS to modulate both empathy and impulsivity. It adds to the wider pool of knowledge in the field. The findings should be interpreted in the light of strengths and limitations highlighted in the following sections. .

8.3.1 Strengths

8.3.1.1 Strengths of systematic reviews with meta-analyses

The systematic reviews were broad in scope and included multiple electronic databases using a broad range of search terms. The PRISMA guidelines for

systematic reviews (Liberati et al., 2009b; Moher et al., 2009) were followed, and findings have been presented in a standardised manner. The quality assessments were conducted using a well validated tool (National Collaborating Centre for Methods and Tools, 2008) that has been recommended by the Cochrane group (Sterne et al., 2011). It is noteworthy that multiple methods were used to assess publication bias and meta-regressions were employed to further examine the possible sources of between-study heterogeneity. The multi-level meta-analysis was used in the second systematic review and meta-analysis to address issues related to reporting multiple effect sizes for studies involving the same participants.

8.3.1.2 Strengths of empirical rTMS studies

To the best of my knowledge, the two empirical studies were the first to examine the effects of excitatory rTMS at rIFG and LDLPFC on empathy and impulsivity in healthy individuals. Findings from our systematic reviews, suggest that the majority of previous studies employed counter-balanced designs, which is of weak methodological quality. Participants were randomly allocated to either rTMS or sham condition to attain a higher strength level in research evidence. The use of standardised and well-validated computerised tasks such the SST and IST of the CANTAB is a notable strength, allowing other researchers to replicate our findings. In addition, these two empirical rTMS studies reported on TMS about adverse effects, allowing researchers to aggregate data on the safety of TMS administration. The use of trait measures as covariates in the ANCOVAs should be treated as a strength considering previous studies tended to overlook the issue.

8.3.2 Limitations

The work suffered a number of limitations. The findings should be interpreted with these in mind.

8.3.2.1 Limitations of systematic reviews with meta-analyses

Firstly, it is recommended in the PRISMA guidelines to register the protocols of meta-analytic studies to avoid duplication and to increase the transparency (Liberati et al., 2009b; Moher et al., 2015). However, such registration was overlooked although the rest of the guidelines were complied with. Secondly, due to the heterogeneous nature of both impulsivity and empathy, the search terms used in the two systematic reviews might not have sufficiently captured all the relevant studies in the field. For example, one recent systematic review (Brevet-Aeby et al., 2016) aimed at examining the effects of non-invasive brain stimulation at the prefrontal cortex on impulsivity regarded sustained and divided attention as subdomains of impulsivity, whereas our reviews did not. Thirdly, due to relative lack of resources, data extraction and quality assessments were conducted by only the PhD candidate. Fourthly, although generally no evidence of publication bias was found in the meta-analyses using visual inspection of the funnel plots, the Egger test, and the Begg and Mazumdar rank correlation test, these methods are susceptible to bias given the volume of unpublished work in the field (Héroux et al., 2015). Furthermore, in spite of using no language filters, it is still possible that studies published in languages other than English may have been missed. Moreover, the country of origin for each study might have acted as an important source of inter-study variations, which the meta-analytic studies of this thesis failed to measure..

Finally, low-powered meta-analyses based on a small number of studies should be noticed and a formal test of power analysis is required to perform future meta-analysis (Jackson & Turner, 2017).

8.3.2.2 Limitations of empirical rTMS studies

A major limitation of both studies is the small samples sizes. This was despite the best effort over several months. Sampling and selection biases were evident as participants were recruited within the University of Nottingham and limited to individuals who were exposed to the recruitment advertisements, and were available to attend the study. As enrolled participants were young male adults in university education from mixed ethnic backgrounds, results may not be generalisable to older, low-educated individuals, females or White Caucasians in other parts of the world. The exclusion criteria were based on self-report. It is possible individuals with mental disorder or substance misuse problems were inadvertently included in the study. Considering the limited manpower, a single-blind design was selected in the two studies; however, a double-blind design is highly recommended for future studies, which may also use concurrent rTMS and neuroimaging methods to assess the neurobiological underpinning of rTMS.

8.3.3 Summary

This thesis demonstrated a range of methodological strengths, such as including studies from multiple electronic bibliographic databases, examining and quantifying their quality using a valid quality assessment instrument, and applying advanced analytic methods in the meta-analyses. However, relative lack of statistical power, not employing navigation techniques for site

localisation, and sampling and selection biases represent major limitations for the empirical studies. Consequently, a cautious approach should be taken when interpreting the present findings.

8.4 DIRECTIONS AND IMPLICATIONS FOR FUTURE RESEARCH

While the thesis demonstrated several strengths, the existing methodological weaknesses highlight the need for replication, modification, and further investigation. Future studies should be conducted using larger samples to attain larger statistical powers than the ones attained in this thesis. This is applicable to both systematic reviews and empirical studies. Future research should address the other limitations highlighted in this research. Moreover, the presence of potential moderators is noteworthy to examine in meta-analytic and prospective studies, particularly the baseline traits of the individuals.

8.4.1 Systematic review and meta-analytic research

Although neuroscientific evidence suggested a range of domains subordinating empathy (Dvash & Shamay-Tsoory, 2014), conceptualisation of empathy may merit further investigation. Additionally, given that the hierarchical structure proposed in cognitive empathy, such as first-order vs. second-order ToM (Miller, 2009) and fundamental vs. advanced ToM (Baron-Cohen et al., 2001) , future research may apply advanced methods like multi-level meta-analysis to elucidate the effects of rTMS on subdomains empathy. Furthermore, considering that patients with specific mental disorders, such as ASD, SUDs, personality disorders, and schizophrenia

manifest remarkable deficits in empathic or impulse control abilities, it is highly recommended to conduct a meta-analysis regarding the effects of rTMS on empathy and/or impulsivity in these populations. There is a growing body of literature on the use tDCS in this field. There is a merit in conducting broader reviews on the effects of neuromodulation on empathy and impulsivity, for instance by including both rTMS and tDCS studies in future meta-analyses. Given that a substantial number of unpublished papers may exist in this field (Héroux et al., 2015), researchers are required to search more vigorously for grey literature or contact academics in the field. Lastly, future meta-analytic research may benefit from using physiological outcome measures, particularly in relation to the effects of rTMS on affective empathy.

8.4.2 Empirical rTMS studies

Given that a single session of active rTMS may not be indicative to major changes in behavioural measures, a prospective study design with multiple rTMS sessions is required to ascertain the true effects of TMS on both empathy and impulsivity. This could help elucidate the long-term effects of rTMS which appears to have attracted little attention in the literature.

Future studies should consider recruiting patients with low empathy or poor impulse control and using validated instruments to measure empathy or impulsivity. Publishers are urged to take more interest in publication of negative findings to minimise the risk of publication bias in the field.

Several suggestions can be provided for future studies in practice. Firstly, the considerable dropout rates in the two empirical studies may inspire the researchers to estimate the sample size conservatively while writing the study

protocol, to allow more time to recruit participants, to access a variety of resources for participant recruitment, to work in partnership with other research teams, and to develop strategies to increase the participant adherence to study. Secondly, some characteristics of participants leaving prematurely, such as high impulsive traits in the second study, may weaken clinical implications and generalisability of the study. This may be improved through a comprehensive explanation of the study protocol, clarification of their expectation on the intervention, and mutual communication during the whole process. Thirdly, the adverse event in the second study highlights the importance of the screening of TMS eligibility, safety monitoring, and training of management of emergency. Finally, it is vital to report adverse events as not all studies in the two systematic reviews reported information concerning the participants' tolerability of rTMS.

8.4.3 Clinical implications

Apart from reducing motor and temporal impulsivity, which may be directly beneficial for specific mental disorders, such as SUDs or impulse control disorders, the positive effect of rTMS on motor impulsivity may demonstrate other clinical utility. Given that motor impulsivity has been suggested to strongly predict suicide attempts in healthy young adults and patients with mood disorders or SUDs (Colborn et al., 2017; Khemiri et al., 2016; Wang et al., 2017), it would be expected that the rTMS effect on motor impulsivity reduction may be reproduced on suicide intervention. This idea has been supported by recent studies employing an intense schedule of multiple sessions, high-dose rTMS, which significantly reduced suicidal ideation

(Croarkin et al., 2018; Weissman et al., 2018). Therefore, rTMS may have the potential to play a role in acute suicidal intervention.

With regard to the clinical implications of the effect of rTMS on empathy enhancement, it would be assumed that people with ASD should be the target population. While the true potential of rTMS in ASD has yet to be delineated with limited evidence (Oberman et al., 2016; Oberman, Rotenberg, & Pascual-Leone, 2015), well designed and properly controlled clinical trials are warranted to evaluate this novel, possibly transformative approach to the treatment of neurodevelopmental disorders.

The findings of the thesis may not able to answer the question that “How impulsive or low empathetic would one need the rTMS intervention?” since the risk-to-benefit ratio heavily depends on inter-individual differences and further research is required. Moreover, considering that only immediate outcomes were analysed in the two systematic reviews, long-term effects of rTMS on impulsivity and empathy have remained unclear. This issue should be examined beforehand for clinicians to formulate a standard rTMS therapeutic programme in the future.

Finally, although using rTMS to improve empathy and reduce impulsivity is suggested to have a potential to intervene in violence, further rTMS studies recruiting participants with high risk of violence directly address this issue is merited.

8.4.4 Ethical considerations

As rTMS has been officially approved as a treatment only for alleviating symptoms of mildly treatment-resistant depression, the use of rTMS for modulating empathy and impulsivity remains in the research field rather than in clinical practice (Horvath, Perez, Forrow, Fregni, & Pascual-Leone, 2011). For all rTMS research studies, it is mandatory to obtain approval from the Institutional Review Board and a signed informed consent from the study participants (Rossi et al., 2009). Although guidelines concerning rTMS administration have been updated (Rossi et al., 2009), official rTMS training is still not currently required for people employing rTMS (Horvath et al., 2011). This may increase the heterogeneity among rTMS studies and decrease the reproducibility of each rTMS study. Standardised requirements for rTMS administration should be proposed.

8.5 CONCLUSIONS

This thesis attempted to further examine the neuromodulation effects of rTMS on empathy and impulsivity in healthy adults using meta-analyses and empirical methods. Empathy and impulsivity have been suggested to play important roles in clinical and forensic populations. There is a growing body of literature on using rTMS to modulate empathy and impulsivity. The systematic reviews with meta-analyses revealed some significant effects but the heterogeneity among studies and lacked studies in some specific domains highlighting the need for further and more detailed investigations. Neither the rIFG nor LDLPFC stimulation in the thesis effectively modulated impulsivity and/or empathy. The negative findings at least contributed to the sparse and

divergent evidence in this field. This raises questions regarding the issue that which rTMS protocol(s) can effectively enhance empathy and reduce impulsivity in people with the need of treatment. Given the growing advances in this field, related issues are expected to be further investigated.

REFERENCES

Aboulafia-Brakha, T., Christe, B., Martory, M. D., & Annoni, J. M. (2011). Theory of mind tasks and executive functions: A systematic review of group studies in neurology. *Journal of Neuropsychology, 5*(1), 39-55. doi: 10.1348/174866410X533660

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* (5 ed.). Washington: American Psychiatric Publishing.

Arends, L. R., Voko, Z., & Stijnen, T. (2003). Combining multiple outcome measures in a meta-analysis: an application. *Statistics in Medicine, 22*(8), 1335-1353. doi: 10.1002/sim.1370

Armstrong, R., Waters, E., & Doyle, J. (2011). Chapter 21: Reviews in Public Health and Health Promotion. In J. P. Higgins & S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011): The Cochrane Collaboration. Retrieved from www.handbook.cochrane.org.

Aron, A. R. (2007). The neural basis of inhibition in cognitive control. *Neuroscientist, 13*(3), 214-228. doi: 10.1177/1073858407299288

Aron, A. R. (2011). From Reactive to Proactive and Selective Control: Developing a Richer Model for Stopping Inappropriate Responses. *Biological Psychiatry, 69*(12), E55-E68. doi: 10.1016/j.biopsych.2010.07.024

Aron, A. R., Behrens, T. E., Smith, S., Frank, M. J., & Poldrack, R. A. (2007). Triangulating a cognitive control network using diffusion-weighted

magnetic resonance imaging (MRI) and functional MRI. *Journal of Neuroscience, 27*(14), 3743-3752. doi: 10.1523/Jneurosci.0519-07.2007

Aron, A. R., Fletcher, P. C., Bullmore, E. T., Sahakian, B. J., & Robbins, T. W. (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience, 6*(2), 115-116. doi: 10.1038/nn1003

Aron, A. R., & Poldrack, R. A. (2005). The cognitive neuroscience of response inhibition: Relevance for genetic research in attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*(11), 1285-1292. doi: 10.1016/j.biopsych.2004.10.026

Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2014). Inhibition and the right inferior frontal cortex: one decade on. *Trends in Cognitive Sciences, 18*(4), 177-185. doi: 10.1016/j.tics.2013.12.003

Awiszus, F. (2003). Chapter 2 TMS and threshold hunting. In W. Paulus, F. Tergau, M. A. Nitsche, J. G. Rothwell, U. Ziemann, & M. Hallett (Eds.), *Supplements to Clinical Neurophysiology* (Vol. 56, pp. 13-23): Elsevier.

Awiszus, F. (2011). Fast estimation of transcranial magnetic stimulation motor threshold: is it safe? *Brain Stimulation, 4*(1), 58-59. doi: 10.1016/j.brs.2010.09.004

Axelsen, M. C., Jepsen, J. R. M., & Bak, N. (2017). The Choice of Prior in Bayesian Modeling of the Information Sampling Task. *Biological Psychiatry*. doi:10.1016/j.biopsych.2017.04.021

Bae, E. H., Schrader, L. M., Machii, K., Alonso-Alonso, M., Riviello, J. J., Pascual-Leone, A., & Rotenberg, A. (2007). Safety and tolerability of

repetitive transcranial magnetic stimulation in patients with epilepsy: a review of the literature. *Epilepsy & Behavior, 10*(4), 521-528. doi: 10.1016/j.yebeh.2007.03.004

Bakker, N., Shahab, S., Giacobbe, P., Blumberger, D. M., Daskalakis, Z. J., Kennedy, S. H., & Downar, J. (2015). rTMS of the Dorsomedial Prefrontal Cortex for Major Depression: Safety, Tolerability, Effectiveness, and Outcome Predictors for 10 Hz Versus Intermittent Theta-burst Stimulation. *Brain Stimulation, 8*(2), 208-215. doi: 10.1016/j.brs.2014.11.002

Balconi, M., & Bortolotti, A. (2012). Detection of the facial expression of emotion and self-report measures in empathic situations are influenced by sensorimotor circuit inhibition by low-frequency rTMS. *Brain Stimulation, 5*(3), 330-336. doi: 10.1016/j.brs.2011.05.004

Balconi, M., & Bortolotti, A. (2013). Emotional face recognition, empathic trait (BEES), and cortical contribution in response to positive and negative cues. the effect of rTMS on dorsal medial prefrontal cortex. *Cognitive Neurodynamics, 7*(1), 13-21. doi: 10.1007/s11571-012-9210-4

Balconi, M., Bortolotti, A., & Gonzaga, L. (2011). Emotional face recognition, EMG response, and medial prefrontal activity in empathic behaviour. *Neuroscience Research, 71*(3), 251-259. doi: 10.1016/j.neures.2011.07.1833

Balconi, M., & Canavesio, Y. (2014). High-frequency rTMS on DLPFC increases prosocial attitude in case of decision to support people. *Social Neuroscience, 9*(1), 82-93. doi: 10.1080/17470919.2013.861361

Balconi, M., & Canavesio, Y. (2016). Empathy, approach attitude, and rTMS on left DLPFC affect emotional face recognition and facial feedback (EMG). *Journal of Psychophysiology, 30*(1), 17-28. doi: 10.1027/0269-8803/a000150

Balconi, M., Crivelli, D., & Bortolotti, A. (2010). Detection of facial expression of emotion and self-report measures in empathic situations are influenced by ACC inhibition: rTMS evidences. *Neuropsychological Trends, 8*, 95-99.

Ballard, K., & Knutson, B. (2009). Dissociable neural representations of future reward magnitude and delay during temporal discounting. *NeuroImage, 45*(1), 143-150. doi: 10.1016/j.neuroimage.2008.11.004

Banca, P., Lange, I., Worbe, Y., Howell, N. A., Irvine, M., Harrison, N. A., . . . Voon, V. (2016). Reflection impulsivity in binge drinking: behavioural and volumetric correlates. *Addiction Biology, 21*(2), 504-515. doi: 10.1111/adb.12227

Bari, A., & Robbins, T. W. (2013). Inhibition and impulsivity: Behavioral and neural basis of response control. *Progress in Neurobiology, 108*, 44-79. doi: 10.1016/j.pneurobio.2013.06.005

Barker, A. T., & Freeston, I. L. (1985). Medical Applications of Electric and Magnetic-Fields. *Electronics and Power, 31*(10), 757-760.

Barker, A. T., Freeston, I. L., Jalinous, R., Merton, P. A., & Morton, H. B. (1985). Magnetic Stimulation of the Human-Brain. *Journal of Physiology-London, 369*(Dec), P3-P3.

Barker, A. T., & Jalinous, R. (1985). Non-Invasive Magnetic Stimulation of Human Motor Cortex. *Lancet, 1*(8437), 1106-1107.

Baron-Cohen, S. (1989). The autistic child's theory of mind: a case of specific developmental delay. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 30*(2), 285-297.

Baron-Cohen, S., Leslie, A. M., & Frith, U. (1985). Does the Autistic-Child Have a Theory of Mind. *Cognition, 21*(1), 37-46. doi: 10.1016/0010-0277(85)90022-8

Baron-Cohen, S., Richler, J., Bisarya, D., Gurunathan, N., & Wheelwright, S. (2003). The systemizing quotient: an investigation of adults with Asperger syndrome or high-functioning autism, and normal sex differences. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences, 358*(1430), 361-374. doi: 10.1098/rstb.2002.1206

Baron-Cohen, S., Ring, H. A., Wheelwright, S., Bullmore, E. T., Brammer, M. J., Simmons, A., & Williams, S. C. R. (1999). Social intelligence in the normal and autistic brain: an fMRI study. *European Journal of Neuroscience, 11*(6), 1891-1898. doi: 10.1046/j.1460-9568.1999.00621.x

Baron-Cohen, S., & Wheelwright, S. (2004). The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. *Journal of Autism and Developmental Disorders, 34*(2), 163-175.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. *Journal of Child Psychology and Psychiatry and Allied*

Disciplines, 42(2), 241-251. doi: 10.1017/S0021963001006643

Batson, C. D. (2009). These Things Called Empathy: Eight Related but Distinct Phenomena. In J. Decety & W. Ickes (Eds.), *The Social Neuroscience of Empathy* (pp. 3-15). MA: The MIT Press.

Bechara, A. (2004). The role of emotion in decision-making: evidence from neurological patients with orbitofrontal damage. *Brain and Cognition, 55*(1), 30-40. doi: 10.1016/j.bandc.2003.04.001

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to Future Consequences Following Damage to Human Prefrontal Cortex. *Cognition, 50*(1-3), 7-15. doi: 10.1016/0010-0277(94)90018-3

Begg, C. B., & Mazumdar, M. (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics, 50*(4), 1088-1101.

Behan, B., Stone, A., & Garavan, H. (2015). Right Prefrontal and Ventral Striatum Interactions Underlying Impulsive Choice and Impulsive Responding. *Human Brain Mapping, 36*(1), 187-198. doi: 10.1002/hbm.22621

Bennett, D., Oldham, S., Dawson, A., Parkes, L., Murawski, C., & Yu¨cel, M. (2017). Systematic Overestimation of Reflection Impulsivity in the Information Sampling Task. *Biological Psychiatry, 82*(4), e29-e30. doi: 10.1016/j.biopsych.2016.05.027

Bennett, D., Yücel, M., & Murawski, C. (2017). Reply to: The Choice of Prior in Bayesian Modeling of the Information Sampling Task. *Biological Psychiatry*. doi: 10.1016/j.biopsych.2017.05.023

Benninger, D. H., Iseki, K., Kranick, S., Luckenbaugh, D. A., Houdayer, E., &

Hallett, M. (2012). Controlled Study of 50-Hz Repetitive Transcranial Magnetic Stimulation for the Treatment of Parkinson Disease. *Neurorehabilitation and Neural Repair, 26*(9), 1096-1105. doi: 10.1177/1545968312445636

Berlim, M. T., Mcgirr, A., Beaulieu, M. M., & Turecki, G. (2012). Theory of mind in subjects with major depressive disorder: is it influenced by repetitive transcranial magnetic stimulation? *World Journal of Biological Psychiatry, 13*(6), 474-479. doi: 10.3109/15622975.2011.615861

Bermpohl, F., Fregni, F., Boggio, P. S., Thut, G., Northoff, G., Otachi, P. T., . . . Pascual-Leone, A. (2005). Left prefrontal repetitive transcranial magnetic stimulation impairs performance in affective go/no-go task. *Neuroreport, 16*(6), 615-619.

Besel, L. D. S., & Yuille, J. C. (2010). Individual differences in empathy: The role of facial expression recognition. *Personality and Individual Differences, 49*(2), 107-112. doi: 10.1016/j.paid.2010.03.013

Beszterczey, S., Nestor, P. G., Shirai, A., & Harding, S. (2013). Neuropsychology of decision making and psychopathy in high-risk ex-offenders. *Neuropsychology, 27*(4), 491-497. doi: 10.1037/a0033162

Bickel, W. K., Yi, R., Kowal, B. P., & Gatchalian, K. M. (2008). Cigarette Smokers Discount Past and Future Rewards Symmetrically and More than Controls: Is Discounting a Measure of Impulsivity? *Drug and Alcohol Dependence, 96*(3), 256-262. doi: 10.1016/j.drugalcdep.2008.03.009

Bjørkly, S. (2013). A systematic review of the relationship between impulsivity

and violence in persons with psychosis: Evidence or spin cycle? *Aggression and Violent Behavior, 18*(6), 753-760. doi: 10.1016/j.avb.2013.08.001

Blair, J., Mitchell, D. R., & Blair, K. (2005). *The psychopath: emotion and the brain*. Malden, MA: Blackwell Pub.

Blair, R. J. R. (2005). Responding to the emotions of others: dissociating forms of empathy through the study of typical and psychiatric populations. *Consciousness and Cognition, 14*(4), 698-718. doi: 10.1016/j.concog.2005.06.004

Borenstein, M., Hedges, L., & Rothstein, H. (2007). Meta-Analysis: Fixed effect vs. random effects. Retrieved from https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf.

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009a). Identifying and Quantifying HeterogeneityIntroduction to Meta-Analysis (pp. 107-125): John Wiley & Sons, Ltd. Retrieved from http://dx.doi.org/10.1002/9780470743386.ch16.

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009b). *Introduction to Meta-Analysis* Retrieved from http://dx.doi.org/10.1002/9780470743386

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009c). Meta-Regression. In M. Borenstein, L. V. Hedges, J. P. T. Higgins, & H. R. Rothstein (Eds.), *Introduction to Meta-Analysis* (pp. 187 -203). Chichester, U.K.: John Wiley & Sons.

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009d). Multiple Outcomes or Time-Points within a StudyIntroduction to

Meta-Analysis (pp. 225-238): John Wiley & Sons, Ltd. Retrieved from http://dx.doi.org/10.1002/9780470743386.ch25.

Bradfield, N. I., Reutens, D. C., Chen, J., & Wood, A. G. (2012). Stereotaxic localisation of the dorsolateral prefrontal cortex for transcranial magnetic stimulation is superior to the standard reference position. *Australian and New Zealand Journal of Psychiatry, 46*(3), 232-239. doi: 10.1177/0004867411430602

Bragado-Jimenez, M. D., & Taylor, P. J. (2012). Empathy, schizophrenia and violence: A systematic review. *Schizophrenia Research, 141*(1), 83-90. doi: 10.1016/j.schres.2012.07.019

Brevet-Aeby, C., Brunelin, J., Iceta, S., Padovan, C., & Poulet, E. (2016). Prefrontal cortex and impulsivity: Interest of noninvasive brain stimulation. *Neuroscience and Biobehavioral Reviews, 71*, 112-134. doi: 10.1016/j.neubiorev.2016.08.028

Brooks, S. J., Cedernaes, J., & Schiöth, H. B. (2013). Increased Prefrontal and Parahippocampal Activation with Reduced Dorsolateral Prefrontal and Insular Cortex Activation to Food Images in Obesity: A Meta-Analysis of fMRI Studies. *PloS One, 8*(4), e60393. doi: 10.1371/journal.pone.0060393

Brown, B. W., Jr. (1980). The crossover experiment for clinical trials. *Biometrics, 36*(1), 69-79.

Brunet, E., Sarfati, Y., Hardy-Bayle, M. C., & Decety, J. (2000). A PET investigation of the attribution of intentions with a nonverbal task. *NeuroImage, 11*(2), 157-166. doi: 10.1006/nimg.1999.0525

Buss, A. H., & Plomin, R. (1975). *A temperament theory of personality*

development. Oxford, England: Wiley-Interscience.

Cai, W. D., Cannistraci, C. J., Gore, J. C., & Leung, H. C. (2014). Sensorimotor-independent prefrontal activity during response inhibition. *Human Brain Mapping, 35*(5), 2119-2136. doi: 10.1002/hbm.22315

Cai, Y., Li, S., Liu, J., Li, D., Feng, Z., Wang, Q., . . . Xue, G. (2016). The Role of the Frontal and Parietal Cortex in Proactive and Reactive Inhibitory Control: A Transcranial Direct Current Stimulation Study. *Journal of Cognitive Neuroscience, 28*(1), 177-186. doi: 10.1162/jocn_a_00888

Cairns, E., & Cammock, T. (1978). Development of a More Reliable Version of Matching Familiar Figures Test. *Developmental Psychology, 14*(5), 555-560. doi: 10.1037/0012-1649.14.5.555

Cambridge Cognition. (2015). CANTAB. Retrieved 02-October, 2015, from http://www.cambridgecognition.com/technology

Cambridge Cognition. (2016). CANTAB® [Cognitive assessment software]: CANTAB Technology.

Carmel, A., Rose, M., & Fruzzetti, A. E. (2014). Barriers and Solutions to Implementing Dialectical Behavior Therapy in a Public Behavioral Health System. *Administration and Policy in Mental Health, 41*(5), 608-614. doi: 10.1007/s10488-013-0504-6

Carrington, S. J., & Bailey, A. J. (2009). Are There Theory of Mind Regions in the Brain? A Review of the Neuroimaging Literature. *Human Brain Mapping, 30*(8), 2313-2335. doi: 10.1002/Hbm.20671

Castellanos-Ryan, N., & Séguin, J. R. (2015). Prefrontal and Anterior Cingulate Cortex Mechanisms of Impulsivity. In T. P. Beauchaine & S. P. Hinshaw (Eds.), *The Oxford Handbook of Externalizing Spectrum*

Disorders (pp. 201-219). New York: Oxford University Press.

Castro-Meneses, L. J., Johnson, B. W., & Sowman, P. F. (2016). Vocal response inhibition is enhanced by anodal tDCS over the right prefrontal cortex. *Experimental Brain Research, 234*(1), 185-195. doi: 10.1007/s00221-015-4452-0

Caswell, A. J., Bond, R., Duka, T., & Morgan, M. J. (2015). Further evidence of the heterogeneous nature of impulsivity. *Personality and Individual Differences, 76*, 68-74. doi: 10.1016/j.paid.2014.11.059

Caswell, A. J., Celio, M. A., Morgan, M. J., & Duka, T. (2016). Impulsivity as a Multifaceted Construct Related to Excessive Drinking Among UK Students. *Alcohol and Alcoholism, 51*(1), 77-83. doi: 10.1093/alcalc/agv070

Chambers, C. D., Bellgrove, M. A., Gould, I. C., English, T., Garavan, H., McNaught, E., . . . Mattingley, J. B. (2007). Dissociable mechanisms of cognitive control in prefrontal and premotor cortex. *Journal of Neurophysiology, 98*(6), 3638-3647. doi: 10.1152/jn.00685.2007

Chambers, C. D., Bellgrove, M. A., Stokes, M. G., Henderson, T. R., Garavan, H., Robertson, I. H., . . . Mattingley, J. B. (2006). Executive "brake failure" following deactivation of human frontal lobe. *Journal of Cognitive Neuroscience, 18*(3), 444-455. doi: 10.1162/jocn.2006.18.3.444

Chambers, C. D., Garavan, H., & Bellgrove, M. A. (2009). Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neuroscience & Biobehavioral Reviews, 33*(5), 631-646. doi: 10.1016/j.neubiorev.2008.08.016

Chamorro, J., Bernardi, S., Potenza, M. N., Grante, J. E., Marsh, R., Wang, S., & Blanco, C. (2012). Impulsivity in the general population: A national study. *Journal of Psychiatric Research, 46*(8), 994-1001. doi: 10.1016/j.jpsychires.2012.04.023

Chen, C. Y., Muggleton, N. G., Tzeng, O. J. L., Hung, D. L., & Juan, C. H. (2009). Control of prepotent responses by the superior medial frontal cortex. *NeuroImage, 44*(2), 537-545. doi: 10.1016/j.neuroimage.2008.09.005

Cheng, G. L. F., & Lee, T. M. C. (2016). Altering risky decision-making: Influence of impulsivity on the neuromodulation of prefrontal cortex. *Social Neuroscience, 11*(4), 353-364. doi: 10.1080/17470919.2015.1085895

Cherek, D. R., & Lane, S. D. (1999). Laboratory and psychometric measurements of impulsivity among violent and nonviolent female parolees. *Biological Psychiatry, 46*(2), 273-280.

Cho, S. S., Ko, J. H., Pellecchia, G., Van Eimeren, T., Cilia, R., & Strafella, A. P. (2010). Continuous theta burst stimulation of right dorsolateral prefrontal cortex induces changes in impulsivity level. *Brain Stimulation, 3*(3), 170-176. doi: 10.1016/j.brs.2009.10.002

Cho, S. S., Koshimori, Y., Aminian, K., Obeso, I., Rusjan, P., Lang, A. E., . . . Strafella, A. P. (2015). Investing in the future: stimulation of the medial prefrontal cortex reduces discounting of delayed rewards. *Neuropsychopharmacology, 40*(3), 546-553. doi: 10.1038/npp.2014.211

Cho, S. S., Pellecchia, G., Aminian, K., Ray, N., Segura, B., Obeso, I., &

Strafella, A. P. (2013). Morphometric Correlation of Impulsivity in Medial Prefrontal Cortex. *Brain Topography, 26*(3), 479-487. doi: 10.1007/s10548-012-0270-x

Cho, S. S., Pellecchia, G., Ko, J. H., Ray, N., Obeso, I., Houle, S., & Strafella, A. P. (2012). Effect of continuous theta burst stimulation of the right dorsolateral prefrontal cortex on cerebral blood flow changes during decision making. *Brain Stimulation, 5*(2), 116-123. doi: 10.1016/j.brs.2012.03.007

Chou, Y. H., Hickey, P. T., Sundman, M., Song, A. W., & Chen, N. K. (2015). Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson disease: a systematic review and meta-analysis. *JAMA Neurol, 72*(4), 432-440. doi: 10.1001/jamaneurol.2014.4380

Christopoulos, G. I., Tobler, P. N., Bossaerts, P., Dolan, R. J., & Schultz, W. (2009). Neural correlates of value, risk, and risk aversion contributing to decision making under risk. *Journal of Neuroscience, 29*(40), 12574-12583. doi: 10.1523/JNEUROSCI.2614-09.2009

Clark, L., & Manes, F. (2004). Social and emotional decision-making following frontal lobe injury. *Neurocase, 10*(5), 398-403. doi: 10.1080/13554790490882799

Clark, L., & Robbins, T. W. (2017). Reply to: Systematic Overestimation of Reflection Impulsivity in the Information Sampling Task. *Biological Psychiatry, 82*(4), e31. doi: 10.1016/j.biopsych.2016.06.018

Clark, L., Robbins, T. W., Ersche, K. D., & Sahakian, B. J. (2006). Reflection impulsivity in current and former substance users. *Biological Psychiatry,*

60(5), 515-522. doi: 10.1016/j.biopsych.2005.11.007

Cohen, J. (1988). The t Test for Means *Statistical power analysis for the behavioral sciences* (2nd ed., pp. 19-74). Hillsdale, N.J.: L. Erlbaum Associates.

Cohen, J. R., Berkman, E. T., & Lieberman, M. D. (2013). Intentional and Incidental Self-Control in Ventrolateral Prefrontal Cortex. In D. T. Stuss & R. T. Knight (Eds.), *Principles of Frontal Lobe Function* (2nd ed., pp. 417-440): Oxford University Press.

Colborn, V. A., LaCroix, J. M., Neely, L. L., Tucker, J., Perera, K., Daruwala, S. E., . . . Ghahramanlou-Holloway, M. (2017). Motor impulsivity differentiates between psychiatric inpatients with multiple versus single lifetime suicide attempts. *Psychiatry Research, 253*, 18-21. doi: 10.1016/j.psychres.2017.03.026

Conners, C. K. (2000). *Conners' Continuous Performance Test user's manual*. Toronto, Canada: Multi-Health Systems.

Conners, C. K., Epstein, J. N., Angold, A., & Klaric, J. (2003). Continuous performance test performance in a normative epidemiological sample. *Journal of Abnormal Child Psychology, 31*(5), 555-562. doi: 10.1023/A:1025457300409

Corcoran, R., Cahill, C., & Frith, C. D. (1997). The appreciation of visual jokes in people with schizophrenia: A study of 'mentalizing' ability. *Schizophrenia Research, 24*(3), 319-327. doi: 10.1016/s0920-9964(96)00117-x

Costa, A., Torriero, S., Oliveri, M., & Caltagirone, C. (2008). Prefrontal and temporo-parietal involvement in taking others' perspective: TMS

evidence. *Behavioural Neurology, 19*(1-2), 71-74.

Cox, C. L., Gotimer, K., Roy, A. K., Castellanos, F. X., Milham, M. P., & Kelly, C. (2010). Your resting brain CAREs about your risky behavior. *PloS One, 5*(8), e12296. doi: 10.1371/journal.pone.0012296

Croarkin, P. E., Nakonezny, P. A., Deng, Z. D., Romanowicz, M., Voort, J. L. V., Camsari, D. D., . . . Lewis, C. P. (2018). High-frequency repetitive TMS for suicidal ideation in adolescents with depression. *Journal of Affective Disorders, 239*, 282-290. doi: 10.1016/j.jad.2018.06.048

Cyders, M. A. (2013). Impulsivity and the Sexes: Measurement and Structural Invariance of the UPPS-P Impulsive Behavior Scale. *Assessment, 20*(1), 86-97. doi: 10.1177/1073191111428762

Cyders, M. A., Smith, G. T., Spillane, N. S., Fischer, S., Annus, A. M., & Peterson, C. (2007). Integration of impulsivity and positive mood to predict risky behavior: Development and validation of a measure of positive urgency. *Psychological Assessment, 19*(1), 107-118. doi: 10.1037/1040-3590.19.1.107

Dadds, M. R., Hunter, K., Hawes, D. J., Frost, A. D. J., Vassallo, S., Bunn, P., . . . Masry, Y. E. (2008). A Measure of Cognitive and Affective Empathy in Children Using Parent Ratings. *Child Psychiatry and Human Development, 39*(2), 111-122. doi: 10.1007/s10578-007-0075-4

Dal Monte, O., Schintu, S., Pardini, M., Berti, A., Wassermann, E. M., Grafman, J., & Krueger, F. (2014). The left inferior frontal gyrus is crucial for reading the mind in the eyes: Brain lesion evidence. *Cortex, 58*, 9-17. doi: 10.1016/j.cortex.2014.05.002

Dambacher, F., Sack, A. T., Lobbestael, J., Arntz, A., Brugmann, S., & Schuhmann, T. (2014). The role of right prefrontal and medial cortex in response inhibition: interfering with action restraint and action cancellation using transcranial magnetic brain stimulation. *Journal of Cognitive Neuroscience, 26*(8), 1775-1784. doi: 10.1162/jocn_a_00595

Dambacher, F., Schuhmann, T., Lobbestael, J., Arntz, A., Brugman, S., & Sack, A. T. (2015). No Effects of Bilateral tDCS over Inferior Frontal Gyrus on Response Inhibition and Aggression. *PloS One, 10*(7). doi: 10.1371/journal.pone.0132170

Davis, M. H. (1983). Measuring Individual-Differences in Empathy - Evidence for a Multidimensional Approach. *Journal of Personality and Social Psychology, 44*(1), 113-126. doi: 10.1037//0022-3514.44.1.113

Day, A., Casey, S., & Gerace, A. (2010). Interventions to improve empathy awareness in sexual and violent offenders: Conceptual, empirical, and clinical issues. *Aggression and Violent Behavior, 15*(3), 201-208. doi: 10.1016/j.avb.2009.12.003

de Berker, A. O., Bikson, M., & Bestmann, S. (2013). Predicting the behavioral impact of transcranial direct current stimulation: issues and limitations. *Frontiers in Human Neuroscience, 7*, 613. doi: 10.3389/fnhum.2013.00613

de Graaf, T. A., & Sack, A. T. (2011). Null results in TMS: From absence of evidence to evidence of absence. *Neuroscience & Biobehavioral Reviews, 35*(3), 871-877. doi: 10.1016/j.neubiorev.2010.10.006

Decety, J., & Jackson, P. L. (2004). The Functional Architecture of Human Empathy. *Behavioral and Cognitive Neuroscience Reviews, 3*(2),

71-100. doi: 10.1177/1534582304267187

Deeks, J. J., Higgins, J., & Altman, D. G. (2011). Analysing data and undertaking meta-analyses. In J. Higgins & S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: The Cochrane Collaboration. Retrieved from http://handbook.cochrane.org.

Demirtas-Tatlidede, A., Vahabzadeh-Hagh, A. M., & Pascual-Leone, A. (2013). Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? *Neuropharmacology, 64*, 566-578. doi: 10.1016/j.neuropharm.2012.06.020

Deng, Z.-D., Lisanby, S. H., & Peterchev, A. V. (2014). Coil design considerations for deep transcranial magnetic stimulation. *Clinical Neurophysiology, 125*(6), 1202-1212. doi: 10.1016/j.clinph.2013.11.038

Dennis, J. A., Khan, O., Ferriter, M., Huband, N., Powney, M. J., & Duggan, C. (2012). Psychological interventions for adults who have sexually offended or are at risk of offending. *Cochrane Database of Systematic Reviews*(12). doi: 10.1002/14651858.CD007507.pub2

Denny, B. T., Kober, H., Wager, T. D., & Ochsner, K. N. (2012). A Meta-analysis of Functional Neuroimaging Studies of Self- and Other Judgments Reveals a Spatial Gradient for Mentalizing in Medial Prefrontal Cortex. *Journal of Cognitive Neuroscience, 24*(8), 1742-1752.

Depue, R. A., & Collins, P. F. (1999). Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. *Behavioral and Brain Sciences, 22*(3), 491-517;

discussion 518-469.

DeVito, E. E., Blackwell, A. D., Clark, L., Kent, L., Dezsery, A. M., Turner, D. C., . . . Sahakian, B. J. (2009). Methylphenidate improves response inhibition but not reflection–impulsivity in children with attention deficit hyperactivity disorder (ADHD). *Psychopharmacology, 202*(1-3), 531-539. doi: 10.1007/s00213-008-1337-y

Dickman, S. J. (1990). Functional and Dysfunctional Impulsivity - Personality and Cognitive Correlates. *Journal of Personality and Social Psychology, 58*(1), 95-102. doi: 10.1037/0022-3514.58.1.95

Ditye, T., Jacobson, L., Walsh, V., & Lavidor, M. (2012). Modulating behavioral inhibition by tDCS combined with cognitive training. *Experimental Brain Research, 219*(3), 363-368. doi: 10.1007/s00221-012-3098-4

Dolan, M., & Fullam, R. (2004). Theory of mind and mentalizing ability in antisocial personality disorders with and without psychopathy. *Psychological Medicine, 34*(6), 1093-1102. doi: 10.1017/S0033291704002028

Dougall, N., Maayan, N., Soares-Weiser, K., McDermott, L. M., & McIntosh, A. (2015). Transcranial magnetic stimulation (TMS) for schizophrenia. *The Cochrane Database of Systematic Reviews, 8*. doi: 10.1002/14651858.CD006081.pub2

Douglas, K. M., & Porter, R. J. (2009). Longitudinal Assessment of Neuropsychological Function in Major Depression. *Australian and New Zealand Journal of Psychiatry, 43*(12), 1105-1117. doi: 10.3109/00048670903279887

Douglas, K. S., Hart, S. D., Webster, C. D., & Belfrage, H. (2013). *HCR-20V3:*

Assessing risk of violence – User guide. . Burnaby, Canada: Mental Health, Law, and Policy Institute, Simon Fraser University.

Du, W., Green, L., & Myerson, J. (2002). Cross-Cultural Comparisons of Discounting Delayed and Probabilistic Rewards. *The Psychological Record, 52*(4), 479-492. doi: 10.1007/bf03395199

Duggan, C., & Dennis, J. (2014). The place of evidence in the treatment of sex offenders. *Criminal Behaviour and Mental Health, 24*(3), 153-162. doi: 10.1002/cbm.1904

Duval, S., & Tweedie, R. (2000). Trim and Fill: A Simple Funnel-Plot–Based Method of Testing and Adjusting for Publication Bias in Meta-Analysis. *Biometrics, 56*(2), 455-463. doi: 10.1111/j.0006-341X.2000.00455.x

Dvash, J., & Shamay-Tsoory, S. G. (2014). Theory of Mind and Empathy as Multidimensional Constructs Neurological Foundations. *Topics in Language Disorders, 34*(4), 282-295. doi: 10.1097/Tld.0000000000000040

Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ, 315*(7109), 629-634.

Egger, M., & Smith, G. D. (1995). Misleading meta-analysis. *British Medical Journal, 310*(6982), 752-754.

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal, 315*(7109), 629-634.

Ehrlich, S., Geisler, D., Ritschel, F., King, J. A., Seidel, M., Boehm, I., . . . Kroemer, N. B. (2015). Elevated cognitive control over reward

processing in recovered female patients with anorexia nervosa. *Journal of Psychiatry & Neuroscience : JPN, 40*(5), 307-315. doi: 10.1503/jpn.140249

Eisenberg, N. (2000). Emotion, regulation, and moral development. *Annual Review of Psychology, 51*, 665-697. doi: 10.1146/annurev.psych.51.1.665

Eisenegger, C., Treyer, V., Fehr, E., & Knoch, D. (2008). Time-course of "off-line" prefrontal rTMS effects - a PET study. *NeuroImage, 42*(1), 379-384. doi: 10.1016/j.neuroimage.2008.04.172

Ekman, P., & Friesen, W. V. (1976). *Pictures of Facial Affect*. Palo Alto, California: Consulting Psychologists Press.

Elchlepp, H., Lavric, A., Chambers, C. D., & Verbruggen, F. (2016). Proactive inhibitory control: A general biasing account. *Cognitive Psychology, 86*, 27-61. doi: 10.1016/j.cogpsych.2016.01.004

Endrass, T., Schuermann, B., Kaufmann, C., Spielberg, R., Kniesche, R., & Kathmann, N. (2010). Performance monitoring and error significance in patients with obsessive-compulsive disorder. *Biological Psychology, 84*(2), 257-263. doi: 10.1016/j.biopsycho.2010.02.002

Enticott, P. G., Fitzgibbon, B. M., Kennedy, H. A., Arnold, S. L., Elliot, D., Peachey, A., . . . Fitzgerald, P. B. (2014). A Double-blind, Randomized Trial of Deep Repetitive Transcranial Magnetic Stimulation (rTMS) for Autism Spectrum Disorder. *Brain Stimulation, 7*(2), 206-211. doi: 10.1016/j.brs.2013.10.004

Enticott, P. G., Ogloff, J. R. P., & Bradshaw, J. L. (2006). Associations between laboratory measures of executive inhibitory control and

self-reported impulsivity. *Personality and Individual Differences, 41*(2), 285-294. doi: 10.1016/j.paid.2006.01.011

Enzi, B., Amirie, S., & Brune, M. (2016). Empathy for pain-related dorsolateral prefrontal activity is modulated by angry face perception. *Experimental Brain Research, 234*(11), 3335-3345. doi: 10.1007/s00221-016-4731-4

Evenden, J. L. (1999a). Impulsivity: a discussion of clinical and experimental findings. *Journal of Psychopharmacology, 13*(2), 180-192.

Evenden, J. L. (1999b). Varieties of impulsivity. *Psychopharmacology, 146*(4), 348-361. doi: 10.1007/Pl00005481

Evren, C., Yilmaz, A., Can, Y., Bozkurt, M., Evren, B., & Umut, G. (2014). Severity of Impulsivity and Aggression at a 12-Month Follow-Up Among Male Heroin Dependent Patients. *Klinik Psikofarmakoloji Bulteni-Bulletin of Clinical Psychopharmacology, 24*(2), 158-167. doi: 10.5455/bcp.20131218094342

Eysenck, S. B., & Eysenck, H. J. (1977). The place of impulsiveness in a dimensional system of personality description. *British Journal of Social and Clinical Psychology, 16*(1), 57-68.

Fan, Y., Duncan, N. W., de Greck, M., & Northoff, G. (2011). Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. *Neuroscience & Biobehavioral Reviews, 35*(3), 903-911. doi: 10.1016/j.neubiorev.2010.10.009

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*(2), 175-191.

Fecteau, S., Pascual-Leone, A., Zald, D. H., Liguori, P., Theoret, H., Boggio, P.

S., & Fregni, F. (2007). Activation of prefrontal cortex by transcranial direct current stimulation reduces appetite for risk during ambiguous decision making. *Journal of Neuroscience, 27*(23), 6212-6218. doi: 10.1523/Jneurosci.0314-07.2007

Fernández-Abascal, E. G., Cabello, R., Fernández-Berrocal, P., & Baron-Cohen, S. (2013). Test-retest reliability of the 'Reading the Mind in the Eyes' test: a one-year follow-up study. *Molecular Autism, 4*, 33-33. doi: 10.1186/2040-2392-4-33

Figner, B., Knoch, D., Johnson, E. J., Krosch, A. R., Lisanby, S. H., Fehr, E., & Weber, E. U. (2010). Lateral prefrontal cortex and self-control in intertemporal choice. *Nature Neuroscience, 13*(5), 538-539. doi: 10.1038/nn.2516

Fineberg, N. A., Chamberlain, S. R., Goudriaan, A. E., Stein, D. J., Vanderschuren, L. J. M. J., Gillan, C. M., . . . Potenza, M. N. (2014). New developments in human neurocognition: clinical, genetic, and brain imaging correlates of impulsivity and compulsivity. *CNS Spectrums, 19*(1), 69-89. doi: 10.1017/S1092852913000801

Fitzgibbon, B. M., Kirkovski, M., Bailey, N. W., Thomson, R. H., Eisenberger, N., Enticott, P. G., & Fitzgerald, P. B. (2017). Low-frequency brain stimulation to the left dorsolateral prefrontal cortex increases the negative impact of social exclusion among those high in personal distress. *Social Neuroscience, 12*(3), 237-241. doi: 10.1080/17470919.2016.1166154

Floden, D., Vallesi, A., & Stuss, D. T. (2011). Task Context and Frontal Lobe Activation in the Stroop Task. *Journal of Cognitive Neuroscience, 23*(4),

867-879. doi: 10.1162/jocn.2010.21492

Fok, C. C. T., & Henry, D. (2015). Increasing the Sensitivity of Measures to Change. *Prevention science : the official journal of the Society for Prevention Research, 16*(7), 978-986. doi: 10.1007/s11121-015-0545-z

Fray, P. J., Robbins, T. W., & Sahakian, B. J. (1996). Neuropsychiatric applications of CANTAB. *International Journal of Geriatric Psychiatry, 11*(4), 329-336.

Frith, C. D., & Frith, U. (1999). Interacting minds--a biological basis. *Science, 286*(5445), 1692-1695.

Frye, C. C. J., Galizio, A., Friedel, J. E., DeHart, W. B., & Odum, A. L. (2016). Measuring Delay Discounting in Humans Using an Adjusting Amount Task. *Journal of Visualized Experiments*(107), e53584. doi: 10.3791/53584

Gallese, V. (2003). The roots of empathy: The shared manifold hypothesis and the neural basis of intersubjectivity. *Psychopathology, 36*(4), 171-180. doi: 10.1159/000072786

Gamboa, O. L., Antal, A., Moliadze, V., & Paulus, W. (2010). Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. *Experimental Brain Research, 204*(2), 181-187. doi: 10.1007/s00221-010-2293-4

Gaynes, B. N., Lloyd, S. W., Lux, L., Gartlehner, G., Hansen, R. A., Brode, S., . . . Lohr, K. N. (2014). Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. *Journal of Clinical Psychiatry, 75*(5), 477-489; quiz 489. doi: 10.4088/JCP.13r08815

Giardina, A., Caltagirone, C., & Oliveri, M. (2011). Temporo-parietal junction is involved in attribution of hostile intentionality in social interactions: An rTMS study. *Neuroscience Letters, 495*(2), 150-154. doi: 10.1016/j.neulet.2011.03.059

Glannon, W. (2014). Intervening in the psychopath's brain. *Theoretical Medicine and Bioethics, 35*(1), 43-57. doi: 10.1007/s11017-013-9275-z

Glenn, A. L., & Raine, A. (2008). The neurobiology of psychopathy. *Psychiatric Clinics of North America, 31*(3), 463-475. doi: 10.1016/j.psc.2008.03.004

Glenn, A. L., & Raine, A. (2014). *Psychopathy : an introduction to biological findings and their implications*. New York ; London: New York University Press.

Gonzalez-Liencres, C., Shamay-Tsoory, S. G., & Brune, M. (2013). Towards a neuroscience of empathy: Ontogeny, phylogeny, brain mechanisms, context and psychopathology. *Neuroscience and Biobehavioral Reviews, 37*(8), 1537-1548. doi: 10.1016/j.neubiorev.2013.05.001

Goodwill, A. M., Lum, J. A. G., Hendy, A. M., Muthalib, M., Johnson, L., Albein-Urios, N., & Teo, W.-P. (2017). Using non-invasive transcranial stimulation to improve motor and cognitive function in Parkinson's disease: a systematic review and meta-analysis. *Scientific Reports, 7*(1), 14840. doi: 10.1038/s41598-017-13260-z

Gordon, B. (1983). Lexical access and lexical decision: mechanisms of frequency sensitivity. *Journal of Verbal Learning and Verbal Behavior, 22*(1), 24-44. doi: 10.1016/S0022-5371(83)80004-8

Gordon, B., & Caramazza, A. (1982). Lexical decision for open- and

closed-class words: failure to replicate differential frequency sensitivity. *Brain and Language, 15*(1), 143-160.

Gottfredson, M. R., & Hirschi, T. (1990). *A general theory of crime*. California: Stanford University Press.

Gough, P. M., Nobre, A. C., & Devlin, J. T. (2005). Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. *Journal of Neuroscience, 25*(35), 8010-8016. doi: 10.1523/JNEUROSCI.2307-05.2005

Grant, J. E., & Kim, S. W. (2014). Brain circuitry of compulsivity and impulsivity. *CNS Spectrums, 19*(1), 21-27. doi: 10.1017/S109285291300028x

Greco, T., Zangrillo, A., Biondi-Zoccai, G., & Landoni, G. (2013). Meta-analysis: pitfalls and hints. *Heart, Lung and Vessels, 5*(4), 219-225.

Groppa, S., Oliviero, A., Eisen, A., Quartarone, A., Cohen, L. G., Mall, V., . . . Siebner, H. R. (2012). A practical guide to diagnostic transcranial magnetic stimulation: Report of an IFCN committee. *Clinical Neurophysiology, 123*(5), 858-882. doi: 10.1016/j.clinph.2012.01.010

Grossheinrich, N., Rau, A., Pogarell, O., Hennig-Fast, K., Reinl, M., Karch, S., . . . Padberg, F. (2009). Theta Burst Stimulation of the Prefrontal Cortex: Safety and Impact on Cognition, Mood, and Resting Electroencephalogram. *Biological Psychiatry, 65*(9), 778-784. doi: 10.1016/j.biopsych.2008.10.029

Héroux, M. E., Taylor, J. L., & Gandevia, S. C. (2015). The Use and Abuse of Transcranial Magnetic Stimulation to Modulate Corticospinal Excitability in Humans. *PloS One, 10*(12), e0144151. doi:

10.1371/journal.pone.0144151

Hallett, M. (2000). Transcranial magnetic stimulation and the human brain. *Nature, 406*(6792), 147-150. doi: 10.1038/35018000

Hallett, M. (2007). Transcranial magnetic stimulation: A primer. *Neuron, 55*(2), 187-199. doi: 10.1016/j.neuron.2007.06.026

Hamada, M., Hanajima, R., Terao, Y., Arai, N., Furubayashi, T., Inomata-Terada, S., . . . Ugawa, Y. (2007). Quadro-pulse stimulation is more effective than paired-pulse stimulation for plasticity induction of the human motor cortex. *Clinical Neurophysiology, 118*(12), 2672-2682. doi: 10.1016/j.clinph.2007.09.062

Hamada, M., Terao, Y., Hanajima, R., Shirota, Y., Nakatani-Enomoto, S., Furubayashi, T., . . . Ugawa, Y. (2008). Bidirectional long-term motor cortical plasticity and metaplasticity induced by quadripulse transcranial magnetic stimulation. *Journal of Physiology-London, 586*(16), 3927-3947. doi: 10.1113/jphysiol.2008.152793

Hamilton, K. R., Littlefield, A. K., Anastasio, N. C., Cunningham, K. A., Fink, L. H., Wing, V. C., . . . Potenza, M. N. (2015). Rapid-response impulsivity: definitions, measurement issues, and clinical implications. *Personal Disord, 6*(2), 168-181. doi: 10.1037/per0000100

Happé, F., Brownell, H., & Winner, E. (1999). Acquired 'theory of mind' impairments following stroke. *Cognition, 70*(3), 211-240. doi: 10.1016/s0010-0277(99)00005-0

Happé, F. G. E. (1994). An advanced test of theory of mind - understanding of story characters thoughts and feelings by able autistic, mentally-handicapped, and normal-children and adults. *Journal of*

Autism and Developmental Disorders, 24(2), 129-154. doi: 10.1007/bf02172093

Hecht, D., Walsh, V., & Lavidor, M. (2013). Bi-frontal direct current stimulation affects delay discounting choices. *Cognitive Neuroscience, 4*(1), 7-11. doi: 10.1080/17588928.2011.638139

Hedges, L. V. (1981). Distribution Theory for Glass's Estimator of Effect Size and Related Estimators. *Journal of Educational Statistics, 6*(2), 107-128. doi: 10.2307/1164588

Herwig, U., Padberg, F., Unger, J., Spitzer, M., & Schönfeldt-Lecuona, C. (2001). Transcranial magnetic stimulation in therapy studies: examination of the reliability of “standard” coil positioning by neuronavigation. *Biological Psychiatry, 50*(1), 58-61. doi: 10.1016/S0006-3223(01)01153-2

Hetu, S., Taschereau-Dumouchel, V., & Jackson, P. L. (2012). Stimulating the brain to study social interactions and empathy. *Brain Stimulation, 5*(2), 95-102.

Higgins, J. P., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine, 21*(11), 1539-1558. doi: 10.1002/sim.1186

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ, 327*(7414), 557-560. doi: 10.1136/bmj.327.7414.557

Hoekert, M., Vingerhoets, G., & Aleman, A. (2010). Results of a pilot study on the involvement of bilateral inferior frontal gyri in emotional prosody perception: an rTMS study. *BMC Neuroscience, 11*, 93. doi:

10.1186/1471-2202-11-93

Hoffman, J. I. E. (2015). Chapter 36 - Meta-analysis *Biostatistics for Medical and Biomedical Practitioners* (pp. 645-653): Academic Press.

Hoffman, M. L. (1987). The contribution of empathy to justice and moral judgment *Empathy and its development.* (pp. 47-80). New York: Cambridge University Press.

Hogan, R. (1969). Development of an Empathy Scale. *Journal of Consulting and Clinical Psychology, 33*(3), 307-&. doi: 10.1037/H0027580

Holroyd, C. B., & Umemoto, A. (2016). The research domain criteria framework: The case for anterior cingulate cortex. *Neuroscience and Biobehavioral Reviews, 71*, 418-443. doi: 10.1016/j.neubiorev.2016.09.021

Hoogendam, J. M., Ramakers, G. M. J., & Di Lazzaro, V. (2010). Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimulation, 3*(2), 95-118. doi: 10.1016/j.brs.2009.10.005

Horvath, J. C., Perez, J. M., Forrow, L., Fregni, F., & Pascual-Leone, A. (2011). Transcranial magnetic stimulation: a historical evaluation and future prognosis of therapeutically relevant ethical concerns. *Journal of Medical Ethics, 37*(3), 137-143. doi: 10.1136/jme.2010.039966

Hsu, W. Y., Ku, Y., Zanto, T. P., & Gazzaley, A. (2015). Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis. *Neurobiology of Aging, 36*(8), 2348-2359. doi: 10.1016/j.neurobiolaging.2015.04.016

Huang, C. C., Su, T. P., Shan, I. K., & Wei, I. H. (2004). Effect of 5 Hz repetitive transcranial magnetic stimulation on cognition during a

Go/NoGo task. *Journal of Psychiatric Research, 38*(5), 513-520. doi: 10.1016/j.jpsychires.2004.01.006

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45*(2), 201-206. doi: 10.1016/j.neuron.2004.12.033

Hwang, J. H., Kim, S. H., Park, C. S., Bang, S. A., & Kim, S. E. (2010). Acute high-frequency rTMS of the left dorsolateral prefrontal cortex and attentional control in healthy young men. *Brain Research, 1329*, 152-158. doi: 10.1016/j.brainres.2010.03.013

Iribarren, M. M., Jimenez-Gimenez, M., Garcia-de Cecilia, J. M., & Rubio-Valladolid, G. (2011). Validation and psychometric properties of the State Impulsivity Scale (SIS). *Actas Españolas de Psiquiatría: Acepsi, 39*(1), 49-60.

Iwabuchi, S. J., Raschke, F., Auer, D. P., Liddle, P. F., Lankappa, S. T., & Palaniyappan, L. (2017). Targeted transcranial theta-burst stimulation alters fronto-insular network and prefrontal GABA. *NeuroImage, 146*, 395-403. doi: 10.1016/j.neuroimage.2016.09.043

Jackson, D., & Turner, R. (2017). Power analysis for random-effects meta-analysis. *Research Synthesis Methods, 8*(3), 290-302. doi: 10.1002/jrsm.1240

Jacobson, L., Javitt, D. C., & Lavidor, M. (2011). Activation of inhibition: diminishing impulsive behavior by direct current stimulation over the inferior frontal gyrus. *Journal of Cognitive Neuroscience, 23*(11), 3380-3387. doi: 10.1162/jocn_a_00020

Johnson, K. A., Baig, M., Ramsey, D., Lisanby, S. H., Avery, D., McDonald, W.

M., . . . Nahas, Z. (2013). Prefrontal rTMS for Treating Depression: Location and Intensity Results from the OPT-TMS Multi-Site Clinical Trial. *Brain Stimulation, 6*(2), 108-117. doi: 10.1016/j.brs.2012.02.003

Jolliffe, D., & Farrington, D. P. (2004). Empathy and offending: A systematic review and meta-analysis. *Aggression and Violent Behavior, 9*(5), 441-476. doi: 10.1016/j.avb.2003.03.001

Jolliffe, D., & Farrington, D. P. (2006). Development and validation of the Basic Empathy Scale. *Journal of Adolescence, 29*(4), 589-611. doi: 10.1016/j.adolescence.2005.08.010

Jolliffe, D., & Farrington, D. P. (2007). Examining the relationship between low empathy and self-reported offending. *Legal and Criminological Psychology, 12*, 265-286. doi: 10.1348/135532506x147413

Juan, C. H., & Muggleton, N. G. (2012). Brain stimulation and inhibitory control. *Brain Stimulation, 5*(2), 63-69. doi: 10.1016/j.brs.2012.03.012

Kagan, J. (1965). *Matching Familiar Figures Test*. Cambridge: Harvard University.

Kalbe, E., Schlegel, M., Sack, A. T., Nowak, D. A., Dafotakis, M., Bangard, C., . . . Kessler, J. (2010). Dissociating cognitive from affective theory of mind: A TMS study. *Cortex, 46*(6), 769-780. doi: 10.1016/j.cortex.2009.07.010

Karsen, E. F., Watts, B. V., & Holtzheimer, P. E. (2014). Review of the Effectiveness of Transcranial Magnetic Stimulation for Post-traumatic Stress Disorder. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 7*(2), 151-157. doi: 10.1016/j.brs.2013.10.006

Katayama, T., & Rothwell, J. C. (2007). Modulation of somatosensory evoked potentials using transcranial magnetic intermittent theta burst stimulation. *Clinical Neurophysiology, 118*(11), 2506-2511. doi: 10.1016/j.clinph.2007.08.011

Keuken, M. C., Hardie, A., Dorn, B. T., Dev, S., Paulus, M. P., Jonas, K. J., . . . Pineda, J. A. (2011). The role of the left inferior frontal gyrus in social perception: An rTMS study. *Brain Research, 1383*, 196-205. doi: 10.1016/j.brainres.2011.01.073

Khemiri, L., Jokinen, J., Runeson, B., & Jayaram-Lindstrom, N. (2016). Suicide Risk Associated with Experience of Violence and Impulsivity in Alcohol Dependent Patients. *Scientific Reports, 6*. doi: 10.1038/srep19373

Kim, S. H., Han, H. J., Ahn, H. M., Kim, S. A., & Kim, S. E. (2012). Effects of five daily high-frequency rTMS on Stroop task performance in aging individuals. *Neuroscience Research, 74*(3-4), 256-260. doi: 10.1016/j.neures.2012.08.008

Kirby, K. N. (2009). One-year temporal stability of delay-discount rates. *Psychon Bull Rev, 16*(3), 457-462. doi: 10.3758/PBR.16.3.457

Kirby, K. N., Petry, N. M., & Bickel, W. K. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *Journal of Experimental Psychology: General, 128*(1), 78-87.

Klomjai, W., Katz, R., & Lackmy-Vallée, A. (2015). Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Annals of Physical and Rehabilitation Medicine, 58*(4), 208-213. doi: 10.1016/j.rehab.2015.05.005

Knoch, D., Gianotti, L. R. R., Pascual-Leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of right prefrontal cortex by low-frequency repetitive transcranial magnetic stimulation induces risk-taking behavior. *Journal of Neuroscience, 26*(24), 6469-6472. doi: 10.1523/Jneurosci.0804-06.2006

Koffarnus, M. N., Jarmolowicz, D. P., Mueller, E. T., & Bickel, W. K. (2013). Changing delay discounting in the light of the competing neurobehavioral decision systems theory: a review. *Journal of the Experimental Analysis of Behavior, 99*(1), 32-57. doi: 10.1002/jeab.2

Krain, A. L., Wilson, A. M., Arbuckle, R., Castellanos, F. X., & Milham, M. P. (2006). Distinct neural mechanisms of risk and ambiguity: A meta-analysis of decision-making. *NeuroImage, 32*(1), 477-484. doi: 10.1016/j.neuroimage.2006.02.047

Krall, S. C., Volz, L. J., Oberwelland, E., Grefkes, C., Fink, G. R., & Konrad, K. (2016). The right temporoparietal junction in attention and social interaction: A transcranial magnetic stimulation study. *Human Brain Mapping, 37*(2), 796-807. doi: 10.1002/hbm.23068

Krause, L., Enticott, P. G., Zangen, A., & Fitzgerald, P. B. (2012). The role of medial prefrontal cortex in theory of mind: A deep rTMS study. *Behavioural Brain Research, 228*(1), 87-90. doi: 10.1016/j.bbr.2011.11.037

Krug, E. G., Mercy, J. A., Dahlberg, L. L., Zwi, A. B., & Lozano, R. (Eds.). (2002). *World report on violence and health*. Geneva: World Health Organization.

Kynast, J., & Schroeter, M. L. (2018). Sex, Age, and Emotional Valence:

Revealing Possible Biases in the ‘Reading the Mind in the Eyes’ Task. *Frontiers in Psychology, 9*(570). doi: 10.3389/fpsyg.2018.00570

Laisney, M., Bon, L., Guiziou, C., Daluzeau, N., Eustache, F., & Desgranges, B. (2013). Cognitive and affective Theory of Mind in mild to moderate Alzheimer's disease. *Journal of Neuropsychology, 7*(1), 107-120. doi: 10.1111/j.1748-6653.2012.02038.x

Lee, H. W., Lu, M. S., Chen, C. Y., Muggleton, N. G., Hsu, T. Y., & Juan, C. H. (2016). Roles of the pre-SMA and rIFG in conditional stopping revealed by transcranial magnetic stimulation. *Behavioural Brain Research, 296*, 459-467. doi: 10.1016/j.bbr.2015.08.024

Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., . . . Garcia-Larrea, L. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology, 125*(11), 2150-2206. doi: 10.1016/j.clinph.2014.05.021

Lejuez, C. W., Read, J. P., Kahler, C. W., Richards, J. B., Ramsey, S. E., Stuart, G. L., . . . Brown, R. A. (2002). Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). *Journal of Experimental Psychology: Applied, 8*(2), 75-84.

Lev-Ran, S., Shamay-Tsoory, S. G., Zangen, A., & Levkovitz, Y. (2012). Transcranial magnetic stimulation of the ventromedial prefrontal cortex impairs theory of mind learning. *European Psychiatry, 27*(4), 285-289. doi: 10.1016/j.eurpsy.2010.11.008

Levy, B. J., & Wagner, A. D. (2011). Cognitive control and right ventrolateral prefrontal cortex: reflexive reorienting, motor inhibition, and action

updating. *Year in Cognitive Neuroscience, 1224*, 40-62. doi: 10.1111/j.1749-6632.2011.05958.x

Leyman, L., De Raedt, R., Vanderhasselt, M. A., & Baeken, C. (2009). Influence of high-frequency repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex on the inhibition of emotional information in healthy volunteers. *Psychological Medicine, 39*(6), 1019-1028. doi: 10.1017/S0033291708004431

Li, C.-s. R., Huang, C., Yan, P., Paliwal, P., Constable, R. T., & Sinha, R. (2008). Neural Correlates of Post-error Slowing during a Stop Signal Task: A Functional Magnetic Resonance Imaging Study. *Journal of Cognitive Neuroscience, 20*(6), 1021-1029. doi: 10.1162/jocn.2008.20071

Li, Y. H., Chiu, M. J., Yeh, Z. T., Liou, H. H., Cheng, T. W., & Hua, M. S. (2013). Theory of Mind in Patients with Temporal Lobe Epilepsy. *Journal of the International Neuropsychological Society, 19*(5), 594-600. doi: 10.1017/S1355617713000143

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J. P. A., . . . Moher, D. (2009a). The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *Annals of Internal Medicine, 151*(4), W65-W94.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J. P. A., . . . Moher, D. (2009b). The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLoS*

Medicine, 6(7). <Go to ISI>://WOS:000268452400006

Loftus, A. M., Yalcin, O., Baughman, F. D., Vanman, E. J., & Hagger, M. S. (2015). The impact of transcranial direct current stimulation on inhibitory control in young adults. *Brain and Behavior, 5*(5), e00332. doi: 10.1002/brb3.332

Logan, G. D. (1994). On the ability to inhibit thought and action. A users' guide to the stop signal paradigm. In D. Dagenbach & T. H. Carr (Eds.), *Inhibitory processes in attention, memory and language* (pp. 189--236). San Diego (CA): Academic Press.

Logan, G. D., & Cowan, W. B. (1984). On the Ability to Inhibit Thought and Action - a Theory of an Act of Control. *Psychological Review, 91*(3), 295-327. doi: 10.1037/0033-295x.91.3.295

Lovett, B. J., & Sheffield, R. A. (2007). Affective empathy deficits in aggressive children and adolescents: A critical review. *Clinical Psychology Review, 27*(1), 1-13. doi: 10.1016/j.cpr.2006.03.003

Luber, B., & Lisanby, S. H. (2014). Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). *NeuroImage, 85*, 961-970. doi: 10.1016/j.neuroimage.2013.06.007

Lynam, D. R., Smith, G. T., Whiteside, S. P., & Cyders, M. A. (2006). *The UPPS–P: Assessing five personality pathways to impulsive behavior (Technical Report)*. Purdue University. West Lafayette, IN.

Möbius, M., Lacomblé, L., Meyer, T., Schutter, D. J. L. G., Gielkens, T., Becker, E. S., . . . van Eijndhoven, P. (2017). Repetitive transcranial magnetic stimulation modulates the impact of a negative mood induction. *Social Cognitive and Affective Neuroscience, 12*(4), 526-533. doi:

10.1093/scan/nsw180

Machii, K., Cohen, D., Ramos-Estebanez, C., & Pascual-Leone, A. (2006). Safety of rTMS to non-motor cortical areas in healthy participants and patients. *Clinical Neurophysiology, 117*(2), 455-471. doi: 10.1016/j.clinph.2005.10.014

Mann, R. E., & Barnett, G. D. (2013). Victim Empathy Intervention With Sexual Offenders:Rehabilitation, Punishment, or Correctional Quackery? *Sexual Abuse, 25*(3), 282-301. doi: 10.1177/1079063212455669

Mantovani, A., Simpson, H. B., Fallon, B. A., Rossi, S., & Lisanby, S. H. (2010). Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. *International Journal of Neuropsychopharmacology, 13*(2), 217-227. doi: 10.1017/S1461145709990435

Matsuzawa, D., Shirayama, Y., Niitsu, T., Hashimoto, K., & Iyo, M. (2015). Deficits in emotion based decision-making in schizophrenia; a new insight based on the Iowa Gambling Task. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 57*, 52-59. doi: 10.1016/j.pnpbp.2014.10.007

Mazur, J. E. (1987). An adjusting procedure for studying delayed reinforcement *The effect of delay and of intervening events on reinforcement value.* (pp. 55-73). Hillsdale, NJ, US: Lawrence Erlbaum Associates, Inc.

McClure, S. M., Ericson, K. M., Laibson, D. I., Loewenstein, G., & Cohen, J. D. (2007). Time discounting for primary rewards. *Journal of Neuroscience,*

27(21), 5796-5804. doi: 10.1523/Jneurosci.4246-06.2007

McKinley, R. A., Bridges, N., Walters, C. M., & Nelson, J. (2012). Modulating the brain at work using noninvasive transcranial stimulation. *NeuroImage, 59*(1), 129-137. doi: 10.1016/j.neuroimage.2011.07.075

Mehrabian, A. (2000). Beyond IQ: Broad-based measurement of individual success potential or "emotional intelligence". *Genetic Social and General Psychology Monographs, 126*(2), 133-239.

Mehrabian, A., & Epstein, N. (1972). Measure of Emotional Empathy. *Journal of Personality, 40*(4), 525-543. doi: 10.1111/j.1467-6494.1972.tb00078.x

Meyer, H. C., & Bucci, D. J. (2016). Neural and behavioral mechanisms of proactive and reactive inhibition. *Learning & Memory, 23*(10), 504-514. doi: 10.1101/lm.040501.115

Michael, J., Sandberg, K., Skewes, J., Wolf, T., Blicher, J., Overgaard, M., & Frith, C. D. (2014). Continuous theta-burst stimulation demonstrates a causal role of premotor homunculus in action understanding. *Psychological Science, 25*(4), 963-972. doi: 10.1177/0956797613520608

Michaels, T. M., Horan, W. P., Ginger, E. J., Martinovich, Z., Pinkham, A., & Smith, M. J. (2015). Cognitive Empathy Contributes to Poor Social Functioning in Schizophrenia: Evidence from a New Self-Report Measure of Cognitive and Affective Empathy. *Schizophrenia Bulletin, 41*, S56-S56.

Miller, P. A., & Eisenberg, N. (1988). The Relation of Empathy to Aggressive and Externalizing Antisocial-Behavior. *Psychological Bulletin, 103*(3),

324-344. doi: 10.1037//0033-2909.103.3.324

Miller, S. A. (2009). Children's understanding of second-order mental states. *Psychological Bulletin, 135*(5), 749-773. doi: 10.1037/a0016854

Minati, L., Campanhã, C., Critchley, H. D., & Boggio, P. S. (2012). Effects of transcranial direct-current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) during a mixed-gambling risky decision-making task. *Cognitive Neuroscience, 3*(2), 80-88. doi: 10.1080/17588928.2011.628382

Moeller, F. G., Barratt, E. S., Dougherty, D. M., Schmitz, J. M., & Swann, A. C. (2001). Psychiatric Aspects of Impulsivity. *American Journal of Psychiatry, 158*(11), 1783-1793. doi: 10.1176/appi.ajp.158.11.1783

Moffitt, T. E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R. J., Harrington, H., . . . Caspi, A. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences of the United States of America, 108*(7), 2693-2698. doi: 10.1073/pnas.1010076108

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & The PRISMA Group. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine, 6*(7), e1000097. doi: 10.1371/journal.pmed.1000097

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., . . . Group, P.-P. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews, 4*, 1-9. doi: 10.1186/2046-4053-4-1

Morris, S. B. (2008). Estimating Effect Sizes From Pretest-Posttest-Control

Group Designs. *Organizational Research Methods, 11*(2), 364-386. doi: 10.1177/1094428106291059

Muggleton, N. G., Chen, C. Y., Tzeng, O. J. L., Hung, D. L., & Juan, C. H. (2010). Inhibitory Control and the Frontal Eye Fields. *Journal of Cognitive Neuroscience, 22*(12), 2804-2812. doi: 10.1162/jocn.2010.21416

Musser, E. D., Galloway-Long, H. S., Frick, P. J., & Nigg, J. T. (2013). Emotion regulation and heterogeneity in attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(2), 163-171 e162. doi: 10.1016/j.jaac.2012.11.009

Najib, U., & Horvath, J. C. (2014). Transcranial Magnetic Stimulation (TMS) Safety Considerations and Recommendations. In A. Rotenberg, J. C. Horvath, & A. Pascual-Leone (Eds.), *Transcranial Magnetic Stimulation* (pp. 15-30). New York, NY: Springer New York.

National Collaborating Centre for Methods and Tools. (2008). *Quality Assessment Tool for Quantitative Studies Method*. McMaster University. Hamilton, ON. Retrieved from http://www.nccmt.ca/registry/view/eng/15.html

Nejati, V., Salehinejad, M. A., & Nitsche, M. A. (2018). Interaction of the Left Dorsolateral Prefrontal Cortex (l-DLPFC) and Right Orbitofrontal Cortex (OFC) in Hot and Cold Executive Functions: Evidence from Transcranial Direct Current Stimulation (tDCS). *Neuroscience, 369*, 109-123. doi: 10.1016/j.neuroscience.2017.10.042

Neto, R. d. C. A., & True, M. (2011). The development and treatment of impulsivity. *Psico, 42*(1), 134-141.

Neumann, D. L., Chan, R. C. K., Boyle, G. J., Wang, Y., & Westbury, H. R. (2015). Measures of Empathy: Self-Report, Behavioral, and Neuroscientific Approaches *Measures of Personality and Social Psychological Constructs* (pp. 257-289). San Diego: Academic Press.

Neumann, D. L., & Westbury, H. R. (2011). The Psychophysiological Measurement of Empathy. In D. J. Scapaletti (Ed.), *Psychology of Empathy* (pp. 119-142). New York: Nova Science Publishers.

Oberman, L., Edwards, D., Eldaief, M., & Pascual-Leone, A. (2011). Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. *Journal of Clinical Neurophysiology, 28*(1), 67-74. doi: 10.1097/WNP.0b013e318205135f

Oberman, L., & Pascual-Leone, A. (2009). Report of seizure induced by continuous theta burst stimulation. *Brain Stimulation, 2*(4), 246-247. doi: 10.1016/j.brs.2009.03.003

Oberman, L. M., Enticott, P. G., Casanova, M. F., Rotenberg, A., Pascual-Leone, A., McCracken, J. T., & the TMS in ASD Consensus Group. (2016). Transcranial magnetic stimulation in autism spectrum disorder: Challenges, promise, and roadmap for future research. *Autism research : official journal of the International Society for Autism Research, 9*(2), 184-203. doi: 10.1002/aur.1567

Oberman, L. M., Rotenberg, A., & Pascual-Leone, A. (2015). Use of Transcranial Magnetic Stimulation in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders, 45*(2), 524-536. doi: 10.1007/s10803-013-1960-2

Obeso, I., Robles, N., Munoz-Marron, E., & Redolar-Ripoll, D. (2013).

Dissociating the role of the pre-SMA in response inhibition and switching: A combined online and offline TMS approach. *Frontiers in Human Neuroscience.*(pagination). doi: 10.3389/fnhum.2013.00150

Odum, A. L. (2011). Delay discounting: Trait variable? *Behavioural Processes, 87*(1), 1-9. doi: 10.1016/j.beproc.2011.02.007

Panwar, K., Rutherford, H. J. V., Mencl, W. E., Lacadie, C. M., Potenza, M. N., & Mayes, L. C. (2014). Differential associations between impulsivity and risk-taking and brain activations underlying working memory in adolescents. *Addictive Behaviors, 39*(11), 1606-1621. doi: 10.1016/j.addbeh.2013.12.007

Pascual-Leone, A., Freitas, C., Oberman, L., Horvath, J. C., Halko, M., Eldaief, M., . . . Rotenberg, A. (2011). Characterizing Brain Cortical Plasticity and Network Dynamics Across the Age-Span in Health and Disease with TMS-EEG and TMS-fMRI. *Brain Topography, 24*(3-4), 302-315. doi: 10.1007/s10548-011-0196-8

Pascual-Leone, A., Rubio, B., Pallardó, F., & Catalá, M. D. (1996). Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *The Lancet, 348*(9022), 233-237. doi: 10.1016/S0140-6736(96)01219-6

Pascual-Leone, A., Walsh, V., & Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience--virtual lesion, chronometry, and functional connectivity. *Current Opinion in Neurobiology, 10*(2), 232-237.

Pastor, D. A., & Lazowski, R. A. (2018). On the Multilevel Nature of Meta-Analysis: A Tutorial, Comparison of Software Programs, and

Discussion of Analytic Choices. *Multivariate Behavioral Research, 53*(1), 74-89. doi: 10.1080/00273171.2017.1365684

Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology, 51*(6), 768-774.

Peper, J. S., Mandl, R. C. W., Braams, B. R., de Water, E., Heijboer, A. C., Koolschijn, P. C. M. P., & Crone, E. A. (2013). Delay Discounting and Frontostriatal Fiber Tracts: A Combined DTI and MTR Study on Impulsive Choices in Healthy Young Adults. *Cerebral Cortex, 23*(7), 1695-1702. doi: 10.1093/cercor/bhs163

Peters, J., & Buchel, C. (2011). The neural mechanisms of inter-temporal decision-making: understanding variability. *Trends in Cognitive Sciences, 15*(5), 227-239. doi: 10.1016/j.tics.2011.03.002

Pobric, G., & Hamilton, A. F. (2006). Action understanding requires the left inferior frontal cortex. *Current Biology, 16*(5), 524-529. doi: 10.1016/j.cub.2006.01.033

Pokhvisneva, I., Léger, É., Meaney, M. J., & Silveira, P. P. (2018). Systematic Overestimation of Reflection Impulsivity in the Information Sampling Task: Age Dependency in Children. *Biological Psychiatry, 83*(2), e33-e34. doi: 10.1016/j.biopsych.2016.12.027

Poletti, M., Enrici, I., & Adenzato, M. (2012). Cognitive and affective Theory of Mind in neurodegenerative diseases: Neuropsychological, neuroanatomical and neurochemical levels. *Neuroscience and Biobehavioral Reviews, 36*(9), 2147-2164. doi: 10.1016/j.neubiorev.2012.07.004

Premack, D., & Woodruff, G. (1978). Does the chimpanzee have a theory of mind? *Behavioral and Brain Sciences, 1*(4), 515-526. doi: 10.1017/S0140525X00076512

Preston, S. D., & de Waal, F. B. M. (2002). Empathy: Its ultimate and proximate bases. *Behavioral and Brain Sciences, 25*(1), 1-20.

Qi, F., Wu, A. D., & Schweighofer, N. (2011). Fast estimation of transcranial magnetic stimulation motor threshold. *Brain Stimulation, 4*(1), 50-57. doi: 10.1016/j.brs.2010.06.002

Rêgo, G. G., Lapenta, O. M., Marques, L. M., Costa, T. L., Leite, J., Carvalho, S., . . . Boggio, P. S. (2015). Hemispheric dorsolateral prefrontal cortex lateralization in the regulation of empathy for pain. *Neuroscience Letters, 594*, 12-16. doi: 10.1016/j.neulet.2015.03.042

Rabe-Hesketh, S., Skrondal, A., & Pickles, A. (2002). Reliable estimation of generalized linear mixed models using adaptive quadrature. *Stata Journal, 2*(1), 1-21.

Rabe-Hesketh, S., Skrondal, A., & Pickles, A. (2005). Maximum likelihood estimation of limited and discrete dependent variable models with nested random effects. *Journal of Econometrics, 128*(2), 301-323. doi: 10.1016/j.jeconom.2004.08.017

Reidy, D. E., Kearns, M. C., & DeGue, S. (2013). Reducing psychopathic violence: A review of the treatment literature. *Aggression and Violent Behavior, 18*(5), 527-538. doi: 10.1016/j.avb.2013.07.008

Reniers, R. L. E. P., Corcoran, R., Drake, R., Shryane, N. M., & Völlm, B. A. (2011). The QCAE: A Questionnaire of Cognitive and Affective Empathy. *Journal of Personality Assessment, 93*(1), 84-95. doi:

10.1080/00223891.2010.528484

Reniers, R. L. E. P., Völlm, B. A., Elliott, R., & Corcoran, R. (2014). Empathy, ToM, and self-other differentiation: An fMRI study of internal states. *Social Neuroscience, 9*(1), 50-62. doi: 10.1080/17470919.2013.861360

Robertson, E. M., Theoret, H., & Pascual-Leone, A. (2003). Studies in cognition: The problems solved and created by transcranial magnetic stimulation. *Journal of Cognitive Neuroscience, 15*(7), 948-960. doi: 10.1162/089892903770007344

Rogers, R. D., Owen, A. M., Middleton, H. C., Williams, E. J., Pickard, J. D., Sahakian, B. J., & Robbins, T. W. (1999). Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. *Journal of Neuroscience, 19*(20), 9029-9038.

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2011). Screening questionnaire before TMS: An update. *Clinical Neurophysiology, 122*(8), 1686-1686. doi: 10.1016/j.clinph.2010.12.037

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & The Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology, 120*(12), 2008-2039. doi: 10.1016/j.clinph.2009.08.016

Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., . . . Tomberg, C. (1994). Noninvasive Electrical and Magnetic Stimulation of the Brain, Spinal-Cord and Roots - Basic Principles and Procedures for Routine Clinical-Application - Report of

an IFCN Committee. *Electroencephalography and Clinical Neurophysiology, 91*(2), 79-92. doi: 10.1016/0013-4694(94)90029-9

Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., Di Iorio, R., . . . Ziemann, U. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an IFCN Committee. *Clinical Neurophysiology, 126*(6), 1071-1107. doi: 10.1016/j.clinph.2015.02.001

Rotenberg, A., Bae, E. H., Muller, P. A., Riviello, J. J., Bourgeois, B. F., Blum, A. S., & Pascual-Leone, A. (2009). In-session seizures during low-frequency repetitive transcranial magnetic stimulation in patients with epilepsy. *Epilepsy & Behavior, 16*(2), 353-355. doi: 10.1016/j.yebeh.2009.08.010

Rotenberg, A., Horvath, J. C., & Pascual-Leone, A. (2014). The Transcranial Magnetic Stimulation (TMS) Device and Foundational Techniques. In A. Rotenberg, J. C. Horvath, & A. Pascual-Leone (Eds.), *Transcranial Magnetic Stimulation* (pp. 3-13). New York, NY: Springer New York.

Roth, Y., Amir, A., Levkovitz, Y., & Zangen, A. (2007). Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. *Journal of Clinical Neurophysiology, 24*(1), 31-38. doi: 10.1097/WNP.0b013e31802fa393

Rudebeck, P. H., Walton, M. E., Smyth, A. N., Bannerman, D. M., & Rushworth, M. F. (2006). Separate neural pathways process different decision costs. *Nature Neuroscience, 9*(9), 1161-1168. doi:

10.1038/nn1756

Ruggieri, V. L. (2013). Empathy, social cognition and autism spectrum disorders. *Revista de Neurología, 56*, S13-S21.

Ruohonen, J., & Karhu, J. (2010). Navigated transcranial magnetic stimulation. *Neurophysiologie Clinique/Clinical Neurophysiology, 40*(1), 7-17. doi: 10.1016/j.neucli.2010.01.006

Sabesan, P., Lankappa, S., Khalifa, N., Krishnan, V., Gandhi, R., & Palaniyappan, L. (2015). Transcranial magnetic stimulation for geriatric depression: Promises and pitfalls. *World Journal of Psychiatry, 5*(2), 170-181. doi: 10.5498/wjp.v5.i2.170

Sack, A. T. (2010). Does TMS need functional imaging? *Cortex, 46*(1), 131-133. doi: 10.1016/j.cortex.2009.02.004

Sandrini, M., Umilta, C., & Rusconi, E. (2011). The use of transcranial magnetic stimulation in cognitive neuroscience: A new synthesis of methodological issues. *Neuroscience and Biobehavioral Reviews, 35*(3), 516-536. doi: 10.1016/j.neubiorev.2010.06.005

Schneider, W., Eschman, A., & Zuccolotto, A. (2002). E-Prime (Version 2.0.8.22) [Computer software]. Pittsburgh, PA: Psychology Software Tools.

Schrader, L. M., Stern, J. M., Koski, L., Nuwer, M. R., & Engel, J. (2004). Seizure incidence during single- and paired-pulse transcranial magnetic stimulation (TMS) in individuals with epilepsy. *Clinical Neurophysiology, 115*(12), 2728-2737. doi: 10.1016/j.clinph.2004.06.018

Schreiter, S., Pijnenborg, G. H. M., & aan het Rot, M. (2013). Empathy in

adults with clinical or subclinical depressive symptoms. *Journal of Affective Disorders, 150*(1), 1-16. doi: 10.1016/j.jad.2013.03.009

Schuwerk, T., Langguth, B., & Sommer, M. (2014). Modulating functional and dysfunctional mentalizing by transcranial magnetic stimulation. *Frontiers in Psychology, 5*. doi: 10.3389/Fpsyg.2014.01309

Schuwerk, T., Schecklmann, M., Langguth, B., Dohnel, K., Sodian, B., & Sommer, M. (2014). Inhibiting the posterior medial prefrontal cortex by rTMS decreases the discrepancy between self and other in Theory of Mind reasoning. *Behavioural Brain Research, 274*, 312-318. doi: 10.1016/j.bbr.2014.08.031

Sebastian, C. L., Fontaine, N. M. G., Bird, G., Blakemore, S. J., De Brito, S. A., McCrory, E. J. P., & Viding, E. (2012). Neural processing associated with cognitive and affective Theory of Mind in adolescents and adults. *Social Cognitive and Affective Neuroscience, 7*(1), 53-63. doi: 10.1093/scan/nsr023

Serafini, G., Pompili, M., Belvederi Murri, M., Respino, M., Ghio, L., Girardi, P., . . . Amore, M. (2015). The effects of repetitive transcranial magnetic stimulation on cognitive performance in treatment-resistant depression. A systematic review. *Neuropsychobiology, 71*(3), 125-139. doi: 10.1159/000381351

Shamay-Tsoory, S. G., & Aharon-Peretz, J. (2007). Dissociable prefrontal networks for cognitive and affective theory of mind: A lesion study. *Neuropsychologia, 45*(13), 3054-3067. doi: 10.1016/j.neuropsychologia.2007.05.021

Shamay-Tsoory, S. G., Aharon-Peretz, J., & Perry, D. (2009). Two systems for

empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain, 132*, 617-627. doi: 10.1093/brain/awn279

Shamay-Tsoory, S. G., Tomer, R., Berger, B. D., Goldsher, D., & Aharon-Peretz, J. (2005). Impaired "affective theory of mind" is associated with right ventromedial prefrontal damage. *Cognitive and Behavioral Neurology, 18*(1), 55-67.

Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., . . . Group, P.-P. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ, 349*, g7647. doi: 10.1136/bmj.g7647

Sheffer, C. E., Mennemeier, M., Landes, R. D., Bickel, W. K., Brackman, S., Dornhoffer, J., . . . Brown, G. (2013). Neuromodulation of delay discounting, the reflection effect, and cigarette consumption. *Journal of Substance Abuse Treatment, 45*(2), 206-214. doi: 10.1016/j.jsat.2013.01.012

Shen, B., Yin, Y., Wang, J., Zhou, X., McClure, S. M., & Li, J. (2016). High-definition tDCS alters impulsivity in a baseline-dependent manner. *NeuroImage, 143*, 343-352. doi: 10.1016/j.neuroimage.2016.09.006

Shimoni, H. N., Weizman, A., Yoran, R. H., & Raviv, A. (2012). Theory of mind, severity of autistic symptoms and parental correlates in children and adolescents with Asperger syndrome. *Psychiatry Research, 197*(1-2), 85-89. doi: 10.1016/j.psychres.2012.02.021

Sibon, I., Strafella, A. P., Gravel, P., Ko, J. H., Booij, L., Soucy, J. P., . . . Benkelfat, C. (2007). Acute prefrontal cortex TMS in healthy volunteers:

Effects on brain 11C-αMtrp trapping. *NeuroImage, 34*(4), 1658-1664. doi: 10.1016/j.neuroimage.2006.08.059

Silani, G., Lamm, C., Ruff, C. C., & Singer, T. (2013). Right supramarginal gyrus is crucial to overcome emotional egocentricity bias in social judgments. *Journal of Neuroscience, 33*(39), 15466-15476. doi: 10.1523/JNEUROSCI.1488-13.2013

Singh, J. P., Serper, M., Reinharth, J., & Fazel, S. (2011). Structured assessment of violence risk in schizophrenia and other psychiatric disorders: a systematic review of the validity, reliability, and item content of 10 available instruments. *Schizophrenia Bulletin, 37*(5), 899-912. doi: 10.1093/schbul/sbr093

Smith, A. (2006). Cognitive empathy and emotional empathy in human behavior and evolution. *Psychological Record, 56*(1), 3-21. doi: 10.1007/Bf03395534

Smittenaar, P., Rutledge, R. B., Zeidman, P., Adams, R. A., Brown, H., Lewis, G., & Dolan, R. J. (2015). Proactive and Reactive Response Inhibition across the Lifespan. *PloS One, 10*(10). doi:10.1371/journal.pone.0140383

Soderstrom, H. (2003). Psychopathy as a disorder of empathy. *European Child and Adolescent Psychiatry, 12*(5), 249-252. doi: 10.1007/s00787-003-0338-y

Spreng, R. N., McKinnon, M. C., Mar, R. A., & Levine, B. (2009). The Toronto Empathy Questionnaire: Scale Development and Initial Validation of a Factor-Analytic Solution to Multiple Empathy Measures. *Journal of Personality Assessment, 91*(1), 62-71. doi:

10.1080/00223890802484381

Stanford, M. S., Mathias, C. W., Dougherty, D. M., Lake, S. L., Anderson, N. E., & Patton, J. H. (2009). Fifty years of the Barratt Impulsiveness Scale: An update and review. *Personality and Individual Differences, 47*(5), 385-395. doi: 10.1016/j.paid.2009.04.008

StataCorp. (2013). Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.

Stephens, D. W., & Anderson, D. (2001). The adaptive value of preference for immediacy: when shortsighted rules have farsighted consequences. *Behavioral Ecology, 12*(3), 330-339. doi: 10.1093/beheco/12.3.330

Sterne, J. A., Egger, M., & Moher, D. (2011). Addressing Reporting Biases. In J. P. Higgins & S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011) (pp. 297-333): The Cochrane Collaboration. Retrieved from www.handbook.cochrane.org.

Stone, V. E., Baron-Cohen, S., & Knight, R. T. (1998). Frontal lobe contributions to theory of mind. *Journal of Cognitive Neuroscience, 10*(5), 640-656. doi: 10.1162/089892998562942

Strasser, E. S., Haffner, P., Fiebig, J., Quinlivan, E., Adli, M., & Stamm, T. J. (2016). Behavioral measures and self-report of impulsivity in bipolar disorder: no association between Stroop test and Barratt Impulsiveness Scale. *Int J Bipolar Disord, 4*(1), 16. doi: 10.1186/s40345-016-0057-1

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: administration, norms, and commentary*.

New York, Oxford: Oxford University Press.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18*, 643-662. doi: 10.1037/0096-3445.121.1.15

Stuphorn, V., & Emeric, E. E. (2012). Proactive and reactive control by the medial frontal cortex. *Frontiers in Neuroengineering, 5*, 9. doi: 10.3389/fneng.2012.00009

Thompson, S. G., & Higgins, J. P. T. (2002). How should meta-regression analyses be undertaken and interpreted? *Statistics in Medicine, 21*(11), 1559-1573. doi: 10.1002/sim.1187

Thut, G., & Pascual-Leone, A. (2010). A Review of Combined TMS-EEG Studies to Characterize Lasting Effects of Repetitive TMS and Assess Their Usefulness in Cognitive and Clinical Neuroscience. *Brain Topography, 22*(4), 219-232. doi: 10.1007/s10548-009-0115-4

Tomko, R. L., Bountress, K. E., & Gray, K. M. (2016). Personalizing substance use treatment based on pre-treatment impulsivity and sensation seeking: A review. *Drug and Alcohol Dependence, 167*, 1-7. doi: 10.1016/j.drugalcdep.2016.07.022

Trevizol, A. P., Shiozawa, P., Cook, I. A., Sato, I. A., Kaku, C. B., Guimaraes, F. B., . . . Cordeiro, Q. (2016). Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: An Updated Systematic Review and Meta-analysis. *Journal of ECT, 32*(4), 262-266. doi: 10.1097/yct.0000000000000335

Tu, P. C., Kuan, Y. H., Li, C. T., & Su, T. P. (2017). Structural correlates of trait impulsivity in patients with bipolar disorder and healthy controls: a

surface-based morphometry study. *Psychological Medicine, 47*(7), 1292-1299. doi: 10.1017/S0033291716003299

Uddin, L. Q., Molnar-Szakacs, I., Zaidel, E., & Iacoboni, M. (2006). rTMS to the right inferior parietal lobule disrupts self-other discrimination. *Social Cognitive and Affective Neuroscience, 1*(1), 65-71. doi: 10.1093/Scan/Nsl003

Upton, D. J., Cooper, N. R., Laycock, R., Croft, R. J., & Fitzgerald, P. B. (2010). A combined rTMS and ERP investigation of dorsolateral prefrontal cortex involvement in response inhibition. *Clinical EEG & Neuroscience: Official Journal of the EEG & Clinical Neuroscience Society (ENCS), 41*(3), 127-131.

Völlm, B., Richardson, P., McKie, S., Elliott, R., Deakin, J. F. W., & Anderson, I. M. (2006). Serotonergic modulation of neuronal responses to behavioural inhibition and reinforcing stimuli: an fMRI study in healthy volunteers. *European Journal of Neuroscience, 23*(2), 552-560. doi: 10.1111/j.1460-9568.2005.04571.x

Völlm, B. A., Taylor, A. N. W., Richardson, P., Corcoran, R., Stirling, J., McKie, S., . . . Elliott, R. (2006). Neuronal correlates of theory of mind and empathy: A functional magnetic resonance imaging study in a nonverbal task. *NeuroImage, 29*(1), 90-98. doi: 10.1016/j.neuroimage.2005.07.022

van de Mortel, T. F. (2008). Faking it: social desirability response bias in self-report research. *Australian Journal of Advanced Nursing, 25*(4), 40-48.

van Langen, M. A. M., Wissink, I. B., van Vugt, E. S., Van der Stouwe, T., &

Stams, G. J. J. M. (2014). The relation between empathy and offending: A meta-analysis. *Aggression and Violent Behavior, 19*(2), 179-189. doi: 10.1016/j.avb.2014.02.003

Vanderhasselt, M.-A., De Raedt, R., Baeken, C., Leyman, L., & D'haenen, H. (2006). The influence of rTMS over the left dorsolateral prefrontal cortex on Stroop task performance. *Experimental Brain Research, 169*(2), 279-282. doi: 10.1007/s00221-005-0344-z

Vanderhasselt, M. A., De Raedt, R., Baeken, C., Leyman, L., Clerinx, P., & D'Haenen, H. (2007). The influence of rTMS over the right dorsolateral prefrontal cortex on top-down attentional processes. *Brain Research, 1137*(1), 111-116.

Vanderveen, J. D., & Cyders, M. A. (2014). Examining the Relationship between Impulsivity Laboratory Tasks, the Upps-P Impulsive Behavior Scale, and Maladaptive Drinking Behaviors. *Alcoholism-Clinical and Experimental Research, 38*, 185a.

Varnava, A., Stokes, M. G., & Chambers, C. D. (2011). Reliability of the 'observation of movement' method for determining motor threshold using transcranial magnetic stimulation. *Journal of Neuroscience Methods, 201*(2), 327-332. doi: 10.1016/j.jneumeth.2011.08.016

Verbruggen, F., Aron, A. R., Stevens, M. A., & Chambers, C. D. (2010). Theta burst stimulation dissociates attention and action updating in human inferior frontal cortex. *Proceedings of the National Academy of Sciences of the United States of America, 107*(31), 13966-13971. doi: 10.1073/pnas.1001957107

Verbruggen, F., & Logan, G. D. (2008). Response inhibition in the stop-signal

paradigm. *Trends in Cognitive Sciences, 12*(11), 418-424. doi: 10.1016/j.tics.2008.07.005

Verbruggen, F., & Logan, G. D. (2009). Proactive Adjustments of Response Strategies in the Stop-Signal Paradigm. *Journal of Experimental Psychology-Human Perception and Performance, 35*(3), 835-854. doi: 10.1037/a0012726

Verdejo-Garcia, A., Lawrence, A. J., & Clark, L. (2008). Impulsivity as a vulnerability marker for substance-use disorders: Review of findings from high-risk research, problem gamblers and genetic association studies. *Neuroscience and Biobehavioral Reviews, 32*(4), 777-810. doi: 10.1016/j.neubiorev.2007.11.003

Verheul, R., Van Den Bosch, L. M., Koeter, M. W., De Ridder, M. A., Stijnen, T., & Van Den Brink, W. (2003). Dialectical behaviour therapy for women with borderline personality disorder: 12-month, randomised clinical trial in The Netherlands. *British Journal of Psychiatry, 182*, 135-140.

Wagner, M., Rihs, T. A., Mosimann, U. P., Fisch, H. U., & Schlaepfer, T. E. (2006). Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex affects divided attention immediately after cessation of stimulation. *Journal of Psychiatric Research, 40*(4), 315-321.

Wagner, T., Valero-Cabre, A., & Pascual-Leone, A. (2007). Noninvasive human brain stimulation. *Annual Review of Biomedical Engineering, 9*, 527-565. doi: 10.1146/annurev.bioeng.9.061206.133100

Waldowski, K., Seniow, J., Lesniak, M., Iwanski, S., & Czlonkowska, A. (2012). Effect of low-frequency repetitive transcranial magnetic stimulation on naming abilities in early-stroke aphasic patients: a prospective,

randomized, double-blind sham-controlled study. *Scientific World Journal, 2012*, 518568. doi: 10.1100/2012/518568

Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nature Reviews Neuroscience, 1*(1), 73-79. doi: 10.1038/35036239

Wang, Y. G., Chen, S., Xu, Z. M., Shen, Z. H., Wang, Y. Q., He, X. Y., . . . Wang, Y. Q. (2017). Family history of suicide and high motor impulsivity distinguish suicide attempters from suicide ideators among college students. *Journal of Psychiatric Research, 90*, 21-25. doi: 10.1016/j.jpsychires.2017.02.006

Wassermann, E. M., & Zimmermann, T. (2012). Transcranial magnetic brain stimulation: therapeutic promises and scientific gaps. *Pharmacology & Therapeutics, 133*(1), 98-107. doi: 10.1016/j.pharmthera.2011.09.003

Watanabe, T., Hanajima, R., Shirota, Y., Ohminami, S., Tsutsumi, R., Terao, Y., . . . Ohtomo, K. (2014). Bidirectional effects on interhemispheric resting-state functional connectivity induced by excitatory and inhibitory repetitive transcranial magnetic stimulation. *Human Brain Mapping, 35*(5), 1896-1905. doi: 10.1002/hbm.22300

Watanabe, T., Hanajima, R., Shirota, Y., Tsutsumi, R., Shimizu, T., Hayashi, T., . . . Konishi, S. (2015). Effects of rTMS of pre-supplementary motor area on fronto basal ganglia network activity during stop-signal task. *Journal of Neuroscience, 35*(12), 4813-4823. doi: 10.1523/JNEUROSCI.3761-14.2015

Weber, M. J., Messing, S. B., Rao, H., Detre, J. A., & Thompson-Schill, S. L. (2014). Prefrontal Transcranial Direct Current Stimulation Alters

Activation and Connectivity in Cortical and Subcortical Reward Systems: A tDCS-fMRI Study. *Human Brain Mapping, 35*(8), 3673-3686. doi: 10.1002/hbm.22429

Weissman, C. R., Blumberger, D. M., Brown, P. E., Isserles, M., Rajji, T. K., Downar, J., . . . Daskalakis, Z. J. (2018). Bilateral Repetitive Transcranial Magnetic Stimulation Decreases Suicidal Ideation in Depression. *Journal of Clinical Psychiatry, 79*(3). doi: 10.4088/JCP.17m11692

Westin, G. G., Bassi, B. D., Lisanby, S. H., & Luber, B. (2014). Determination of motor threshold using visual observation overestimates transcranial magnetic stimulation dosage: Safety implications. *Clinical Neurophysiology, 125*(1), 142-147. doi: 10.1016/j.clinph.2013.06.187

Whiteside, S. P., & Lynam, D. R. (2001). The Five Factor Model and impulsivity: using a structural model of personality to understand impulsivity. *Personality and Individual Differences, 30*(4), 669-689. doi: 10.1016/S0191-8869(00)00064-7

Wierenga, C., Bischoff-Grethe, A., Melrose, A. J., Grenesko-Stevens, E., Irvine, Z., Wagner, A., . . . Kaye, W. H. (2014). Altered BOLD Response during Inhibitory and Error Processing in Adolescents with Anorexia Nervosa. *PloS One, 9*(3). doi: 10.1371/journal.pone.0092017

Wilbertz, T., Deserno, L., Horstmann, A., Neumann, J., Villringer, A., Heinze, H. J., . . . Schlagenhauf, F. (2014). Response inhibition and its relation to multidimensional impulsivity. *NeuroImage, 103*, 241-248. doi: 10.1016/j.neuroimage.2014.09.021

Winstanley, C. A., Theobald, D. E., Cardinal, R. N., & Robbins, T. W. (2004).

Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. *Journal of Neuroscience, 24*(20), 4718-4722. doi: 10.1523/JNEUROSCI.5606-03.2004

Wispé, L. (1987). History of the concept of empathy. In N. Eisenberg & J. Strayer (Eds.), *Empathy and its development* (pp. 17-37). Cambridge ; New York: Cambridge University Press.

Yang, C.-C., Khalifa, N., & Völlm, B. (2018a). The effects of repetitive transcranial magnetic stimulation on empathy: a systematic review and meta-analysis. *Psychological Medicine, 48*(5), 737-750. doi: 10.1017/S003329171700232X

Yang, C.-C., Khalifa, N., & Völlm, B. (2018b). Excitatory repetitive transcranial magnetic stimulation applied to the right inferior frontal gyrus has no effect on motor or cognitive impulsivity in healthy adults. *Behavioural Brain Research, 347*, 1-7. doi: 10.1016/j.bbr.2018.02.047

Yang, C.-C., Völlm, B., & Khalifa, N. (2018). The Effects of rTMS on Impulsivity in Normal Adults: a Systematic Review and Meta-Analysis. *Neuropsychology Review*. doi: 10.1007/s11065-018-9376-6

Ye, H., Chen, S., Huang, D., Wang, S., Jia, Y., & Luo, J. (2015). Transcranial direct current stimulation over prefrontal cortex diminishes degree of risk aversion. *Neuroscience Letters, 598*, 18-22. doi: 10.1016/j.neulet.2015.04.050

Young, L., Camprodon, J. A., Hauser, M., Pascual-Leone, A., & Saxe, R. (2010). Disruption of the right temporoparietal junction with transcranial magnetic stimulation reduces the role of beliefs in moral judgments. *Proceedings of the National Academy of Sciences of the United States*

of America, 107(15), 6753-6758. doi: 10.1073/pnas.0914826107

Yu, R. L., Wu, R. M., Chiu, M. J., Tai, C. H., Lin, C. H., & Hua, M. S. (2012). Advanced Theory of Mind in patients at early stage of Parkinson's disease. *Parkinsonism & Related Disorders, 18*(1), 21-24. doi: 10.1016/j.parkreldis.2011.08.003

Zaman, R. (2014). Role of Transcranial magnetic stimulation (TMS & rTMS) in investigation and possible treatment of Impulsivity in neuropsychiatric disorders with ADHD and BPD as examples. *Psychiatria Danubina, 26 Suppl 1*, 347-350.

Zandbelt, B. B., Bloemendaal, M., Hoogendam, J. M., Kahn, R. S., & Vink, M. (2013). Transcranial magnetic stimulation and functional MRI reveal cortical and subcortical interactions during stop-signal response inhibition. *Journal of Cognitive Neuroscience, 25*(2), 157-174. doi: 10.1162/jocn_a_00309

Zandbelt, B. B., Bloemendaal, M., Neggers, S. F. W., Kahn, R. S., & Vink, M. (2013). Expectations and violations: Delineating the neural network of proactive inhibitory control. *Human Brain Mapping, 34*(9), 2015-2024. doi: 10.1002/hbm.22047

Zangen, A., Roth, Y., Voller, B., & Hallett, M. (2005). Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. *Clinical Neurophysiology, 116*(4), 775-779. doi: 10.1016/j.clinph.2004.11.008

Zisner, A., & Beauchaine, T. P. (2016). Neural substrates of trait impulsivity, anhedonia, and irritability: Mechanisms of heterotypic comorbidity between externalizing disorders and unipolar depression.

Development and Psychopathology, 28(4pt1), 1177-1208. doi: 10.1017/S0954579416000754

Zuckerman, M., Eysenck, S., & Eysenck, H. J. (1978). Sensation Seeking in England and America - Cross-Cultural, Age, and Sex Comparisons. *Journal of Consulting and Clinical Psychology, 46*(1), 139-149. doi: 10.1037//0022-006x.46.1.139

Appendix 1 Data Extraction Sheet

Study ID	**Researcher performing data extraction**	**Date of data extraction**
Type of work		
Language of report		
Full citation		
Aims of study		
Design of study (e.g. controlled trial, crossover trial)		
Sub-group analysis?		
Site/setting of intervention • centre (single site, multiple sites) = • setting (hospital, outpatient, prison etc) = • location (city, country etc) = • setting (urban, rural) =		
Ethics committee approval		
Recruitment procedure		
Participants Characteristics Age(e.g. mean, SD, range):		

Ethnicity: Sex (M:F) = Past history: Other demographics
Inclusion criteria
Exclusion criteria
Description of intervention(s)
Carry-over effects prior to commencing intervention
Carry-over effects between phases (cross-over trials only)
Duration of intervention(s)
Length of follow-up
Numbers of participants
Unit of allocation
Power calculation or sample size estimate

Prospectively stated outcome(s)

task performance

Outcome measure used:

How obtained (e.g. self-report, observed by staff, computerised data collection):

Times of measurement:

Any notes/limitations recorded by trial investigators:

tolerability (adverse effects and drop out)

Need to contact the author(s)?

Authors' conclusions (e.g. from abstract)

Quote:

Authors' acknowledged limitations:

Other notes/comments

Appendix 2 Quality assessment tool

Paper	**Scorer**	
Questions	**Rating**	**Rate this section**
(A) Selection bias		
1. Are the individuals selected to participate in the study likely to be representative of the target population?	1 Very likely 2 Somewhat likely 3 Not likely 4 Can't tell	**1 Strong** **2 Moderate** **3 Weak**
2. What percentage of selected individuals agreed to participate?	1 80 - 100% agreement 2 60 – 79% agreement 3 less than 60% agreement 4 Not applicable 5 Can't tell	
(B)Study design		
Indicate the study design	1 Randomised controlled trial 2 Controlled clinical trial 3 Cohort analytic (two group pre + post) 4 Case-control 5 Cohort (one group pre + post (before and after)) 6 Interrupted time series 7 Other specify _____ 8 Can't tell	**1 Strong** **2 Moderate** **3 Weak**
3. Was the study described as randomised?	No, go to Component C Yes	
4. Was the method of randomization described? (See dictionary)	No Yes	
5. Was the method appropriate? (See dictionary)	No Yes	
(C) Confounders		
6. Were there important differences between groups prior to the intervention?	1 Yes, go to Q7 2 No 3 Can't tell	**1 Strong** **2 Moderate** **3 Weak**
7. Indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?	1 80 – 100% (most) 2 60 – 79% (some) 3 Less than 60% (few or none) 4 Can't Tell	
(D) Blinding		
8. Was (were) the outcome assessor(s) aware of the intervention or exposure status	1 Yes 2 No 3 Can't tell	**1 Strong** **2 Moderate** **3 Weak**

of participants?		
9. Were the study participants aware of the research question?	1 Yes 2 No 3 Can't tell	
(E) Data collection method		
10. Were data collection tools shown to be valid?	1 Yes 2 No 3 Can't tell	**1 Strong** **2 Moderate** **3 Weak**
11. Were data collection tools shown to be reliable?	1 Yes 2 No 3 Can't tell	
(F) Withdrawals and dropouts		
12. Were withdrawals and dropouts reported in terms of numbers and/or reasons per group?	1 Yes 2 No 3 Can't tell 4 Not Applicable (i.e. one time surveys or interviews)	**1 Strong** **2 Moderate** **3 Weak** **Not Applicable**
13. Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).	1 80 -100% 2 60 - 79% 3 less than 60% 4 Can't tell 5 Not Applicable (i.e. Retrospective case-control)	
(G) Intervention integrity		
14. What percentage of participants received the allocated intervention or exposure of interest?	1 80 -100% 2 60 - 79% 3 less than 60% 4 Can't tell	
15. Was the consistency of the intervention measured?	1 Yes 2 No 3 Can't tell	
16. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	1 Yes 2 No 3 Can't tell	
(H)Analyses		
17. Indicate the unit of allocation (circle one)	community organization/institution practice/office individual	
18. Indicate the unit of analysis (circle one)	community organization/institution practice/office individual	
19. Are the statistical methods appropriate for the study	1 Yes 2 No	

design?	3 Can't tell	
20. Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?	1 Yes 2 No 3 Can't tell	

Component ratings											
A		B		C		D		E		F	

Global rating for this paper (circle one):	**1 Strong** (no Weak ratings) **2 Moderate** (one Weak rating) **3 Weak** (two or more Weak ratings)
With both reviewers discussing the ratings:	
Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?	No Yes
If yes, indicate the reason for the discrepancy	1 Oversight 2 Differences in interpretation of criteria 3 Differences in interpretation of study
Final decision of both reviewers (circle one)	**1 Strong** **2 Moderate** **3 Weak**

Appendix 3 rTMS Screening Questionnaire

Mark Y or N

1) Do you have epilepsy or have you ever had a convulsion or a seizure?
2) Have you ever had a fainting spell or syncope? If yes, please describe on which occasion(s)?
3) Have you ever had a head trauma that was diagnosed as a concussion or was associated with loss of consciousness?
4) Do you have any hearing problems or ringing in your ears?
5) Do you have cochlear implants?
6) Are you pregnant or is there any chance that you might be?
7) Do you have metal in the brain, skull or elsewhere in your body (e.g., splinters, fragments, clips, etc.)? If so, specify the type of metal.
8) Do you have an implanted neurostimulator (e.g., DBS, epidural/subdural, VNS)?
9) Do you have a cardiac pacemaker or intracardiac lines?
10) Do you have a medication infusion device?
11) Are you taking any medications? (please list)
12) Did you ever undergo TMS in the past? If so, were there any problems.
13) Did you ever undergo MRI in the past? If so, were there any problems.

Note to researcher: Affirmative answers to one or more questions 1-13 do not represent absolute contraindications to TMS but risk/benefit must be weighted up

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & The Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology, 120*(12), 2008-2039. doi:10.1016/j.clinph.2009.08.016

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2011). Screening questionnaire before TMS: An update. *Clinical Neurophysiology, 122*(8), 1686-1686. doi: 10.1016/j.clinph.2010.12.037

Appendix 4 rTMS Tolerability Questionnaire

	Session 1		Session 2	
	Yes	**No**	**Yes**	**No**
Participant to complete				
Head ache				
Eye pain				
Tooth ache				
Neck pain				
Local pain				
Ear discomfort				
Tinnitus				
Feelings of faintness				
Any changes in mood				
Researcher to complete				
Scalp burns				
Seizure				
Syncope				
Hypomania induction				

Are there any other side effects or unusual sensations that you have experienced as a result of the study? If so please let us know

_____
_____
_____
_____
_____
_____

Appendix 5 Search syntax for empathy studies

OVID: PsycINFO 1806 to July Week 1 2015

#	Searches	Results
1	transcranial magnetic stimulation.mp.	6598
2	TMS.mp.	3368
3	Theory of mind.mp.	6491
4	ToM.mp.	3039
5	mentaliz*.mp.	1917
6	mentalis*.mp.	1232
7	role taking.mp.	2524
8	perspective taking.mp.	2992
9	empath*.mp.	24461
10	1 or 2	7003
11	3 or 4 or 5 or 6 or 7 or 8 or 9	37725
12	**10 and 11**	**54**

OVID: Embase 1980 to 2015 Week 27

#	Searches	Results
1	transcranial magnetic stimulation.mp.	16394
2	TMS.mp.	11663
3	Theory of mind.mp.	4332
4	ToM.mp.	3304
5	mentaliz*.mp.	1160
6	mentalis*.mp.	800
7	role taking.mp.	164
8	perspective taking.mp.	1206
9	empath*.mp.	21823
10	1 or 2	21127
11	3 or 4 or 5 or 6 or 7 or 8 or 9	29827
12	**10 and 11**	**106**

OVID MEDLINE(R) 1946 to July Week 1 2015

#	Searches	Results

1	transcranial magnetic stimulation.mp.	10130
2	TMS.mp.	7284
3	Theory of mind.mp.	2727
4	ToM.mp.	2116
5	mentaliz*.mp.	667
6	mentalis*.mp.	552
7	role taking.mp.	148
8	perspective taking.mp.	776
9	empath*.mp.	17738
10	1 or 2	13005
11	3 or 4 or 5 or 6 or 7 or 8 or 9	22866
12	**10 and 11**	**55**

AMED (Allied and Complementary Medicine) 1985 to July 2015

#	**Searches**	**Results**
1	transcranial magnetic stimulation.mp.	261
2	TMS.mp.	112
3	Theory of mind.mp.	54
4	ToM.mp.	25
5	mentaliz*.mp.	6
6	mentalis*.mp.	4
7	role taking.mp.	2
8	perspective taking.mp.	5
9	empath*.mp.	394
10	1 or 2	286
11	3 or 4 or 5 or 6 or 7 or 8 or 9	468
12	**10 and 11**	**1**

Cochrane Library: Cochrane Database of Systematic Reviews : Issue 7 of 12, July 2015; Cochrane Central Register of Controlled

#	**Searches**	**Results**
#1	transcranial magnetic stimulation	1880
#2	TMS	713

#3	Theory of mind	319
#4	ToM	667
#5	mentaliz*	27
#6	mentalis*	20
#7	role taking	2837
#8	perspective taking	1351
#9	empath*	709
#10	#1 or #2	2078
#11	#3 or #4 or #5 or #6 or #7 or #8 or #9	5136
#12	#10 and #11	36

Web of Science Core Collection: Citation Indexes: Science Citation Index Expanded (SCI-EXPANDED) --1900-present; Social Sciences Citation Index (SSCI) --1956-present; Arts & Humanities Citation Index (A&HCI) --1975-present; Conference Proceedings Citation Index- Science (CPCI-S) --1990-present; Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) --1990-present

#	Searches	Results
#1	"transcranial magnetic stimulation"	14859
#2	TMS	12498
#3	"Theory of mind"	4978
#4	ToM	10281
#5	mentaliz*	1269
#6	mentalis*	943
#7	"role taking"	428
#8	"perspective taking"	2778
#9	empath*	16972
#10	#1 or #2	21762
#11	#3 or #4 or #5 or #6 or #7 or #8 or #9	34285
#12	#10 and #11	103

Pubmed 10072015

#	Searches	Results
#1	Search transcranial magnetic stimulation	11505
#2	Search TMS	8262
#3	Search theory of mind	5485
#4	Search ToM	9120
#5	Search mentaliz* Schema: nomesh	839
#6	Search mentalis*	603
#7	Search role taking	19827
#8	Search perspective taking	4251
#9	Search empath*	18936
#10	Search (TMS) OR transcranial magnetic stimulation	14886
#11	Search ((((((theory of mind) OR ToM) OR mentaliz*) OR mentalis*) OR role taking) OR perspective taking) OR empath*	55820
#12	Search (#10) AND #11	110

Appendix 6 PICOS Checklist Form
Study (including Author and Date):

	Inclusion	**Exclusion**
Population	Healthy subjects, People with mental disorders, Adults aged 18-65	People with learning disability, cognitive impairment including dementia, chronic pain, and neurological conditions such as migraine, epilepsy and brain injury
Intervention	Repetitive TMS: -Theta burst, -High frequency, -Low frequency	Studies on transcranial direct current stimulation given in isolation; single-pulse or paired-pulse TMS; TMS not used as an intervention tool
Comparator	Sham TMS, Active TMS on a control site, no intervention, psychotherapy, or other relevant comparators Different methods of application: High frequency vs low frequency Theta burst vs rTMS Single vs rTMS Direct current stimulation vs TMS	
Outcomes	Behavioural measures assessing empathy or ToM	Tasks not assessing empathy or ToM directly
Study design	RCTs Cross-sectional studies Prospective cohort studies Retrospective cohort studies	Reviews Expert opinions Editorials Letter Case Studies Conference abstracts

Decision: Include/Exclude

Appendix 7 The list of the excluded relevant empathy studies

Excluded due to the type of publication

Agnew, Z. K., Bhakoo, K. K., & Puri, B. K. (2007). The human mirror system: A motor resonance theory of mind-reading. Brain Research Reviews, 54(2), 286-293. doi: 10.1016/j.brainresrev.2007.04.003
Andrews, S. C., Enticott, P. G., Hoy, K. E., & Fitzgerald, P. B. (2013). Mirror systems and social cognition in schizophrenia. Schizophrenia Bulletin, 39, S218. doi: 10.1093/schbul/sbt011
Avenanti, A. (2010). Neurophysiological markers of empathy for pain. European Journal of Neurology, 17, 10. doi: 10.1111/j.1468-1331.2010.03230.x
Avenanti, A., Candidi, M., & Urgesi, C. (2013). Vicarious motor activation during action perception: beyond correlational evidence. Frontiers in Human Neuroscience, 7. doi: 10.3389/fnhum.2013.00185
Avenanti, A., & Urgesi, C. (2011). Understanding 'what' others do: mirror mechanisms play a crucial role in action perception. Social Cognitive and Affective Neuroscience, 6(3), 257-259. doi: 10.1093/scan/nsr004
Baeken, C. (2011). One left-sided dorsolateral prefrontal cortical HF-rTMS session affects emotional neuronal processing in healthy women. Clinical Neurophysiology, 122, S144-S145. doi: 10.1016/S1388-2457%2811%2960516-6
Baeken, C., Van Schuerbeek, P., De Raedt, R., De Mey, J., Vanderhasselt, M. A., Santermans, L., . . . Luypaert, R. (2011). The effect of one left-sided prefrontal HF-rTMS session on emotional brain processes. European Psychiatry, 26. doi: 10.1016/S0924-9338%2811%2972838-3
Balconi, M., & Canavesio, Y. (2013). High-frequency rTMS stimulation improves the facial mimicry and detection responses in an empathic emotional task. Clinical Neurophysiology, 124 (10), e115-e116. doi: 10.1016/j.clinph.2013.04.184
Balconi, M., & Canavesio, Y. (2013). rTMS stimulation improves the facial mimicry and detection responses in an empathic emotional task. Behavioural Neurology, 27 (3), 418. doi: 10.3233/BEN-139900
Bernhardt, B. C., & Singer, T. (2012). The neural basis of empathy (pp. 1-23). 4139 El Camino Way, P.O. Box 10139, Palo Alto CA 94306, United States: Annual Reviews Inc.
Bernier, R., & Dawson, G. (2009). The role of mirror neuron dysfunction in autism Mirror neuron systems: The Role of Mirroring Processes in Social Cognition (pp. 261-286). Totowa, NJ: Humana Press; US.
Bouaziz, N., Benadhira, R., Sidhoumi, D., & Januel, D. (2011). Transcranial magnetic stimulation (rTMS) concerning the treatment of schizophrenia: Interests and perspectives. Annales Medico-Psychologiques, 169(3), 192-195. doi: 10.1016/j.amp.2011.02.013
Christov-Moore, L., Simpson, E. A., Coude, G., Grigaityte, K., Iacoboni, M., & Ferrari, P. F. (2014). Empathy: Gender effects in brain and behavior. Neuroscience and Biobehavioral Reviews, 46(P4), 604-627. doi: 10.1016/j.neubiorev.2014.09.001
Cooper, N. R., Puzzo, I., & Pawley, A. D. (2008). Contagious yawning: The mirror neuron system may be a candidate physiological mechanism. Medical

Hypotheses, 71(6), 975-976. doi: 10.1016/j.mehy.2008.07.023

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The Reorienting System of the Human Brain: From Environment to Theory of Mind. Neuron, 58(3), 306-324. doi: 10.1016/j.neuron.2008.04.017

Demirtas-Tatlidede, A., & Schmahmann, J. D. (2013). Morality: Incomplete without the cerebellum? Brain, 136(8), e244. doi: 10.1093/brain/awt070

Enticott, P. G., Kennedy, H. A., Rinehart, N. J., May, S., Rossell, S., Tonge, B. J., . . . Fitzgerald, P. B. (2011). Social cognitive impairments in autism spectrum disorders: Insights from neuropsychiatry. Clinical EEG and Neuroscience, 42 (2), 130.

Fumagalli, M., & Priori, A. (2012). Functional and clinical neuroanatomy of morality. Brain, 135(Pt 7), 2006-2021. doi: 10.1093/brain/awr334

Hetu, S., Taschereau-Dumouchel, V., & Jackson, P. L. (2012). Stimulating the brain to study social interactions and empathy. Brain Stimulation, 5(2), 95-102. doi: 10.1016/j.brs.2012.03.005

Iacoboni, M. (2012). The human mirror neuron system and its role in imitation and empathy The primate mind: Built to connect with other minds (pp. 32-47). Cambridge, MA: Harvard University Press; US.

Iacoboni, M., & Dapretto, M. (2006). The mirror neuron system and the consequences of its dysfunction. Nature Reviews Neuroscience, 7(12), 942-951. doi: 10.1038/nrn2024

Jankowiak-Siuda, K., Siemieniuk, K., & Grabowska, A. (2009). Neurobiological basis of empathy. [Polish]

Neurobiologiczne podstawy empatii. Neuropsychiatria i Neuropsychologia, 4(2), 51-58.

Krippl, M., & Karim, A. A. (2011). "EuroTheory of mind" and its neuronal correlates in forensically relevant disorders. Nervenarzt, 82(7), 843-852. doi: 10.1007/s00115-010-3073-x

Li, H., Wang, J., Li, C., & Xiao, Z. (2014). Repetitive transcranial magnetic stimulation (rTMS) for panic disorder in adults. Cochrane Database of Systematic Reviews, (9). doi: 10.1002/14651858.CD009083.pub2

Mak, A. D. P., & Lam, L. C. W. (2013). Neurocognitive profiles of people with borderline personality disorder. Current Opinion in Psychiatry, 26(1), 90-96. doi: 10.1097/YCO.0b013e32835b57a9

Mehta, U. M., Basavaraju, R., Thirthalli, J., & Gangadhar, B. N. (2012). Mirror neuron dysfunction-a neuro-marker for social cognition deficits in drug naive schizophrenia. Biological Psychiatry, 1), 314S. doi: 10.1016/j.biopsych.2012.02.014

Mehta, U. M., Basavaraju, R., Thirthalli, J., & Gangadhar, B. N. (2013). Mirror neuron dysfunction in schizophrenia and its association with social cognition. Schizophrenia Bulletin, 39, S242. doi: 10.1093/schbul/sbt011

Miniussi, C., Cappa, S. F., Cohen, L. G., Floel, A., Fregni, F., Nitsche, M. A., . . . Walsh, V. (2008). Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. Brain Stimul, 1(4), 326-336. doi: 10.1016/j.brs.2008.07.002

Molnar-Szakacs, I. (2011). From actions to empathy and morality - A neural perspective. Journal of Economic Behavior & Organization, 77(1), 76-85. doi: 10.1016/j.jebo.2010.02.019

Newlin, D. B., & Renton, R. M. (2010). A Self in the Mirror: Mirror Neurons, Self-Referential Processing, and Substance Use Disorders. Substance Use and Misuse, 45(11), 1697-1726. doi: 10.3109/10826084.2010.482421

Obhi, S. S., & Sebanz, N. (2011). Moving together: Toward understanding the mechanisms of joint action. Experimental Brain Research, 211(3-4), 329-336. doi: 10.1007/s00221-011-2721-0

O'Malley, M. K., Ro, T., & Levin, H. S. (2006). Assessing and inducing neuroplasticity with transcranial magnetic stimulation and robotics for motor function. Archives of Physical Medicine and Rehabilitation, 87(12 Suppl 2), S59-66. doi: 10.1016/j.apmr.2006.08.332

Perkins, T., Stokes, M., McGillivray, J., & Bittar, R. (2010). Mirror neuron dysfunction in autism spectrum disorders. Journal of Clinical Neuroscience, 17(10), 1239-1243. doi: 10.1016/j.jocn.2010.01.026

Schuwerk, T., Langguth, B., & Sommer, M. (2014). Modulating functional and dysfunctional mentalizing by transcranial magnetic stimulation. Frontiers in Psychology, 5. doi: 10.3389/fpsyg.2014.01309

Singer, T., & Frith, C. (2005). The painful side of empathy. Nature Neuroscience, 8(7), 845-846. doi: 10.1038/nn0705-845

Suttrup, J., Keysers, C., & Thioux, M. (2015). The role of the theory of mind network in action observation-an rTMS study. Brain Stimulation, 8 (2), 415-416.

van Honk, J., & Schutter, D. J. (2006). Unmasking feigned sanity: A neurobiological model of emotion processing in primary psychopathy. Cognitive Neuropsychiatry, 11(3), 285-306. doi: 10.1080/13546800500233728

Excluded due to no TMS involved after reviewing abstracts

Aziz-Zadeh, L., Sheng, T., & Gheytanchi, A. (2010). Common Premotor Regions for the Perception and Production of Prosody and Correlations with Empathy and Prosodic Ability. PloS One, 5(1). doi: 10.1371/journal.pone.0008759

Benuzzi, F., Lui, F., Duzzi, D., Nichelli, P. F., & Porro, C. A. (2008). Does it look painful or disgusting? Ask your parietal and cingulate cortex. Journal of Neuroscience, 28(4), 923-931. doi: 10.1523/jneurosci.4012-07.2008

Lepage, J.-F. (2011). Developpement et fonctionnement des mecanismes de resonance motrice chez l'humain. Dissertation Abstracts International: Section B: The Sciences and Engineering, 72(4-B), 2475.

Marsh, L. E., Mullett, T. L., Ropar, D., & de, C. (2014). Responses to irrational actions in action observation and mentalising networks of the human brain. Neuroimage, 103, 81-90. doi: 10.1016/j.neuroimage.2014.09.020

Parkinson, C., & Wheatley, T. (2014). Relating Anatomical and Social Connectivity: White Matter Microstructure Predicts Emotional Empathy. Cerebral Cortex, 24(3), 614-625. doi: 10.1093/cercor/bhs347

Excluded due to intervention (not rTMS) after reviewing abstracts

Andrews, S. C., Enticott, P. G., Hoy, K. E., Thomson, R. H., & Fitzgerald, P. B. (2015). No evidence for mirror system dysfunction in schizophrenia from a multimodal TMS/EEG study. Psychiatry Research. doi: 10.1016/j.psychres.2015.05.067

Andrews, S. C., Enticott, P. G., Hoy, K. E., Thomson, R. H., & Fitzgerald, P. B. (2015). Reduced mu suppression and altered motor resonance in euthymic bipolar disorder: Evidence for a dysfunctional mirror system? Social Neuroscience, 1-12. doi: 10.1080/17470919.2015.1029140

Bolognini, N., Rossetti, A., Fusaro, M., Vallar, G., & Miniussi, C. (2014). Sharing social touch in the primary somatosensory cortex. Current Biology, 24(13), 1513-1517. doi: 10.1016/j.cub.2014.05.025

Borgomaneri, S., Gazzola, V., & Avenanti, A. (2012). Motor mapping of implied actions during perception of emotional body language. Brain Stimulation, 5(2), 70-76. doi: 10.1016/j.brs.2012.03.011

Borgomaneri, S., Gazzola, V., & Avenanti, A. (2014). Temporal dynamics of motor cortex excitability during perception of natural emotional scenes. Social Cognitive and Affective Neuroscience, 9(10), 1451-1457. doi: 10.1093/scan/nst139

Fourkas, A. D., Avenanti, A., Urgesi, C., & Aglioti, S. M. (2006). Corticospinal facilitation during first and third person imagery. Experimental Brain Research, 168(1-2), 143-151. doi: 10.1007/s00221-005-0076-0

Lepage, J. F., Tremblay, S., & Theoret, H. (2010). Early non-specific modulation of corticospinal excitability during action observation. European Journal of Neuroscience, 31(5), 931-937. doi: 10.1111/j.1460-9568.2010.07121.x

Liuzza, M. T., Candidi, M., Sforza, A. L., & Aglioti, S. M. (2015). Harm avoiders suppress motor resonance to observed immoral actions. Social Cognitive and Affective Neuroscience, 10(1), 72-77. doi: 10.1093/scan/nsu025

Mahayana, I. T., Banissy, M. J., Chen, C.-Y., Walsh, V., Juan, C.-H., & Muggleton, N. G. (2014). Motor empathy is a consequence of misattribution of sensory information in observers. Frontiers in Human Neuroscience, 8, 47.

Minio-Paluello, I., Baron-Cohen, S., Avenanti, A., Walsh, V., & Aglioti, S. M. (2009). Absence of Embodied Empathy During Pain Observation in Asperger Syndrome. Biological Psychiatry, 65(1), 55-62. doi: 10.1016/j.biopsych.2008.08.006

Excluded due to outcome (not measuring empathy or ToM) after reviewing abstracts

Basavaraju, R., Mehta, U. M., & Thirthalli, J. (2014). Mirror neuron activity and symptom dimensions in drug-naive mania-a transcranial magnetic stimulation study. Bipolar Disorders, 16, 83-84. doi: 10.1111/bdi.12189

Bolognini, N., Rossetti, A., Maravita, A., & Miniussi, C. (2011). Seeing Touch in the Somatosensory Cortex: ATMS Study of the Visual Perception of Touch. Human Brain Mapping, 32(12), 2104-2114. doi: 10.1002/hbm.21172

Brune, M., Scheele, D., Heinisch, C., Tas, C., Wischniewski, J., & Gunturkun, O. (2012). Empathy Moderates the Effect of Repetitive Transcranial Magnetic Stimulation of the Right Dorsolateral Prefrontal Cortex on Costly Punishment. PloS One, 7(9). doi: 10.1371/journal.pone.0044747

Catmur, C., Walsh, V., & Heyes, C. (2007). Sensorimotor learning configures the human mirror system. Current Biology, 17(17), 1527-1531. doi: 10.1016/j.cub.2007.08.006

Cazzato, V., Mian, E., Serino, A., Mele, S., & Urgesi, C. (2015). Distinct

contributions of extrastriate body area and temporoparietal junction in perceiving one's own and others' body. Cognitive Affective & Behavioral Neuroscience, 15(1), 211-228. doi: 10.3758/s13415-014-0312-9

Chiang, T. C., Lu, R. B., Hsieh, S., Chang, Y. H., & Yang, Y. K. (2014). Stimulation in the dorsolateral prefrontal cortex changes subjective evaluation of percepts. PloS One, 9(9), e106943. doi: 10.1371/journal.pone.0106943

Du, D. Q., & Wu, Y. B. (2005). Living ability and cognitive function ameliorated by low frequency repetitive transcranial magnetic stimulation in patients with post-stroke depression: Comparison with drug plus psychological treatment. [Chinese]. Chinese Journal of Clinical Rehabilitation, (16), 22-23. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/568/CN-00557568/frame.html

Fitzgibbon, B. M., Enticott, P. G., Bradshaw, J. L., Giummarra, M. J., Chou, M., Georgiou-Karistianis, N., & Fitzgerald, P. B. (2012). Enhanced corticospinal response to observed pain in pain synesthetes. Cognitive, Affective and Behavioral Neuroscience, 12(2), 406-418. doi: 10.3758/s13415-011-0080-8

Knoch, D., Gianotti, L. R., Pascual-Leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of right prefrontal cortex by low-frequency repetitive transcranial magnetic stimulation induces risk-taking behavior. Journal of Neuroscience, 26(24), 6469-6472. doi: 10.1523/jneurosci.0804-06.2006

Novembre, G., Ticini, L., Schutz-Bosbach, S., & Keller, P. (2013). Motor simulation coordinates joint actions in real time: Music performance meets on-line double-pulse TMS. Clinical Neurophysiology, 124 (10), e82. doi: 10.1016/j.clinph.2013.04.116

Novembre, G., Ticini, L. F., Schutz-Bosbach, S., & Keller, P. E. (2012). Distinguishing self and other in joint action. Evidence from a musical paradigm. Cerebral Cortex, 22(12), 2894-2903. doi: 10.1093/cercor/bhr364

Papeo, L., Corradi-Dell'Acqua, C., & Rumiati, R. I. (2011). "She" Is Not Like "I": The Tie between Language and Action Is in Our Imagination. Journal of Cognitive Neuroscience, 23(12), 3939-3948.

Pretalli, J. B., Nicolier, M., Chopard, G., Vandel, P., Tio, G., Monnin, J., . . . Haffen, E. (2012). Resting motor threshold changes and clinical response to prefrontal repetitive transcranial magnetic stimulation in depressed patients. Psychiatry and Clinical Neurosciences, 66(4), 344-352. doi: 10.1111/j.1440-1819.2012.02341.x

White, N. C., Reid, C., & Welsh, T. N. (2014). Responses of the human motor system to observing actions across species: A transcranial magnetic stimulation study. Brain and Cognition, 92, 11-18. doi: 10.1016/j.bandc.2014.10.004

Excluded due to intervention (not rTMS) after reviewing full-texts

Avenanti, A., & Aglioti, S. M. (2006). Pain in the motor system: One study of transcranial magnetic stimulation. Giornale Italiano di Psicologia, 33(4), 777-792.

Avenanti, A., Bueti, D., Galati, G., & Aglioti, S. M. (2005). Transcranial magnetic stimulation highlights the sensorimotor side of empathy for pain. Nature Neuroscience, 8(7), 955-960. doi: 10.1038/nn1481

Avenanti, A., Minio-Paluello, I., Bufalari, I., & Aglioti, S. M. (2006). Stimulus-driven modulation of motor-evoked potentials during observation of others' pain. Neuroimage, 32(1), 316-324. doi: 10.1016/j.neuroimage.2006.03.010

Avenanti, A., Minio-Paluello, I., Bufalari, I., & Aglioti, S. M. (2009). The pain of a model in the personality of an onlooker: Influence of state-reactivity and personality traits on embodied empathy for pain. Neuroimage, 44(1), 275-283. doi: 10.1016/j.neuroimage.2008.08.001

Avenanti, A., Minio-Paluello, I., Sforza, A., & Aglioti, S. M. (2009). Freezing or escaping? Opposite modulations of empathic reactivity to the pain of others. Cortex, 45(9), 1072-1077. doi: 10.1016/j.cortex.2008.10.004

Avenanti, A., Sirigu, A., & Aglioti, S. M. (2010). Racial bias reduces empathic sensorimotor resonance with other-race pain. Current Biology, 20(11), 1018-1022. doi: 10.1016/j.cub.2010.03.071

Borgomaneri, S., Gazzola, V., & Avenanti, A. (2014). Transcranial magnetic stimulation reveals two functionally distinct stages of motor cortex involvement during perception of emotional body language. Brain Structure & Function Jul(Pagination), No Pagination Specified. doi: 10.1007/s00429-014-0825-6

De Coster, L., Andres, M., & Brass, M. (2014). Effects of being imitated on motor responses evoked by pain observation: Exerting control determines action tendencies when perceiving pain in others. The Journal of Neuroscience, 34(20), 6952-6957. doi: 10.1523/JNEUROSCI.5044-13.2014

Donne, C. M., Enticott, P. G., Rinehart, N. J., & Fitzgerald, P. B. (2011). A transcranial magnetic stimulation study of corticospinal excitability during the observation of meaningless, goal-directed, and social behaviour. Neuroscience Letters, 489(1), 57-61. doi: 10.1016/j.neulet.2010.11.067

Enticott, P. G., Harrison, B. A., Arnold, S. L., Nibaldi, K., Segrave, R. A., Fitzgibbon, B. M., . . . Fitzgerald, P. B. (2012). Emotional valence modulates putative mirror neuron activity. Neuroscience Letters, 508(1), 56-59. doi: 10.1016/j.neulet.2011.12.018

Enticott, P. G., Johnston, P. J., Herring, S. E., Hoy, K. E., & Fitzgerald, P. B. (2008). Mirror neuron activation is associated with facial emotion processing. Neuropsychologia, 46(11), 2851-2854. doi: 10.1016/j.neuropsychologia.2008.04.022

Enticott, P. G., Kennedy, H. A., Bradshaw, J. L., Rinehart, N. J., & Fitzgerald, P. B. (2010). Understanding mirror neurons: Evidence for enhanced corticospinal excitability during the observation of transitive but not intransitive hand gestures. Neuropsychologia, 48(9), 2675-2680. doi: 10.1016/j.neuropsychologia.2010.05.014

Enticott, P. G., Kennedy, H. A., Bradshaw, J. L., Rinehart, N. J., & Fitzgerald, P. B. (2011). Motor corticospinal excitability during the observation of interactive hand gestures. Brain Research Bulletin, 85(3-4), 89-95. doi: 10.1016/j.brainresbull.2011.03.018

Fecteau, S., Pascual-Leone, A., & Theoret, H. (2008). Psychopathy and the mirror neuron system: preliminary findings from a non-psychiatric sample. Psychiatry Research, 160(2), 137-144. doi: 10.1016/j.psychres.2007.08.022

Fitzgibbon, B. M., Enticott, P. G., Bradshaw, J. L., Giummarra, M. J., Georgiou-Karistianis, N., Chou, M., & Fitzgerald, P. B. (2012). Motor cortical excitability and inhibition in acquired mirror pain. Neuroscience Letters,

530(2), 161-165. doi: 10.1016/j.neulet.2012.09.036

Guise, K., Kelly, K., Romanowski, J., Vogeley, K., Platek, S. M., Murray, E., & Keenan, J. P. (2007). The anatomical and evolutionary relationship between self-awareness and Theory of mind. Human Nature, 18(2), 132-142. doi: 10.1007/s12110-007-9009-x

Lepage, J. F., Lortie, M., Deal, C. L., & Theoret, H. (2014). Empathy, autistic traits, and motor resonance in adults with Turner syndrome. Social Neuroscience, 9(6), 601-609. doi: 10.1080/17470919.2014.944317

Mehta, U. M., Thirthalli, J., Basavaraju, R., Gangadhar, B. N., & Pascual-Leone, A. (2014). Reduced mirror neuron activity in schizophrenia and its association with theory of mind deficits: Evidence from a transcranial magnetic stimulation study. Schizophrenia Bulletin, 40(5), 1083-1094. doi: 10.1093/schbul/sbt155

Minio-Paluello, I., Avenanti, A., & Aglioti, S. M. (2006). Left hemisphere dominance in reading the sensory qualities of others' pain? Social Neuroscience, 1(3-4), 320-333.

Wood, R., Gallese, V., & Cattaneo, L. (2010). Visuotactile empathy within the primary somatosensory cortex revealed by short-latency afferent inhibition. Neuroscience Letters, 473(1), 28-31. doi: 10.1016/j.neulet.2010.02.012

Excluded due to outcome (not measuring empathy or ToM) after reviewing full-texts

Baeken, C., Van Schuerbeek, P., De Raedt, R., De Mey, J., Vanderhasselt, M. A., Bossuyt, A., & Luypaert, R. (2011). The effect of one left-sided dorsolateral prefrontal sham-controlled HF-rTMS session on approach and withdrawal related emotional neuronal processes. *Clinical Neurophysiology, 122*(11), 2217-2226. doi: 10.1016/j.clinph.2011.04.009

Brune, M., Scheele, D., Heinisch, C., Tas, C., Wischniewski, J., & Gunturkun, O. (2012). Empathy Moderates the Effect of Repetitive Transcranial Magnetic Stimulation of the Right Dorsolateral Prefrontal Cortex on Costly Punishment. PloS One, 7(9). doi: 10.1371/journal.pone.0044747

Cazzato, V., Mian, E., Serino, A., Mele, S., & Urgesi, C. (2015). Distinct contributions of extrastriate body area and temporoparietal junction in perceiving one's own and others' body. Cognitive Affective & Behavioral Neuroscience, 15(1), 211-228. doi: 10.3758/s13415-014-0312-9

David, N., Jansen, M., Cohen, M. X., Osswald, K., Molnar-Szakacs, I., Newen, A., . . . Paus, T. (2009). Disturbances of self-other distinction after stimulation of the extrastriate body area in the human brain. Social Neuroscience, 4(1), 40-48. doi: 10.1080/17470910801938023

Rossetti, A., Miniussi, C., Maravita, A., & Bolognini, N. (2012). Visual perception of bodily interactions in the primary somatosensory cortex. European Journal of Neuroscience, 36(3), 2317-2323. doi: 10.1111/j.1460-9568.2012.08137.x

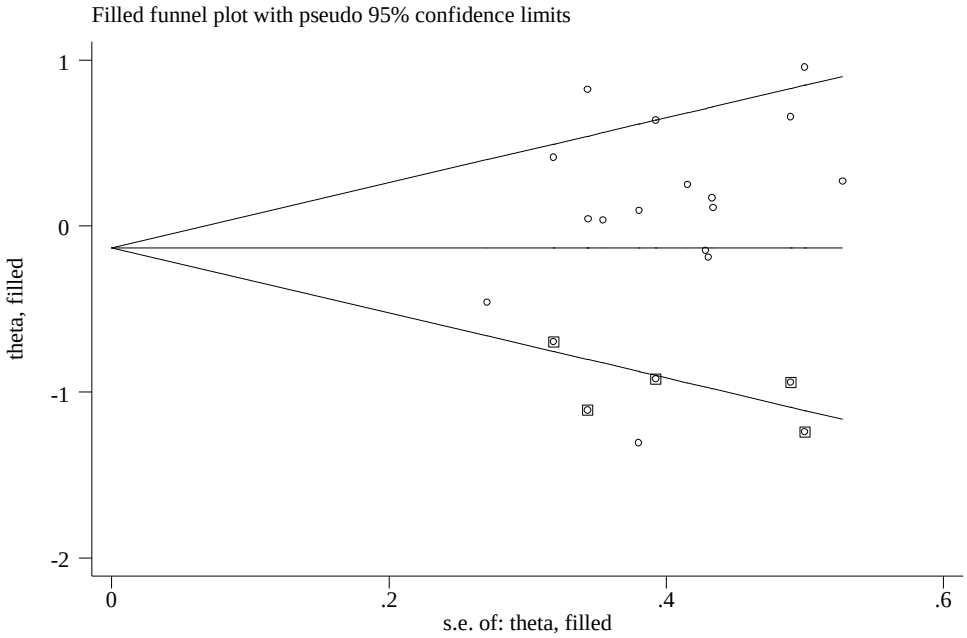
Appendix 8 The component and overall quality ratings of the reviewed rTMS studies in empathy

Study	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Overall
Balconi & Bortolotti, 2012	+	+++	+++	++	+++	+++	++
Balconi & Bortolotti, 2013	+	+++	+++	++	+++	+++	++
Balconi, Bortolotti, & Gonzaga, 2011	+	+++	+++	++	+++	+++	++
Balconi & Canavesio, 2013	+	+++	+++	++	+++	+++	++
Balconi & Canavesio, 2016	+	+++	+++	++	+++	+++	++
Balconi, Crivelli, & Bortolotti, 2010	+	+++	+++	++	+++	+++	++
Bolognini et al., 2013	+	+++	+++	++	+++	+++	++
Costa et al., 2008	+	+++	+++	++	+++	+++	++
Enticott et al., 2014	++	+++	+++	+++	+++	+++	+++
Giardina et al., 2011	+	+++	+++	++	+++	+++	++
Hoekert et al., 2010,	+	+++	+++	++	+++	+++	++
Kalbe et al., 2010	+	+++	+++	++	+++	+++	++
Keuken et al., 2011	+	+++	+++	++	+++	+++	++
Krause et al., 2012	+	+++	+++	++	+++	+++	++
Lev-Ran et al., 2012	+	+++	+++	++	+++	+++	++
Michael et al., 2014	+	+++	+++	++	+	+++	+
Pobric and Hamilton, 2006	+	+++	+++	++	+++	+++	++
Schuwerk et al., 2014	+	+++	+++	++	+++	+++	++

Silani et al., 2013	+	+++	+	++	+++	+++	+
Uddin et al., 2006	+	+++	+++	++	++	+++	++
Young et al., 2010	+	+++	+++	++	+++	+++	++

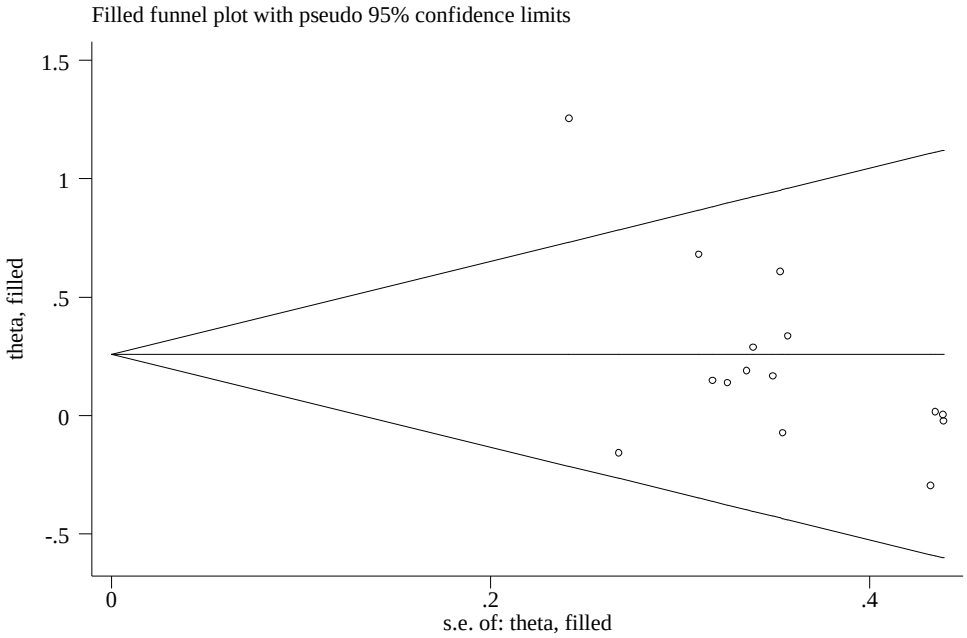
+ = weak, ++ = moderate, +++ = strong

Appendix 9 Outputs of the trim-and-fill procedures



Filled funnel plot of the cognitive ToM trials in the meta-analysis after trim procedure

Empty dots with an outer square represent the imputed missing trials.



Filled funnel plot of the affective ToM trials in the meta-analysis after trim procedure

No missing trials were found

Appendix 10 Search syntax for rTMS studies in impulsivity

AMED (Allied and Complementary Medicine) 1985 to February 2017		
#	**Searches**	**Results**
1	(impulsiv* or self-regulation or inhibitory control or impulse control or delay* discounting or response inhibition or information sampling or stop signal or temporal discounting or inhibition or go-no-go).mp. [mp=abstract, heading words, title]	320
2	("transcranial magnetic stimulation" or TMS or TBS or "theta burst stimulation").mp. [mp=abstract, heading words, title]	335
3	**1 and 2**	**39**

OVID: Embase 1980 to 2017 Week 08		
#	**Searches**	**Results**
1	(impulsiv* or "self-regulation" or "inhibitory control" or "impulse control" or "delay* discounting" or "response inhibition" or "information sampling" or "stop signal" or "temporal discounting" or "stroop" or "inhibition" or "go-no-go").kw.	48718
2	("TMS" or "transcranial magnetic stimulation" or "theta burst stimulation" or "TBS").kw.	7698
3	1 and 2	784
4	limit 3 to (human and embase and (conference abstract or conference paper or conference proceeding or journal or report or short survey) and adult <18 to 64 years>)	**94**

OVID MEDLINE(R) 1946 to February Week 2 2017		
#	**Searches**	**Results**
1	(impulsiv* or self-regulation or inhibitory control or impulse control or delay* discounting or response inhibition or information sampling or stop signal or temporal discounting or inhibition or go-no-go).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	742364
2	("TMS" or "transcranial magnetic stimulation" or "theta burst stimulation" or "TBS").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	16256
3	1 and 2	2639
4	limit 3 to (humans and "all adult (19 plus years)")	**2030**

OVID: PsycINFO 1806 to February Week 2 2017		
#	**Searches**	**Results**
1	(impulsiv* or "self-regulation" or "inhibitory control" or "impulse control" or "delay* discounting" or "response inhibition" or "information sampling" or "stop signal" or "temporal discounting" or "stroop" or "inhibition" or "go-no-go").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests	113070

	& measures]	
2	("TMS" or "transcranial magnetic stimulation" or "theta burst stimulation" or "TBS").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	8961
3	1 and 2	1625
4	limit 3 to (human and adulthood <18+ years> and "300 adulthood <age 18 yrs and older>" and human)	**1260**

Appendix 11 The component and overall quality ratings of the reviewed studies

Study	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Overall	Adverse effect
Cho et al. (2010)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Bermpohl et al., (2005)	+	+++	+++	++	+++	+++	Moderate	Not mentioned
Chambers et al., (2006)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Chambers et al., (2007)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Chen et al., (2009)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Cho et al. (2012)	+	+++	+++	+++	+++	+++	Moderate	No significant discomfort
Cho et al. (2015)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Dambacher et al. (2014)	+	+++	+++	+++	+++	++	Moderate	uncomfortable facial twitches (n =1)
Esterman et al., (2015)	+	+++	+++	++	+++	+++	Moderate	Not mentioned

Figner et al., (2010)	+	+++	+++	+++	+++	+++	Moderate	No participant experienced serious adverse effects or reported any scalp pain, neck pain, or headaches
Grossheinrich et al., (2009)	+	+++	+++	+++	+++	+++	Moderate	headache and muscle twitching during stimulation and nausea and lightheadedness after stimulation (n=1), sweating and feeling dizzy after stimulation(n=1), nausea after stimulation(n=1)
Huang et al., (2004)	+	+++	+++	+++	+++	+++	Moderate	No subjective or objective ad- verse effects were observed in any subject during stimulation
Hwang et al., (2010)	+	+++	+++	+++	+++	+++	Moderate	no adverse event occurred

Kim et al., (2012)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Knoch et al., (2006)	+	+++	+++	+++	+++	+++	Moderate	no adverse side effects
Lee et al., (2016)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Leyman et al., (2009)	+	+++	+++	++	+++	+++	Moderate	Not mentioned
Leyman et al., (2009)	+	+++	+++	++	+++	+++	Moderate	Not mentioned
Lowe et al., (2014)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Muggleton et al., (2010) exp1	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Obeso et al., (2013)	+	+++	+++	+++	+++	+++	Moderate	No participants reported major adverse effects
Sheffer et al., (2013)	++	+++	+++	++	+++	+	Moderate	Not mentioned
Upton et al., (2010)	+	+++	+++	++	+++	+++	Moderate	Not mentioned

Vanderhasselt et al., (2006)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Vanderhasselt et al., (2007)	+	+++	+++	+++	+++	+++	Moderate	Not mentioned
Verbruggen et al., (2010)	+	+++	+++	++	+++	+++	Moderate	No adverse effects
Wagner et al., (2006)	+	+++	+++	++	+++	+++	Moderate	mild headaches (n=3)
Watanabe et al., (2015)	+	+++	+++	++	+++	+++	Moderate	Not mentioned
Zandbelt et al.,(2013)	+	+++	+++	+++	+++	+++	Moderate	no adverse side effects
+ = weak, ++ = moderate, +++ = strong								

Appendix 12 The Barratt Impulsiveness Scale- Version 11

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

① Rarely/Never ② Occasionally ③ Often ④ Almost Always/Always

1	I plan tasks carefully.	① ② ③ ④
2	I do things without thinking.	① ② ③ ④
3	I make-up my mind quickly.	① ② ③ ④
4	I am happy-go-lucky.	① ② ③ ④
5	I don't "pay attention."	① ② ③ ④
6	I have "racing" thoughts.	① ② ③ ④
7	I plan trips well ahead of time.	① ② ③ ④
8	I am self controlled.	① ② ③ ④
9	I concentrate easily.	① ② ③ ④
10	I save regularly.	① ② ③ ④
11	I "squirm" at plays or lectures.	① ② ③ ④
12	I am a careful thinker.	① ② ③ ④
13	I plan for job security.	① ② ③ ④
14	I say things without thinking.	① ② ③ ④
15	I like to think about complex problems.	① ② ③ ④
16	I change jobs.	① ② ③ ④
17	I act "on Impulse."	① ② ③ ④
18	I get easily bored when solving thought problems.	① ② ③ ④
19	I act on the spur of the moment.	① ② ③ ④
20	I am a steady thinker.	① ② ③ ④
21	I change residences.	① ② ③ ④
22	I buy things on impulse.	① ② ③ ④
23	I can only think about one thing at a time.	① ② ③ ④
24	I change hobbies.	① ② ③ ④
25	I spend or charge more than I earn.	① ② ③ ④
26	I often have extraneous thoughts when thinking.	① ② ③ ④
27	I am more interested in the present than the future.	① ② ③ ④
28	I am restless at the theater or lectures.	① ② ③ ④
29	I like puzzles.	① ② ③ ④
30	I am future oriented.	① ② ③ ④

Patton, Stanford, Barratt (1995). *J Clin Psy*, vol. 51, pp. 768-774

Appendix 13 UPPS-P Impulsive Behaviour Scale

Below are a number of statements that describe ways in which people act and think. For each statement, please indicate how much you agree or disagree with the statement. If you **Agree Strongly** circle **1**, if you **Agree Somewhat** circle **2**, if you **Disagree somewhat** circle **3**, and if you **Disagree Strongly** circle **4**. Be sure to indicate your agreement or disagreement for every statement below. Also, there are questions on the following pages.					
1	I have a reserved and cautious attitude toward life.	**1**	**2**	**3**	**4**
2	I have trouble controlling my impulses.	**1**	**2**	**3**	**4**
3	I generally seek new and exciting experiences and sensations.	**1**	**2**	**3**	**4**
4	I generally like to see things through to the end.	**1**	**2**	**3**	**4**
5	When I am very happy, I can't seem to stop myself from doing things that can have bad consequences.	**1**	**2**	**3**	**4**
6	My thinking is usually careful and purposeful.	**1**	**2**	**3**	**4**
7	I have trouble resisting my cravings (for food, cigarettes, etc.).	**1**	**2**	**3**	**4**
8	I'll try anything once.	**1**	**2**	**3**	**4**
9	I tend to give up easily.	**1**	**2**	**3**	**4**
10	When I am in great mood, I tend to get into situations that could cause me problems.	**1**	**2**	**3**	**4**
11	I am not one of those people who blurt out things without thinking.	**1**	**2**	**3**	**4**
12	I often get involved in things I later wish I could get out of.	**1**	**2**	**3**	**4**
13	I like sports and games in which you have to choose your next move very quickly.	**1**	**2**	**3**	**4**
14	Unfinished tasks really bother me.	**1**	**2**	**3**	**4**
15	When I am very happy, I tend to do things that may cause problems in my life.	**1**	**2**	**3**	**4**
16	I like to stop and think things over before I do them.	**1**	**2**	**3**	**4**
17	When I feel bad, I will often do things I later regret in order to make myself feel better now.	**1**	**2**	**3**	**4**
18	I would enjoy water skiing.	**1**	**2**	**3**	**4**
19	Once I get going on something I hate to stop.	**1**	**2**	**3**	**4**

20	I tend to lose control when I am in a great mood.	**1**	**2**	**3**	**4**
21	I don't like to start a project until I know exactly how to proceed.	**1**	**2**	**3**	**4**
22	Sometimes when I feel bad, I can’t seem to stop what I am doing even though it is making me feel worse.	**1**	**2**	**3**	**4**
23	I quite enjoy taking risks.	**1**	**2**	**3**	**4**
24	I concentrate easily.	**1**	**2**	**3**	**4**
25	When I am really ecstatic, I tend to get out of control.	**1**	**2**	**3**	**4**
26	I would enjoy parachute jumping.	**1**	**2**	**3**	**4**
27	I finish what I start.	**1**	**2**	**3**	**4**
28	I tend to value and follow a rational, "sensible" approach to things.	**1**	**2**	**3**	**4**
29	When I am upset I often act without thinking.	**1**	**2**	**3**	**4**
30	Others would say I make bad choices when I am extremely happy about something.	**1**	**2**	**3**	**4**
31	I welcome new and exciting experiences and sensations, even if they are a little frightening and unconventional.	**1**	**2**	**3**	**4**
32	I am able to pace myself so as to get things done on time.	**1**	**2**	**3**	**4**
33	I usually make up my mind through careful reasoning.	**1**	**2**	**3**	**4**
34	When I feel rejected, I will often say things that I later regret.	**1**	**2**	**3**	**4**
35	Others are shocked or worried about the things I do when I am feeling very excited.	**1**	**2**	**3**	**4**
36	I would like to learn to fly an airplane.	**1**	**2**	**3**	**4**
37	I am a person who always gets the job done.	**1**	**2**	**3**	**4**
38	I am a cautious person.	**1**	**2**	**3**	**4**
39	It is hard for me to resist acting on my feelings.	**1**	**2**	**3**	**4**
40	When I get really happy about something, I tend to do things that can have bad consequences.	**1**	**2**	**3**	**4**
41	I sometimes like doing things that are a bit frightening.	**1**	**2**	**3**	**4**
42	I almost always finish projects that I start.	**1**	**2**	**3**	**4**
43	Before I get into a new situation I like to find out what to expect from it.	**1**	**2**	**3**	**4**

44	I often make matters worse because I act without thinking when I am upset.	**1**	**2**	**3**	**4**
45	When overjoyed, I feel like I can't stop myself from going overboard.	**1**	**2**	**3**	**4**
46	I would enjoy the sensation of skiing very fast down a high mountain slope.	**1**	**2**	**3**	**4**
47	Sometimes there are so many little things to be done that I just ignore them all.	**1**	**2**	**3**	**4**
48	I usually think carefully before doing anything.	**1**	**2**	**3**	**4**
49	Before making up my mind, I consider all the advantages and disadvantages.	**1**	**2**	**3**	**4**
50	When I am really excited, I tend not to think of the consequences of my actions.	**1**	**2**	**3**	**4**
51	In the heat of an argument, I will often say things that I later regret.	**1**	**2**	**3**	**4**
52	I would like to go scuba diving.	**1**	**2**	**3**	**4**
53	I tend to act without thinking when I am really excited.	**1**	**2**	**3**	**4**
54	I always keep my feelings under control.	**1**	**2**	**3**	**4**
55	When I am really happy, I often find myself in situations that I normally wouldn't be comfortable with.	**1**	**2**	**3**	**4**
56	I would enjoy fast driving.	**1**	**2**	**3**	**4**
57	When I am very happy, I feel like it is ok to give in to cravings or overindulge.	**1**	**2**	**3**	**4**
58	Sometimes I do impulsive things that I later regret.	**1**	**2**	**3**	**4**
59	I am surprised at the things I do while in a great mood.	**1**	**2**	**3**	**4**

Scoring Instructions

This is a revised version of the UPPS Impulsive Behavior scale (Whiteside & Lynam, 2001). This version, UPPS-P, assesses an additional personality pathway to impulsive behavior, Positive Urgency (Cyders & Smith, 2007), in addition to the four pathways assessed in the original version of the scale--Urgency (now Negative Urgency), (lack of) Premeditation, (lack of) Perseverance, and Sensation Seeking. The scale uses a 1 (agree strongly) to

4 (disagree strongly) response format. Because the items from different scales run in different directions, it is important to make sure that the correct items are reverse-scored. We suggest making all of the scales run in the direction such that higher scores indicate more impulsive behavior. Therefore, we include the scoring key for, (Negative) Urgency, (lack of) Premeditation, (lack of) Perseverance, Sensation Seeking, and Positive Urgency. For each scale, calculate the mean of the available items; this puts the scales on the same metric. We recommend requiring that a participant have at least 70% of the items before a score is calculated.

(Negative) Urgency (all items except 1 are reversed)
items 2 (R), 67(R), 12 (R), 17 (R), 22 (R), 29 (R), 34 (R), 39 (R), 44 (R), 51 (R), 54, 58 (R)

(lack of) Premeditation (no items are reversed)
items 1, 6, 11, 16, 21, 28, 33, 38, 43, 48, 49.

(lack of) Perseverance (two items are reversed)
items 4, 9 (R), 14, 19, 24, 27, 32, 37, 42, 47 (R)

Sensation Seeking (all items are reversed)
items 3 (R), 8 (R), 13 (R), 18 (R), 23 (R), 26 (R), 31 (R), 36 (R), 41 (R), 46 (R), 52 (R), 56 (R)

Positive Urgency (all items are reversed)
items 5 (R), 10 (R), 15 (R), 20 (R), 25 (R), 30 (R), 35 (R), 40 (R), 45 (R), 50 (R), 53 (R), 55 (R), 57 (R), 59 (R)

(R) indicates the item needs to be reverse scored such 1=4, 2=3, 3=2, and 4=1.

Appendix 14 Questionnaire of Cognitive and Affective Empathy

People differ in the way they feel in different situations. Below you are presented with a number of characteristics that may or may not apply to you. Read each characteristic and indicate how much you agree or disagree with the item by ticking the appropriate box. Answer quickly and honestly.		Strongly agree	Slightly agree	Slightly disagree	Strongly disagree
1	I sometimes find it difficult to see things from the “other guy’s” point of view.				
2	I am usually objective when I watch a film or play, and I don’t often get completely caught up in it.				
3	I try to look at everybody’s side of a disagreement before I make a decision.				
4	I sometimes try to understand my friends better by imagining how things look from their perspective.				
5	When I am upset at someone, I usually try to “put myself in his shoes” for a while.				
6	Before criticizing somebody, I try to imagine how I would feel if I was in their place				
7	I often get emotionally involved with my friends’ problems.				
8	I am inclined to get nervous when others around me seem to be nervous.				
9	People I am with have a strong influence on my mood.				
10	It affects me very much when one of my friends seems upset.				
11	I often get deeply involved with the feelings of a character in a film, play, or novel.				
12	I get very upset when I see someone cry.				
13	I am happy when I am with a cheerful group and sad when the others are glum.				

		Strongly agree	Slightly agree	Slightly disagree	Strongly disagree
14	It worries me when others are worrying and panicky				
15	I can easily tell if someone else wants to enter a conversation.				
16	I can pick up quickly if someone says one thing but means another.				
17	It is hard for me to see why some things upset people so much.				
18	I find it easy to put myself in somebody else's shoes.				
19	I am good at predicting how someone will feel.				
20	I am quick to spot when someone in a group is feeling awkward or uncomfortable.				
21	Other people tell me I am good at understanding how they are feeling and what they are thinking.				
22	I can easily tell if someone else is interested or bored with what I am saying.				
23	Friends talk to me about their problems as they say that I am very understanding.				
24	I can sense if I am intruding, even if the other person does not tell me.				
25	I can easily work out what another person might want to talk about.				
26	I can tell if someone is masking their true emotion.				
27	I am good at predicting what someone will do.				

		Strongly agree	Slightly agree	Slightly disagree	Strongly disagree
28	I can usually appreciate the other person's viewpoint, even if I do not agree with it.				
29	I usually stay emotionally detached when watching a film				
30	I always try to consider the other fellow's feelings before I do something.				
31	Before I do something I try to consider how my friends will react to it.				

Scoring of the (sub)scales of the QCAE

Empathy (sub)scale	Item numbers
Cognitive empathy	
Perspective taking	15 - 16 - 19 - 20 - 21 - 22 - 24 - 25 - 26 - 27
Online simulation	1 (R) - 3 - 4 - 5 - 6 - 18 - 28 - 30 -31
Affective empathy	
Emotion contagion	8 - 9 - 13 - 14
Proximal responsivity	7 - 10 - 12 - 23
Peripheral responsivity	2 (R) - 11 – 17 (R) – 29 (R)

(R) indicates the item needs to be reverse scored such 1=4, 2=3, 3=2, and 4=1.

The subscale items are summed to produce the scores on the subscales **(Strongly Agree** = **4**, **Slightly Agree** = **3**, **Slightly Disagree** = **2**, **Strongly Disagree** = **1)**. The two cognitive subscales are summed to produce the score on the cognitive empathy scale and the three affective subscales are summed to produce the affective empathy score. Summation of the cognitive and affective empathy scores gives a total empathy score.

The items of the QCAE originate from the Interpersonal Reactivity Index (IRI; item numbers 1-6), Impulsiveness Venturesomeness Empathy Inventory (IVE; item numbers 7-14), Empathy Quotient (EQ; item numbers 15-29) and Hogan Empathy Scale (HES; item numbers 30-31).

Reniers, R. L. E. P., Corcoran, R., Drake, R., Shryane, N. M., & Völlm, B. A. (2011). The QCAE: A Questionnaire of Cognitive and Affective Empathy. *Journal of Personality Assessment, 93*(1), 84-95.