Excitatory repetitive Transcranial Magnetic Stimulation applied to the right inferior frontal gyrus has no effect on motor or cognitive impulsivity in healthy adults

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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. 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 reflective/cognitive 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

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1. 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 [1]. Besides playing a prominent role in psychopathology [2], impulsivity is a core feature of many psychiatric disorders such as attention deficit hyperactivity disorder (ADHD) [3], schizophrenia [4], obsessive compulsive disorder [5], impulse-control disorders, borderline personality disorder, antisocial personality disorder, bipolar affective disorder, and substance use disorders [6, 7].

There is a general consensus among researchers that impulsivity is a multi-faceted concept [8, 9], 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 [10, 11]. In contrast with TI and RI, MI has received more attention in the scientific literature. Recent evidence [12] 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 [9]. 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 [13], 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 [1] 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, substance use disorders, ADHD), and one that has been implicated in some of

the most serious consequences of impulsivity such as aggression, self-harm and suicidality [14]. 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 [15]. There is no consensus among researchers as to what measure can be used to index proactive inhibitory control [16]. Whilst some researchers have proposed that proactive inhibitory control equates to response slowing [17, 18], others have argued that proactive inhibitory control represents anticipatory regulation of response activation or motor excitability [12, 19].

Several brain areas have been implicated in MI [7] 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 [14]. The rIFG, a crucial region belonging to a fronto-subcortical network connecting the cortical areas and basal ganglia, has been implicated in MI [20-22]. 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 [23]. This brings to the core construct of RI which overlaps significantly with decision making and MI and such overlap

may explain why some people (such as those with personality disorder) habitually make disadvantageous choices in their personal lives, with varying degree of consequences for self or others [24]. Therefore, in this study we included a measure of RI, namely the Information Sampling Task (IST) [25].

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 [26]. 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 [27].

Studies using inhibitory rTMS over the rIFG have found detrimental effects on inhibitory control [28-33], 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 [34]. Hyperactivity in rIFG has been found in risk-averse participants while selecting less risky options [35]. Further, another functional imaging study also found increased activity over the ventral portion of lateral prefrontal cortex, including the rIFG, during risk-taking tasks [36].

While rTMS has been used to elucidate the role the rIFG in impulse control [26, 37], 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 [37]. 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 [38-41], 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 [42]. Secondly, rTMS studies have mainly examined the effects on reactive inhibitory control, the effects on proactive inhibitory control

and the role of rIFG in PIC are relatively under researched [32, 43]. 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 clinical relevant [1] 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.

2. Material and methods

2.1. 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 [44]; 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 subjects 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 [45]. 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 [46]. 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 subjects was estimated for a randomised parallel design study. Since only half of the sample is required for a randomised crossover design [47], 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 subjects 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 and written informed consent was obtained from all participants before commencing the study.

2.2. 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) [48] and UPPS-P Impulsive Behaviour Scale (UPPS-P) [49]. 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 figure out whether they received the active or sham stimulation. All participants received monetary compensation for their time. All evaluations, questionnaires and tasks were administered according to a comprehensive manual of operation instructions in a standardised manner.

2.3. Materials

2.3.1. 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 [50] 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 [51].

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 [2, 52, 53]. 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 [48].

2.3.2. Performance-based (behavioural) measures of impulsivity

The SST and IST, two computerised neuropsychological tasks from the Cambridge Computerised Neuropsychological Battery (CANTAB) [54], 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 [55, 56]. 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 [57].

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 [58]. 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. Subjects 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 [59-61] 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., [59] and also recommended by Clark and Robbins [62], 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 [63]. The time of completing the whole IST is about 15 minutes according to the manual.

2.4. 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). 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) if significant correlations were found between performance-based and self-report measures of impulsivity. A *P* value of < .05 was considered as statistically significant.

3. Results

3.1. Overview

The participants' baseline performance on trait impulsivity measures is presented in Table 1. 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.

3.1. 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.

3.2. 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).

3.3. Correlations between tasks

Table 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.

3.4. Self-report impulsivity as covariates

Since among all performance-based outcome measures, only the Pcorrect in FW correlated with the total scores of BIS-11 and UPPS-P, these two scores were selected as covariates into the ANCOVA to analyse the effects of self-report impulsivity on their performance-based counterparts. No significant effects was found regardless of using the total scores of either BIS-11 or UPPS-P as covariates.

4. 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 [64, 65] suggested that the rIFG is highly involved in MI, especially the reactive inhibitory control. Significant modifications in SSRT result from inhibitory rTMS [28, 29] and anodal tDCS studies [38-41] also support this view. Our findings regarding reactive inhibitory control seem to contradict the existing evidence. A notable exception is a recent study [66] 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 [67] argued that rIFG is involved in proactive inhibitory control as indexed by post-error slowing while others [68] found that stimulation of the rIFG produced no tangible effects on proactive inhibitory control. Our findings also support the view that brain areas other than the rIFG may be implicated in MI [69].

With regard to RI, contrary to existing evidence which implicates the rIFG in risk evaluation [35, 36], 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 [7] 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 [37], 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 using similar protocols reliably demonstrated neuromodulatory effects at prefrontal and striatal brain regions

[70, 71]. 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 [72], 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 [73]. Considering that the rIFG localisation method we used [50] has been verified [51] and TMS studies remain working without imaging assistance [74], it is still highly possible that the rIFG was correctly targetted. Finally, another argument is that the participants recruited were too 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 [75], 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 [76].

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 [1] employing IST have found stable correlations between Pcorrect in FW and in DW conditions using the traditional algorism proposed by Clark, Robbins, Ersche and Sahakian [25]. This may reflect the uniqueness of new Pcorrect since the decision processes in FW and DW are underpinned by different levels of uncertainty [25] and the findings of weak or nil correlation between these two measures should be expected. Although the non-association between the reactive inhibitory control and proactive inhibitory control further supports the view of dual mechanisms of inhibitory control [19], other studies [38] 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 [16], future studies are encouraged to develop a universal agreed index to denote proactive inhibitory control.

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.

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.

Conflict of interest

There is no conflict of interest.

Acknowledgement

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

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Table 1 Baseline performance on trait impulsivity measures

measurements	mean± SD	range
BIS-11 Total	62.30± 10.68	(41 - 81)
Motor	23.70± 5.10	(13 - 32)
Attentional	16.10± 3.11	(12 - 23)
Non-planning	22.50± 4.45	(15 - 33)
UPPS-P Total	131.80± 18.08	(99 - 169)
Negative urgency	26.30± 5.69	(19 - 40)
Premeditation	22.75± 3.71	(16 - 29)
Perservance	17.70± 4.09	(12 - 28)
Sensation Seeking	35.50± 6.71	(19 - 45)
Positive Urgency	29.55± 6.36	(20 - 42)

BIS - 11, Barratt Impulsiveness Scale, Version 11;

Table 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 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 ($p < .05$, ** $p < .01$, *** $p < .001$)