Research paper

Acta Neurobiol Exp 2016, 76: 182–191

ACTA NEUROBIOLOGIÆ EXPERIMENTALIS

Effects of repetitive transcranial magnetic stimulation on non-veridical decision making

Jaan Tulviste[1] *, Elkhonon Goldberg[2], Kenneth Podell[3], and Talis Bachmann[4]

[1] University of Tartu, Institute of Psychology, Tartu, Estonia, [2] NYU School of Medicine and Luria Neuroscience Institute, New York, NY, USA, [3] Houston Methodist Research Institute, Houston, TX, USA, [4] University of Tartu, Institute of Public Law, Tartu, Estonia,
** Email: jaant@ut.ee*

We test the emerging hypothesis that prefrontal cortical mechanisms involved in non-veridical decision making do not overlap with those of veridical decision making. Healthy female subjects performed an experimental task assessing free choice, agent-centered decision making (The Cognitive Bias Task) and a veridical control task related to visuospatial working memory (the Moving Spot Task). Transcranial magnetic stimulation (TMS) was applied to the left and right dorsolateral prefrontal cortex (DLPFC) using 1 Hz and 10 Hz (intermittent) rTMS and sham protocols. Both 1 Hz and 10 Hz stimulation of the DLPFC triggered a shift towards a more context-independent, internal representations driven non-veridical selection bias. A significantly reduced preference for choosing objects based on similarity was detected, following both 1 Hz and 10 Hz treatment of the right as well as 1 Hz rTMS of the left DLPFC. 1 Hz rTMS treatment of the right DLPFC also triggered a significant improvement in visuospatial working memory performance on the veridical task. The effects induced by prefrontal TMS mimicked those of posterior lesions, suggesting that prefrontal stimulation influenced neuronal activity in remote cortical regions interconnected with the stimulation site via longitudinal fasciculi.

Key words: decision making, transcranial magnetic stimulation (TMS), prefrontal cortex, cognitive bias task, moving spot task, agent-centered decision making

INTRODUCTION

In most cases decision making involves a degree of subjectivity, allowing personal preference and subjective choice to guide the selection of one option over another. Decision making has broadly been defined as an executive function enabling the selection of the most advantageous response from a selection of possible behaviors (Bechara et al. 2000). Making a decision involves encoding and representation of perceived options, each being assigned a measure of value and utility (Liu et al. 2011). Researchers acknowledge the complexity of decision making by treating it as a complex function that involves multiple component processes (Krawczyk 2002, Fellows 2004).

Aiming to establish a pertinent classification system, decision making tasks have been grouped into the following categories: multi-dimensional decision making, decision making under uncertainty, and preference-based decision making (Yu 2014). Other models postulate a segregation based on the nature of the decision being made, suggesting a discrimination between "veridical" decisions, where an unequivocally correct, albeit not always obvious answer to a problem exists, and "non-veridical", adaptive decisions, where personal priorities and preferences guide the agent in an ambiguous situation where multiple alternatives exist in solution to a given problem (Goldberg et al. 1994, Bechara et al. 1994).

Decision making: veridical *vs.* non-veridical

Goldberg and Podell (2000) have pointed out that most neuropsychological research as well as a vast majority of tests assessing executive functions have, until recently, been focused on veridical decision making, encountered in structured, unambiguous situations, where an intrinsically "correct" or "incorrect" solution to a problem exists. Even the Wisconsin Card Sorting Test (WCST), a tool widely used for the assessment of executive functions, may be considered a veridical test in nature (Lezak et al. 2004). According to Greve and others (2002), the WCST taps neuropsychological processes relating to cognitive flexibility, problem-solving and response maintenance. Several studies have successfully confirmed the sensitivity

Received 14 December 2015, accepted 21 June 2016

Correspondence should be addressed to J. Tulviste
Email: jaant@ut.ee

of the WCST to frontal lobe lesions (Drewe 1974, Nelson 1976). However, a number of studies have failed to confirm the power of WCST in discriminating between frontal and non-frontal lesions, suggesting that the WCST has limited anatomical specificity (Anderson et al. 1991) and may fail to account for various types of executive performance including "non-veridical" decision making.

The veridical *vs.* non-veridical dichotomy is rooted in lesion studies, where selective impairments of either type of decision making in patients have been reported. Substance abusers show abnormal decision making in unstructured, self-regulated situations, but not in veridical scenarios (Verdejo-Garcia et al. 2006). Developmental studies indicate that the development of decision making skills – along with the maturation of the frontal lobes – follows a path in which non-veridical, agent-centered, ambiguous choice abilities reach mature performance levels later than veridical decision making skills (Aihara et al. 2003).

As opposed to simple maintenance of items in short-term memory, tasks involving a high demand on executive processing require the engagement of lateral prefrontal areas, particularly the mid-dorsolateral (Brodman's area 9/46) cortex (Volle et al. 2008, Rowe et al. 2000). In addition to monitoring and updating temporary information in memory (Postle et al. 2000), the dorsolateral prefrontal cortex (DLPFC) often plays an executive control role by modulating neural activity in other areas related to working memory (Levy and Goldman-Rakic 2000), cognitive control (Miller 2000) and decision-making (Hare et al. 2009). The DLPFC has also been linked to cognitive regulation during value-related decision making tasks (Hutcherson et al. 2012). Camus and others (2009) showed that the right DLPFC directly participates in the stimuli valuation processes during free choice tasks. DLPFC modulation can also determine the frequency of decisions to lie or not to lie (Karton et al. 2011). Unlike veridical selection tasks, subjective decision making, related either to internal preferences or subjective color matching, triggers robust dorsomedial and dorsolateral frontal lobe activation (Johnson et al. 2005).

TMS: Effects of neuromodulatory stimulation on brain function

Transcranial magnetic stimulation (TMS), a non-invasive brain stimulation method, can be used to alter the function of the stimulated cortical region and associated neural circuits transiently in order to study their functional contribution to cognitive and perceptual processing (Pascual-Leone et al. 1994, Ruff et al. 2009). The neural effect of repeatedly applied, repetitive TMS (rTMS) depends on the frequency of stimulation, as well as on the intensity of stimulation and the cortical state of the subject at the time of the procedure (Silvanto and Pascual-Leone 2008). Low frequency rTMS (at rates of 1 Hz or less) generally leads to reduced excitability of the underlying neural tissue (Chen et al. 1997, Romero et al. 2002) whereas high-frequency stimulation (at rates of 10 Hz or higher) causes an increase in cortical excitability (Pascual-Leone et al. 1994, Rossi et al. 2009). High-frequency, 10 Hz rTMS has been shown to reduce intracortical inhibition, leading to increased cortical excitability and long-term potentiation-like (LTP-like) effects, whereas low-frequency, 1 Hz TMS induces opposing, long-term depression-like (LTD-like) behavior in the cat cortex (Kozyrev et al. 2014). High frequency stimulation is often applied in sequences, where rapid bursts of stimulation are repeated at certain intervals. 10 Hz left DLPFC stimulation is a standard protocol for treatment of major depression (Pallanti et al. 2012).

Previous studies have successfully applied rTMS to the DLPFC to modulate spatial working memory (Pascual-Leone and Hallett 1994, Robertson et al. 2001). Stimulation using bursts of high frequency stimulation repeated at certain intervals (intermittent TBS) of the left – but not the right – DLPFC has been shown to impair planning and set-shifting performance (Ko et al. 2008). Monchi and others (2007) observed greater activation in the left DLPFC in older adults during set-shifting tasks. rTMS has been used to confirm the causal role of the right DLPFC in strategic decision making (van 't Wout et al. 2005). The contributions of right and left DLPFC to cognitive tasks tend to vary (Knoch et al. 2006) due to the functional asymmetry of the prefrontal cortex. Clarifying the neuroanatomical targets of prefrontal rTMS is not only of considerable theoretical interest. It is also of great practical importance, since rTMS is increasingly used as a form of treatment for a wide range of psychiatric and neurological disorders (Lefaucheur et al. 2014). In particular, rTMS with prefrontal coil placement is increasingly used in the treatment of depression (O'Reardon et al. 2007). An improved understanding of the large-scale networks affected by this treatment will contribute to the refinement of the clinical rTMS protocols.

Although direct stimulation of frontal cortical areas by (r)TMS triggers various behavioral effects related to executive functions, the mechanisms underlying such causal manipulation of executive behavior cannot be interpreted exclusively as a spatially circumscribed manifestation of a "virtual lesion". Locally targeted TMS not only changes the functionality of the neural circuits directly under the TMS coil, but also triggers cognitive and behavioral effects employing larger functional systems, evoking activity from the stimulated area to connected neural regions (Ilmoniemi et al. 1997). Instead of causing lesion-resembling impairments, TMS may result in the facilitation of cognitive performance (Cappa et al. 2002). These long-range effects can reach brain locations in distal cortical areas such as parietal and even occipital regions.

Moreover, recent experiments have indicated that TMS targeted at various frontal locations causes impairment of visual perceptual discrimination and metacognitive visual evaluation (Rutiku et al. 2016). This means that frontal TMS is capable of having long-range connectivity based influences on functions based on more caudal parts of the brain and that this type of effects need not be specific to TMS characteristics.

Using rTMS to study the functional contribution of DLPFC to decision making

The present study was designed to explore the involvement of the DLPFC and interconnected cortical systems in two executive functions related decision-making tasks. Our specific aim was study how non-veridical decision making is affected by TMS neuromodulation, in contrast to changes in veridical judgments.

The Cognitive Bias Task (CBT) – a free choice, agent-centered decision making paradigm – was initially designed to study contextual reasoning in patients with frontal lobe lesions, as well as to serve as an activation task in functional neuroimaging. As an experimental paradigm, the CBT allows to examine decision making preferences made in a cognitive task devoid of intrinsically correct or intrinsically false choice (a non-veridical task). A context-independent selection strategy reflects the person's preference to choose according to pre-existing representations without being driven by the specific features of external stimuli. Context-dependent selection strategy, on the other hand, reflects the use of external target as the decision making context. Using fMRI scanning, Vogeley and colleagues (2003) have demonstrated that CBT triggers significant bilateral activations in DLPFC relative to a veridical decision making control task. Right-handed female patients with both left and right frontal lobe lesions demonstrate strong context-dependent reasoning in the cognitive bias task (Goldberg et al. 1994). The baseline CBT score is known to vary to a large extent in healthy, right-handed, female adults (mean CBT=14.9; SD=12.4) (Goldberg et al. 1994, Verdejo-Garcia et al. 2006).

Based on evidence from lesion studies using the CBT paradigm (Goldberg et al. 1994), we hypothesized that the rTMS-induced "virtual lesions" in the DLPFC would replicate the robust cognitive effects of prefrontal lesions on CBT scores evident in clinical studies. Thus, we expected both left and right prefrontal (low-frequency) stimulation to produce a shift toward an extreme context-dependent selection bias relative to the individual baseline CBT score.

We also utilized a high-frequency (intermittent 10 Hz), excitability increasing rTMS protocol to explore potential facilitating effects on task performance, in contrast to inhibitory low-frequency stimulation.

To establish the specificity of rTMS modulation effects to non-veridical decision making, we introduced a veridical, visuospatial working memory task – the Moving Spot Task (MST) – to be used simultaneously with CBT under all conditions serving the function of a control task. In case of significant rTMS induced effects on non-veridical decision making (CBT), the concurrent veridical visuospatial working memory task (MST) would allow to observe whether these effects are specific to non-veridical tasks or more general.

METHOD

Participants

Ten female subjects (mean age=28.3 years; SD=7.5; range 21–47) participated in the experiment (mean years of education=16.6; SD=1.9). All subjects were right-handed without first-degree familial left-handedness and had normal or corrected-to-normal vision. Participants were considered right handed if their individual score on the Briggs and Nebes (1975) handedness questionnaire was 41 or greater, out of a possible 48 (Goldberg et al. 1994, Goldberg and Podell 2000). None of the patients had a history of neurological or psychiatric illness. All subjects were checked for TMS exclusion criteria (Wassermann 1998) and written informed consent was obtained from all participants prior to the experiments. Prior to the study, neuroanatomical MRI scans were acquired for all subjects. The study was approved by the Research Ethics Committee of the University of Tartu and was conducted according to the principles set in the Declaration of Helsinki. Each subjects received 5–8 EUR in compensation for participation.

Cognitive Bias Task

The Cognitive Bias Task (CBT) consists of visual stimuli representing simple geometric figures characterized along five binary qualities: color (red/blue), contour (outlined/filled), number (one/two), shape (circle/square), and size (larger/smaller). Based on the binary dimensions a total of 32 possible geometric designs are available. All geometric designs can be related to each other based on the five binary dimensions (similarity range: 0–5). Each trial consisted of three stimuli (one target card+two selection cards) being presented on the computer screen in a vertical alignment. The target card was presented alone for two seconds, followed by the presentation of two selection cards below it (Fig. 1A).

Subjects were instructed to observe the target card carefully and then to select one of the two selection

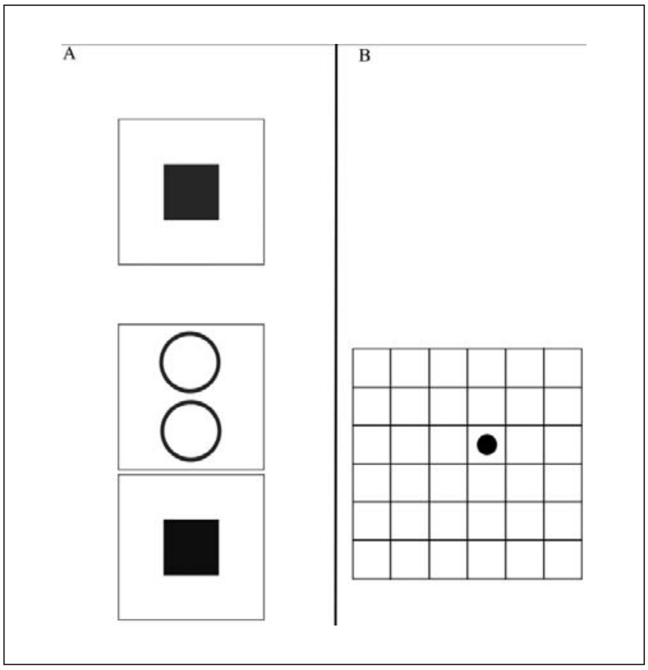

Fig. 1. Experimental tasks used in the experiment. (A) The Cognitive Bias Task related to non-veridical, actor-centered decision making (Goldberg et al. 1994). (B) The Moving Spot Task addressing veridical, visuo-spatial working memory (Attneave and Curlee 1983).

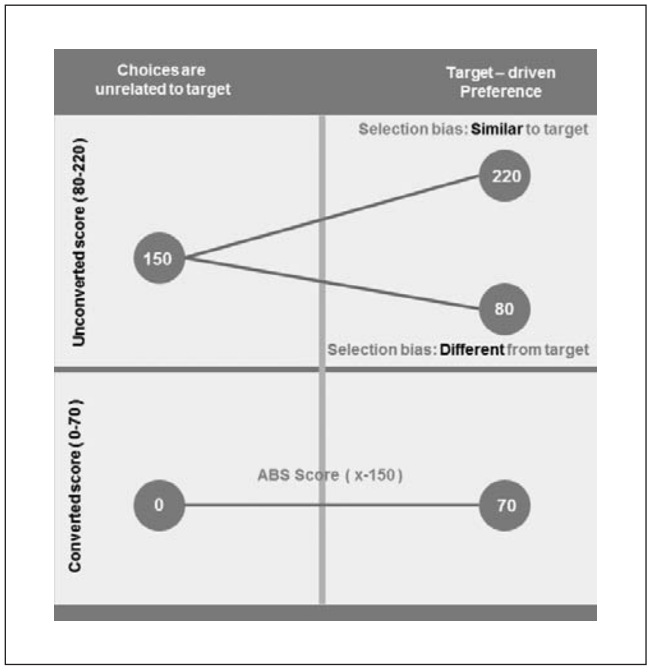

Fig. 2. Scoring of the CBT. The subject is presented with stimuli portraying simple geometric designs characterized along five binary dimensions: color (red/blue), contour (outlined or filled with a homogenous color), number of items (one/two), shape (circle/square), and size (larger/smaller), allowing for a total of 32 possible geometric designs. Any two designs can be compared for the number of concordant dimensions, creating a "similarity range" from 0–5. A similarity index between the subject's choice and the target card (ranging in similarity from 0–5, depending on the overlap of five dimensions) is calculated for each trial. The sum of the similarity indexes across trials provides a CBT unconverted score ranging from 80 to 220, representing the degree of dimensional concordance between the subject's choice relative to the target. A converted CBT score (0–70) is the absolute deviation of the unconverted score from the midpoint (150).

cards. The subject was instructed to pick the card "you liked the best; there is no correct or incorrect choice". Each session comprised of 60 fully counterbalanced trials and the stimuli were presented in such a way that the similarity index (0–5) between the target card and each of the two selection cards was always dissimilar, forcing the subject to make a choice that is either more similar to, or more different from the target. The CBT is structured in a way that the frequency representation of each binary dimension, similarity indices, and the presentation order, are fully counterbalanced. The CBT score is derived by summing up the similarity index between the subject's choice and the target card (range: 0–5) for all trials. The final converted CBT score (see Fig. 2) represents the absolute deviation of the subjects' choices from a score midpoint. A low score (range: 0–70) indicates that the subject shows a context-independent decision-making bias (does not use the target card as context), whereas a high CBT score indicates a context-dependent decision-making bias (consistently chooses similar/different relative to the target, indicating guidance by the properties of the target).

Moving Spot Task

As a measure of visuospatial working memory performance, the Moving Spot Task was employed in this study, corresponding to a concept originally developed by Attneave and Curlee (1983). Subjects are presented with a 6×6 grid of cells and must visualize the step-by-step movements of the spot on an imaginary grid. The subject is instructed to memorize the starting position of the spot and then to close the eyes, prior to listening to a sequence of auditory instructions regarding moves of the spot: "up", "down", "right" or "left", delivered in a quasi-random order with the constraint that a spot must not be moved out of the grid. After a sequence of 10 moves the instructions terminate and the subject is expected to specify the final position the spot has reached in the grid. The method has previously been employed as a visuospatial task, but also for studying interplay between imagery and interfering verbal-propositional codes (Bachmann and Oit 1992) (Fig. 1B).

Both tasks were presented on a computer screen (SUN CM751U monitor, 1024×768 pixels; 100 Hz refresh rate) from a viewing distance of approximately one meter. The task order and stimulation condition sequences (TMS, sham control), and protocols (low *vs.* high-frequency TMS) were fully counterbalanced between subjects.

Procedure

Prior to each experimental block, the subject received low-frequency (1 Hz; 360 pulses in total) or high-frequency (10 Hz; 12 trains of 5 s; 360 pulses in total) rTMS for 6 min to the right or to the left DLPFC, complemented by white noise played through earphones. In addition to rTMS treatments, we applied matching sham stimulation blocks for 6 min to the right or left DLPFC for all stimulation conditions. During sham, rTMS impulses were replaced by frequency matched acoustic signals, which were added to the white noise played through earphones. Sham rTMS was carried out at the same locations on the scalp, the coil being positioned upright on the surface as in real TMS. In total, each subject participated in 5 sessions conducted on separate days. The order of experimental tasks (CBT/MST), stimulation conditions (real/sham), protocols (low/high frequency), and lateralization (left/right DLPFC) was randomized and counterbalanced across subjects to avoid order effects.

TMS

Off-line rTMS was applied prior to experimental tasks, using a Nexstim Navigated Brain Stimulation (Nexstim Ltd., Helsinki, Finland) MRI-assisted system with an 8-shaped coil. White noise was played over earplugs in all conditions. In sham conditions, a TMS-mimicking acoustic clicking sequence was added to the white noise to simulate the coil-generated experience of real TMS. Both real rTMS and sham stimulation was immediately followed by experimental tasks. Stimulation intensity was set to 100% of individual motor threshold (measured as a barely noticeable twitch of the thumb), ranging among subjects between 34 and 45% of maximal stimulator output) following intensity recommendations for prefrontally applied TMS (Kähkönen et al. 2004).

Statistical analysis

The statistical analyzes were carried out with SPSS version 22.0 for Windows (Chicago, SPSS, Inc.). Due to the small sample size and non-normally distributed data with outliers, the assumptions of normality were violated. Thus we report medians and median absolute deviations, using non-parametric methods of analysis instead of parametric ANOVA. Comparisons between different stimulation protocols were performed using the Friedman non-parametric test and the Wilcoxon Signed-rank test as a *post hoc* test. Correlation analysis was performed using Spearman rank correlation.

RESULTS

The median baseline CBT score (19.0) shifted to 8.0 (left rTMS) and 9.5 (right rTMS) following 1 Hz treatment, and to 10.0 (both left and right rTMS) after 10 Hz treatment, suggesting a shift towards a more context independent, less

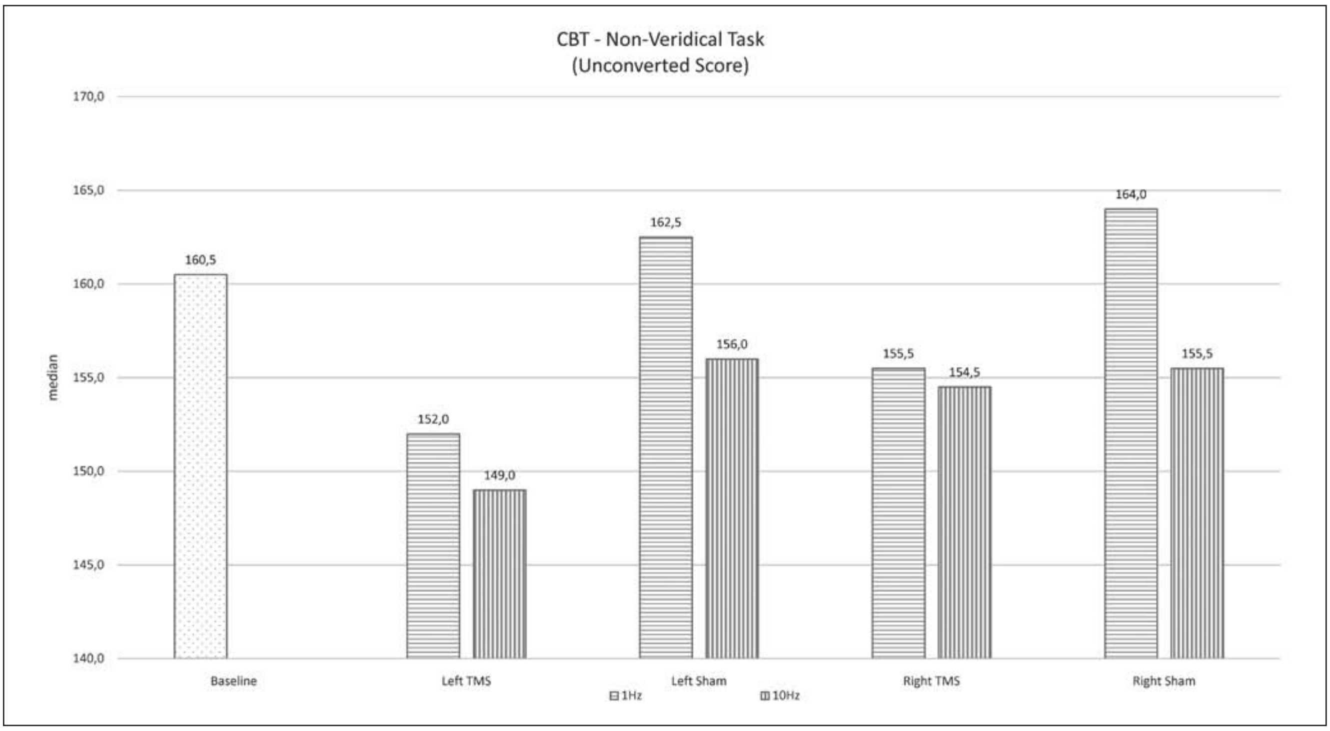

Fig. 3. Comparison of median unconverted scores on the non-veridical task (CBT) for baseline, TMS and Sham treatment conditions.

stimulus-driven decision bias, regardless of the frequency of stimulation.

Considering the scoring algorithm of the CBT test, we first performed an analysis of unconverted CBT scores, which measure directional, quantified changes in subjects' selection bias. The Friedman test results (χ^2_4=10.701; P=0.030) and subsequent *post hoc* Wilcoxon Signed-rank test results indicated significant changes in non-veridical decision-making preferences following treatments:

1) 1 Hz rTMS to the left DLPFC (Z=–2.193; P=0.028);

2) 1 Hz rTMS to the right DLPFC (Z=–2.095; P=0.036); and

3) 10 Hz rTMS to the left DLPFC (Z=–2.041; P=0.041) as indicated by CBT unconverted score changes compared to the baseline condition (Fig. 3).

Converted CBT scores represent the absolute deviation of subjects' choices from a score midpoint. Friedman test results for converted CBT scores indicated a similar shift towards a context independent, less stimulus-driven bias as observed on the unconverted scale, although the differences between the mean ranks of baseline and rTMS converted scores did not reach statistical significance (χ^2_4=1.633; P=0.803) (Fig. 4).

No significant differences from baseline were witnessed following sham treatment on unconverted (χ^2_4=4.569; P=0.334) nor converted (χ^2_4=2.749; P=0.601) CBT scores as indicated by a Friedman test. However, sham treatment triggered shifts from baseline were observed, especially in case of 10 Hz protocols, possibly due to various sensory side effects of the treatment, limiting the blinding success of the sham TMS approach. A comparison of left *vs.* right hemisphere stimulation effects indicated that the left hemisphere was slightly more responsive to DLPFC stimulation (Z=–2.255; P=0.024) than the right (Z=–2.045; P=0.041). In both hemispheres, stimulation triggered a shift of the selection bias in the same direction.

There were no overall statistically significant differences in visuospatial working memory performance (see Fig. 5) following rTMS (χ^2_4=4.211; P=0.378) or sham (χ^2_4=4.442; P=0.349) treatments as indicated by a Friedman test. A pairwise comparison indicated that 1 Hz right DLPFC rTMS stimulation elicited a statistically significant improvement in MST performance (Z=–2.018; P=0.044) compared to baseline. Spearman's rank-order correlation analysis did not yield any statistically significant relationships between CBT, MST, or reaction time measures.

DISCUSSION

We aimed to address the question whether non--veridical and veridical decision making are based on similar or different underlying mechanisms of action, thus responding differently to prefrontal stimulation with TMS.

In right-handed females, prefrontal lesions of both the left and right hemispheres are associated with an extremely context-dependent selection bias on the non-veridical task (Goldberg et al. 1994). By contrast, a decrease in CBT median scores – observed following both 1 Hz and 10 Hz active

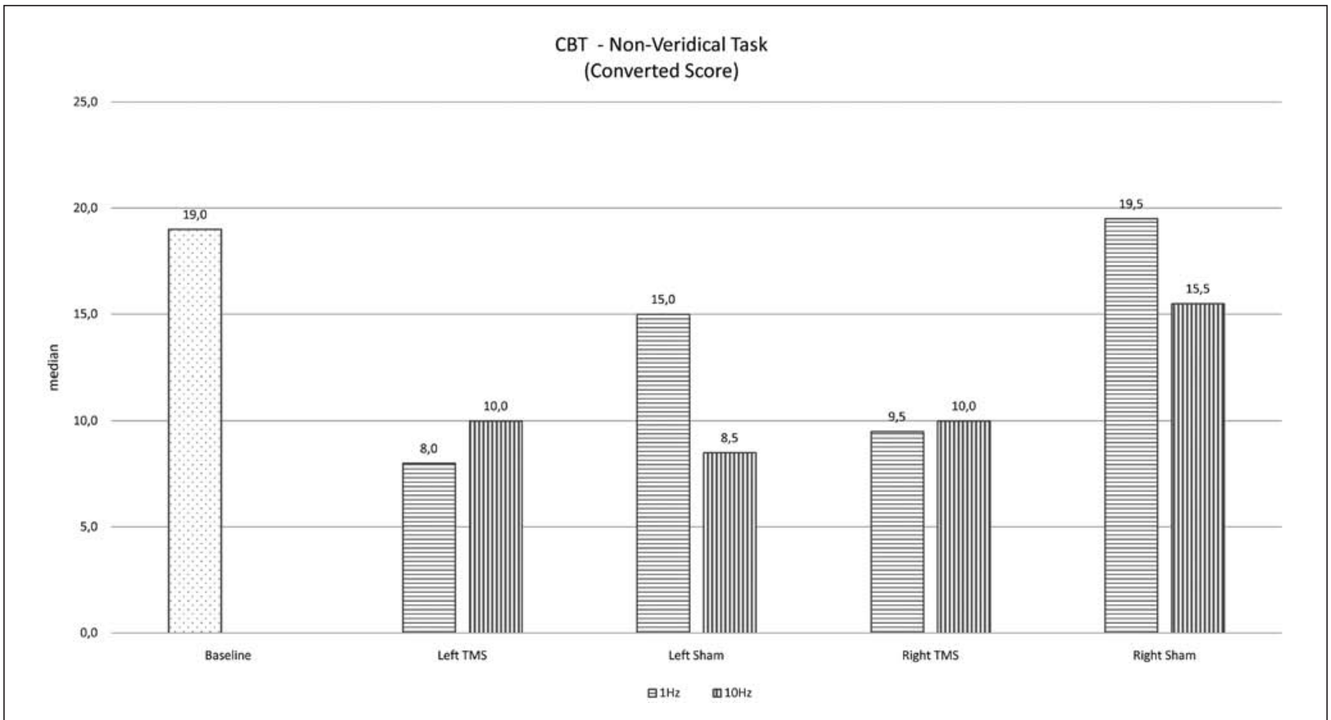

Fig. 4. Comparison of median converted scores on the non-veridical task (CBT) for baseline, TMS and Sham treatment conditions.

rTMS treatments in the current study – indicates a notable shift in the decision bias towards context independent, less stimulus-driven choices. This contradicts findings from lesion studies since a shift towards context-independence is considered characteristic of posterior lesions rather than frontal lesions.

The apparent contradiction between the lesion and rTMS results suggests that the effects of focal rTMS application in our study are not limited to areas immediately under the coil, but involve distal, interconnected regions. This explanation is made particularly plausible since direct connectivity exists between the cortical regions at the site of rTMS application and those where the changes following such application could be demonstrated. Indeed, the rTMS effects documented in our study are similar to the effects of lesions in the parietal cortices (Goldberg et al. 1994). These cortices receive input from the superior longitudinal fasciculi originating in DLPFC. Furthermore, the treatment effect was more pronounced in the left than right hemisphere, which is consistent with the lateralized parietal lesion effects (Goldberg et al. 1994). As dorsolateral prefrontal and posterior parietal regions are part of the large-scale Central Executive Network known to activate together (Toro et al. 2008), this lends additional support to the "distal rTMS effect" explanation of our findings. A recent study showed that frontal TMS caused impairments in visual- and meta-cognitive performance mediated by electrophysiologically non-specific neuromodulatory top-down activity (Rutiku et al. 2016), suggesting that different types of TMS-perturbations of frontal cortex may evoke a process that is non-specific in terms of excitatory-inhibitory volleys, but specific in terms of the effects depending on which ones of the more caudally located neural circuits become affected by these non-specific bioelectrical processes. The similarity of effects triggered by 1 Hz and 10 Hz stimulation protocols is surprising, since low-frequency stimulation (1 Hz) is expected to result in inhibitory, whereas high-frequency (10 Hz) stimulation in facilitating effects on cortical excitability.

Our findings suggest that both 1 Hz and 10 Hz stimulation of the left and right DLPFC may trigger posterior lesion-mimicking effects in decision making in the healthy brain by exerting suppressing effects on the parietal lobes. These effects are likely caused by neuromodulatory changes in distal interconnected regions following prefrontal stimulation. Distal effects of DLPFC stimulation were reported by Woźniak-Kwaśniewska and others (2013), who found that both 1 Hz and intermittent 10 Hz rTMS to the left and right DLPFC for 15 min resulted in EEG changes not only in the ipsilateral and contralateral DPLFC, but also in parietal and temporal regions in low EEG frequencies.

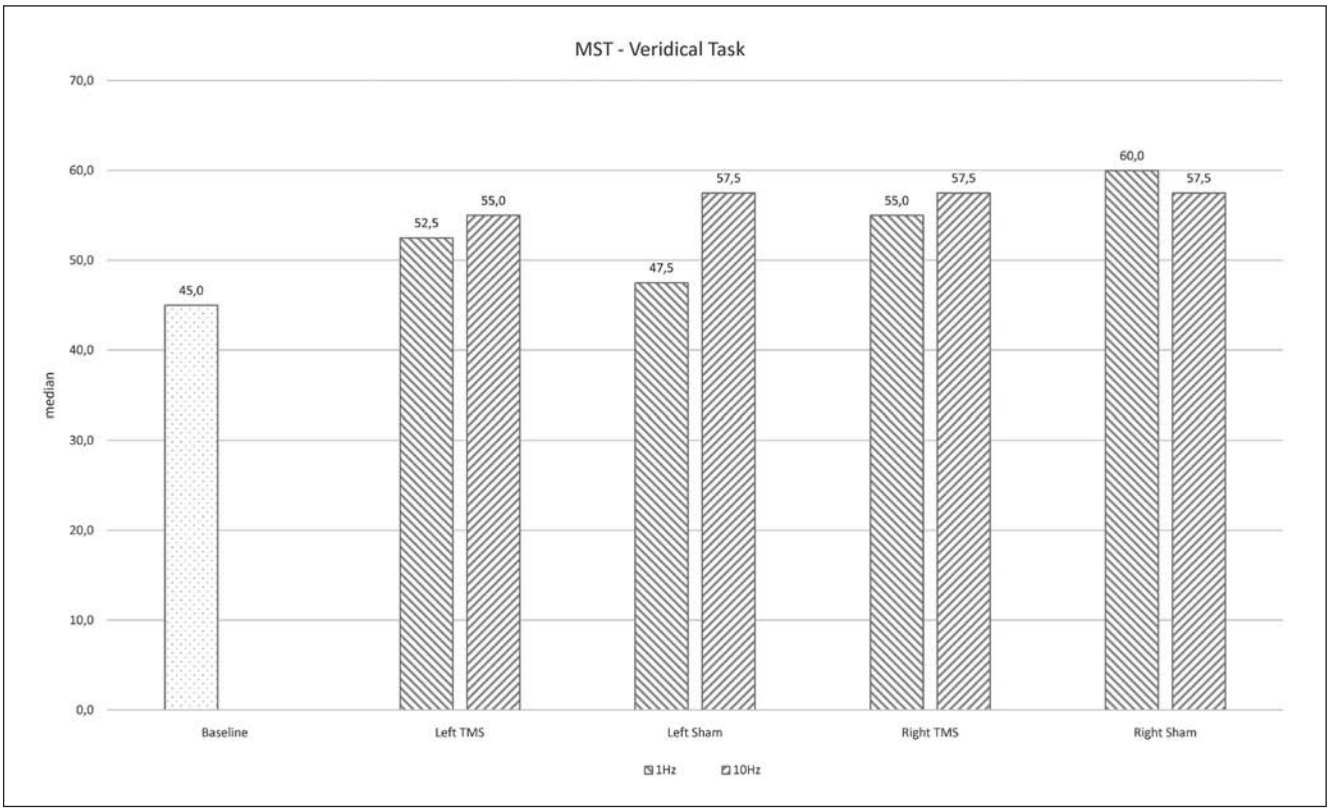

Fig. 5. Median score changes on the veridical task related to visuospatial working memory (MST) for baseline, TMS and Sham treatment conditions.

Activity in low frequency bands (delta and theta) is generally associated with cortical inhibition. Single-pulse stimulation of the left DLPFC has been shown to activate the site of stimulation, then propagate to the contralateral DLPFC and finally activate the posterior cortical region at (ca 120 ms after the pulse), triggering oscillatory patterns in the delta (0–4 Hz) and theta (4–8 kHz) frequency range mainly (Chung et al. 2015). Reductions of activation in the temporal lobes have similarly been shown after 20 min low-frequency stimulation of the left DLPFC, affecting off-line resting-state brain activation over long-range functional connectivity (van der Werf et al. 2010). Thus, DLPFC stimulation may increase or decrease cortical excitability in distal brain regions via ipsilateral cortico-cortical association fibers, transcallosal pathways, or possibly even cortico-subcortical pathways affecting non-veridical decision making reflected in CBT score changes.

The effects of right and left frontal stimulation were similar, as suggested by previous findings from lesion studies conducted on female subjects using CBT. Only low-frequency stimulation of the right DLPFC resulted in significant changes in both, non-veridical decision making and visuospatial working memory performance. These results imply that there is a shared demand for right DLPFC resources by both cognitive domains related to executive functions: non-veridical decision making as well as visuospatial working-memory performance. In contrast, the observed impact of left rTMS on non-veridical decision-making, but not veridical visuospatial performance may suggest that the left prefrontal areas are dedicated more specifically to non-veridical tasks. The results are supportive of the BAS/BIS comparative theory (Carver and White 1994) according to which left-hemisphere frontal areas are involved in approach behavior and disinhibition while right-hemisphere frontal areas are involved in impulse control and behavioral inhibition. Non-veridical decision making assumes less restricted and unregulated cognitive functioning related to personal initiative and therefore must be relatively more related to left-hemisphere functions. Significant improvement on the veridical task following right, but not left frontal stimulation, may also imply that left DLPFC activity modulation was more efficient at blocking learning gains reflected in performance. On the whole, the rTMS effects were more significant for the non-veridical than veridical task, further highlighting the differences in their respective neural mechanisms.

It is likely that the length of rTMS stimulation (6 min) was insufficient to induce the expected inhibitory or excitatory changes in the underlying cortex. Although similar protocols have successfully been used before to trigger neuromodulatory changes (e.g. Fitzgerald et al. 2006), the repetition of the study with longer rTMS sequences may bring about more robust effects. Since educational level may have an effect on decision making (Evans et al. 2004), the current sample may be biased by the relatively high educational level of subjects (mean years of education=16.6; SD=1.9).

CONCLUSION

Our experimental results combined with their theoretical analysis showed that the long-range neuromodulatory rTMS effect can be specific to the type of task, but non-specific to the rTMS protocol. The results of our study highlight the importance of considering distal effects of focal neuromodulatory interventions both in research involving healthy subjects and in clinical interventions in patients. The latter consideration is particularly important in light of an increasing use of rTMS and other forms of neuromodulation in the treatment of a wide range of neuropsychiatric and neurological disorders. The possibility of non-focal, distal effects of focally applied neuromodulation is increased when it is applied to particularly richly interconnected cortical regions, such as DLPFC.

ACKNOWLEDGEMENT

Research reported in this paper was supported by the Estonian Science Foundation (grant SF0180027s12).

REFERENCES

Aihara M, Aoyagi K, Goldberg E, Nakazawa S (2003) Age shifts frontal cortical control in a cognitive bias task from right to left: part I. Neuropsychological study. Brain Dev 25(8): 555–559.

Anderson SW, Damasio H, Jones RD, Tranel D (1991) Wisconsin Card Sorting Test performance as a measure of frontal lobe damage. J Clin Exp Neuropsychol 13(6): 909–922.

Attneave F, Curlee TE (1983) Locational representation in imagery: a moving spot task. J Exp Psychol Hum Percept Perform 9(1): 20.

Bachmann T, Oit M (1992) Stroop-like interference in chess players' imagery: An unexplored possibility to be revealed by the adapted moving-spot task. Psychol Res 54(1): 27–31.

Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50(1): 7–15.

Bechara A, Tranel D, Damasio H (2000) Characterization of the decision--making deficit of patients with ventromedial prefrontal cortex lesions. Brain 123(11): 2189–2202.

Briggs GG, Nebes RD (1975) Patterns of hand preference in a student population. Cortex 11(3): 230–238.

Camus M, Halelamien N, Plassmann H, Shimojo S, O'Doherty J, Camerer C, Rangel A (2009) Repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex decreases valuations during food choices. Eur J Neurosci 30(10): 1980–1988.

Cappa SF, Sandrini M, Rossini PM, Sosta K, Miniussi C (2002) The role of the left frontal lobe in action naming: rTMS evidence. Neurology 59: 720–723.

Carver CS, White TL (1994) Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. J Pers Soc Psychol 67(2): 319.

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG (1997) Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 48(5): 1398–1403.

Chung SW, Rogasch NC, Hoy KE, Fitzgerald PB (2015) Measuring Brain Stimulation Induced Changes in Cortical Properties Using TMS-EEG. Brain Stimul 8(6): 1010–1020.

Drewe EA (1974) The effect of type and area of brain lesion on Wisconsin card sorting test performance. Cortex 10(2): 159–170.

Evans CE, Kemish K, Turnbull, OH (2004) Paradoxical effects of education on the Iowa Gambling Task. Brain Cogn 54(3): 240–244.

Fellows LK (2004) The cognitive neuroscience of human decision making: a review and conceptual framework. Behav Cogn Neurosci Rev 3(3): 159–172.

Fitzgerald PB, Fountain S, Daskalakis ZJ (2006) A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol 117(12): 2584–2596.

Goldberg E, Harner R, Lovell M, Podell K, Riggio S (1994) Cognitive bias, functional cortical geometry, and the frontal lobes: laterality, sex, and handedness. J Cogn Neurosci 6(3): 276–296.

Goldberg E, Podell K (2000) Adaptive decision making, ecological validity, and the frontal lobes. J Clin Exp Neuropsychol 22(1): 56–68.

Greve KW, Love JM, Sherwin E, Mathias CW, Ramzinski P, Levy J (2002) Wisconsin Card Sorting Test in chronic severe traumatic brain injury: factor structure and performance subgroups. Brain Inj 16(1): 29–40.

Hare TA, Camerer CF, Rangel A (2009) Self-control in decision-making involves modulation of the vmPFC valuation system. Science 324: 646–648.

Hutcherson CA, Plassmann H, Gross JJ, Rangel A (2012) Cognitive regulation during decision making shifts behavioral control between ventromedial and dorsolateral prefrontal value systems. J Neurosci 32(39): 13543–13554.

Ilmoniemi RJ, Virtanen J, Ruohonen J, Karhu J, Aronen HJ, Näätänen R, Katila T (1997) Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. Neuroreport 8: 3537–3540.

Johnson SC, Schmitz TW, Kawahara-Baccus TN, Rowley HA, Alexander AL, Lee J, Davidson RJ (2005) The cerebral response during subjective choice with and without self-reference. J Cogn Neurosci 17(12): 1897–1906.

Karton I, Bachmann T (2011) Effect of prefrontal transcranial magnetic stimulation on spontaneous truth-telling. Behav Brain Res 225(1): 209–214.

Knoch D, Gianotti LR, 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. J Neurosci 26(24): 6469–6472.

Ko JH, Monchi O, Ptito A, Bloomfield P, Houle S, Strafella AP (2008) Theta burst stimulation-induced inhibition of dorsolateral prefrontal cortex reveals hemispheric asymmetry in striatal dopamine release during a set-shifting task: a TMS-[11C]raclopride PET study. Eur J Neurosci 28(10): 2147–2155.

Kozyrev V, Eysel UT, Jancke D (2014) Voltage-sensitive dye imaging of transcranial magnetic stimulation-induced intracortical dynamics. Proc Natl Acad Sci U S A 111(37): 13553–13558.

Krawczyk DC (2002) Contributions of the prefrontal cortex to the neural basis of human decision making. Neurosci Biobehav Rev 26(6): 631–664.

Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, Devanne H, Di Lazzaro V, Filipović SR, Hummel FC, Jääskeläinen SK, Kimiskidis VK, Koch G, Langguth B, Nyffeler T, Oliviero A, Padberg F, Poulet E, Rossi S, Rossini PM, Rothwell JC, Schönfeldt-Lecuona C, Siebner HR, Slotema CW, Stagg CJ, Valls-Sole J, Ziemann U, Paulus W, Garcia-Larrea L (2014) Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 125(11): 2150–2206.

Levy R, Goldman-Rakic PS (2000) Segregation of working memory functions within the dorsolateral prefrontal cortex. In: Executive control and the frontal lobe: Current issues. Springer Berlin Heidelberg, Germany, p. 23–32.

Lezak MD, Howieson DB, Loring DW, Hannay HJ, Fischer JS (2004) Neuropsychological assessment (Lezak MD Ed.). Oxford University Press, New York, USA.

Liu P, Jin F, Zhang X, Su Y, Wang M (2011) Research on the multi-attribute decision-making under risk with interval probability based on prospect theory and the uncertain linguistic variables. Knowledge-Based Systems 24(4): 554–561.

Miller EK (2000) The prefontral cortex and cognitive control. Nature Rev Neurosc 1(1): 59–65.

Monchi O, Petrides M, Mejia-Constain B, Strafella AP (2007) Cortical activity in Parkinson's disease during executive processing depends on striatal involvement. Brain 130(1): 233–244.

Nelson HE (1976) A modified card sorting test sensitive to frontal lobe defects. Cortex 12(4): 313–324.

O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, McDonald WM, Avery D, Fitzgerald PB, Loo C, Demitrack MA, George MS, Sackeim HA (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 62: 1208–1216.

Pallanti S, Di Rollo A, Antonini S, Cauli G, Hollander E, Quercioli L (2012) Low-frequency rTMS over right dorsolateral prefrontal cortex in the treatment of resistant depression: cognitive improvement is independent from clinical response, resting motor threshold is related to clinical response. Neuropsychobiology 65(4): 227–235.

Pascual-Leone A, Hallett M (1994) Induction of errors in a delayed response task by repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex. Neuroreport 5(18): 2517–2520.

Pascual-Leone A, Valls-Solé J, Wassermann EM, Hallett M (1994) Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 117(4): 847–858.

Postle BR, Zarahn E, D'Esposito M (2000) Using event-related fMRI to assess delay-period activity during performance of spatial and nonspatial working memory tasks. Brain Res Brain Res Protoc 5(1): 57–66.

Robertson EM, Tormos JM, Maeda F, Pascual-Leone A (2001) The role of the dorsolateral prefrontal cortex during sequence learning is specific for spatial information. Cereb Cortex 11(7): 628–635.

Romero JR, Anschel D, Sparing R, Gangitano M, Pascual-Leone A (2002) Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. Clin Neurophysiol 113(1): 101–107.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120(12): 2008–2039.

Rowe JB, Toni I, Josephs O, Frackowiak RS, Passingham RE (2000) The prefrontal cortex: response selection or maintenance within working memory? Science 288(5471): 1656–1660.

Ruff CC, Driver J, Bestmann S (2009) Combining TMS and fMRI: from 'virtual lesions' to functional-network accounts of cognition. Cortex 45(9): 1043–1049.

Rutiku R, Tulver K, Aru J, Bachmann T (2016). Visual masking with frontally applied pre-stimulus TMS and its subject-specific neural correlates. Brain Res 1642(2016): 136–145.

Silvanto J, Pascual-Leone A (2008) State-dependency of transcranial magnetic stimulation. Brain Topogr 21(1): 1–10.

Toro R, Fox PT, Paus T (2008) Functional coactivation map of the human brain. Cereb Cortex 18(11): 2553–2559.

van der Werf YD, Sanz-Arigita EJ, Menning S, van den Heuvel OA (2010) Modulating spontaneous brain activity using repetitive transcranial magnetic stimulation. BMC Neurosci 11(1): 145.

van 't Wout M, Kahn RS, Sanfey AG, Aleman A (2005) Repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex affects strategic decision-making. Neuroreport 16(16): 1849–1852.

Verdejo-Garcia A, Vilar-LoPez R, Pérez-Garcķa M, Podell K, Goldberg E (2006) Altered adaptive but not veridical decision-making in substance dependent individuals. J Int Neuropsychol Soc 12(01): 90–99.

Vogeley K, Podell K, Kukolja J (2003) Recruitment of the left prefrontal cortex in preference-based decisions in males (fMRI study). In: Annual Meeting of the Human Brain Mapping Organization. New York, NY, USA.

Volle E, Kinkingnéhun S, Pochon JB, Mondon K, de Schotten MT, Seassau M, Levy R (2008) The functional architecture of the left posterior and lateral prefrontal cortex in humans. Cereb Cortex 18(10): 2460–2469.

Wassermann EM (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 108(1): 1–16.

Woźniak-Kwaśniewska A, Szekely D, Aussedat P, Bougerol T, David O (2013) Changes of oscillatory brain activity induced by repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in healthy subjects. Neuroimage 88: 91–99.

Yu JA (2014) Decision-Making Tasks. In: Encyclopedia of Computational Neuroscience. Springer, New York, USA, p. 1–8.