

Assessment of memory and executive function in major neuropsychiatric disorders using eye-tracking and neuromodulation

Summary of Ph.D. thesis

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Original research articles related to the thesis

- I. Németh VL**, Csete G, Drótos G, Greminger N, Janka Z, Vécsei L, Must A.

The effect of emotion and reward contingencies on relational memory in major depression: an eye-movement study with follow-up.

Front Psychol. 2016 Nov;7:1849. doi: 10.3389/fpsyg.2016.01849.

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- II. Németh VL**, Kurgis E, Csifcsák G, Maráz A, Almási DA, Drótos G, Szikszay P, Andó B, Janka Z, Must A.

The impact of intermediate-term alcohol abstinence on memory retrieval and suppression. Front Psychol. 2014 Dec;5:1396. doi: 10.3389/fpsyg.2014.01396.

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Review articles related to the thesis

- I. Nemeth VL**, Must A, Horváth S, Király A, Kincses ZT, Vécsei L.

Gender-specific degeneration of dementia-related subcortical structures throughout the lifespan.

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- II. Németh VL**, Csifcsák G, Kincses ZT, Janka Z, Must A.

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- III. Must A, Horváth S, Németh VL**, Janka Z.

The Iowa Gambling Task in depression – what have we learned about sub-optimal decision-making strategies?

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I. Introduction

Alcohol dependence (AD) and major depression (MD) are global health issues in society worldwide. According to a recent study assessing 17 European countries, the highest rate of death caused by alcohol-related diseases was measured in Hungary. Regarding major depression, the World Health Organization (WHO) has ranked it the 4th leading cause of disability to work, and predicts it to become the 2nd by 2020. AD and MD both exert a severe burden not only for the patients, but for their families and relatives as well, significantly deteriorating the quality of their lives. Though the background and characteristics of these major psychiatric disorders have been assessed for decades in order to aim more specific and effective interventions, the number of patients and the extent of negative consequences related to these diseases indicate that they still remain a crucial issue. Our aim was to assess cognitive components of AD and MD which are supposed to influence the success of treatment and the rate of relapses. These cognitive domains include executive functions, e. g. decision-making, cognitive control and inhibition, and memory functions, especially associative memory. We also aimed to establish a neuromodulation protocol to try and understand more thoroughly cognitive deficits in MD.

The main goals of our studies were the following:

- I. To assess the inhibition of control in intermediate-term abstinent AD patients by evaluating their ability to suppress retrieval over episodic memory associations.
- II. To evaluate associative memory and decision-making of patients with MD using an eye-tracking paradigm involving emotional and reward contingencies.
- III. To examine the immediate effect of a specific pattern of transcranial magnetic stimulation (TMS) on cognition in healthy individuals in

order to establish a paradigm using TMS to improve symptoms of depression and certain cognitive deficits in patients with MD.

II. Associative memory and inhibition of recollection in alcohol dependence

II. 1. Background

Chronic alcohol consumption can cause metabolic and structural damage to several brain areas, among which the mediotemporal structures including the hippocampus and prefrontal areas are the most vulnerable. Related to the functional deficit of these areas, patients with AD demonstrate a cognitive deficit characteristic of the disease. A variety of cognitive functions are affected in AD, including selective attention, working memory, learning, cognitive flexibility, control of impulsivity, episodic memory, and executive functions including planning, problem-solving and decision-making. However, several studies confirmed the improvement of neurocognitive functions in AD after a certain period of abstinence.

Deficits of episodic memory in AD were reported in several earlier studies. The level of the deficit is supposed to correlate with the extent of hippocampal atrophy. However, episodic memory deficits show improvement in intermediate-term abstinence and can even return to normal level. The impairment of episodic memory in AD is linked to a reduced ability to learn and memorize new and complex pieces of information. Episodic memory requires binding of an item to a particular context. This aspect of memory is most directly assessed with tests of associative or relational memory, during which previously unrelated items are to be memorized in pairs.

Another core feature of AD is the deficit of inhibitory control, which forms one of the main components of executive functions. Related to the reduced functioning of inhibitory control functions, a number of studies confirmed the elevated level of impulsivity in AD. Control of inhibition is considered a top-down

process, in the regulation of which striatal and ventral tegmental areas play an essential role along with noradrenergic, dopaminergic and serotonergic pathways connected to the prefrontal areas.

One option to investigate inhibition of retrieval is the Think/No-think (TNT) paradigm designed by Anderson and Green. The task involves learning of cue-target stimuli pairs thus activating associative memory processes. Stimuli pairs are studied up to a defined accuracy level to ensure proper encoding in the medial temporal lobe including the hippocampus. After successfully building associative memory, some pairings are trained further to improve subsequent retrieval, some are instructed to be intentionally forgotten, while the remaining items will serve as baseline memory. Reductions from baseline memory for “to be forgotten” associations suggest that cognitive control actually reduces accuracy and depletes memory processes.

Our main hypotheses were the following:

H1: Intermediate-term abstinent AD patients present difficulties in inhibition over retrieval measured with the Think/No-think paradigm and may have difficulties in learning and memorizing the pairings.

H2: AD patients’ performance on the TNT task is influenced by their higher level of impulsivity and affective symptoms.

II.2. Presentation of the study

In this study 36 AD patients were recruited from the Hospital of Szigetvár, Szigetvár, Hungary and 36 healthy control (HC) participants. Participants were asked to complete a TNT task for the assessment of associative memory and inhibition of retrieval. The experimental paradigm included three major phases: (1) Initial training block participants viewed 30 image–word pairs. Training blocks were repeated until the participant succeeded to correctly identify at least 24 (i.e., 80% of the 30 pairs). (2) Think/No-think phase: Following completion of training

all stimulus pairings were randomly classified into three groups (Baseline, Think, and No-think). Subsequently, the cue item was presented only and participants were instructed either to recall, i.e., “think” (with the appearing picture surrounded by a green frame) or suppress, i.e., “not think” of the target stimulus previously paired with the cue (where the picture was framed with red color). (3) Final test: All 30 stimulus pairings were presented and the participant was instructed to recall the missing pair of the cue stimulus.

All participants were assessed using the Hungarian version of the National Adult Reading Test (NART) constructed to predict premorbid IQ measures. Alcohol Use Disorders Identification Test (AUDIT) was used for alcohol consumption-related variables, the Beck Depression Inventory (BDI) to quantify depressive symptoms, the Derogatis’ Symptom Checklist-90 (SCL-90) to evaluate clinical symptoms referring to psychological distress. The Delayed Discounting Task (DDT) and the Barratt Impulsiveness Scale (BIS) were completed to objectively measure the level of impulsivity.

We found a significantly different pattern of performance for AD and HC when assessing the effect of inhibition on retrieval. We found a significant main effect of group (HC vs. AD) \times condition (Think, No-Think, and Baseline) [$F(1.568, 108.198) = 5.408, p \leq 0.01$]. We also found a significant difference for No-Think - Baseline reflecting the ability to suppress No-think items compared to baseline items [$F(1, 70) = 6.400, p \leq 0.01$]. The two groups did not differ significantly in their baseline memory ability as well as effect of practice on retrieval. We found a significant difference between AD and HC groups when comparing the number of block repetitions during the training phase. AD patients had an increased demand for training in order to reach the same levels of accuracy as the control group [$U(72) = 518.15, p < 0.05$].

Several clinical symptom measures correlated with performance achieved on the TNT task. Measures of Delayed Discounting Task correlated negatively with the number of correctly recalled words in the training phase [DDT: $R(36) = -$

0.405, $p \leq 0.05$]. We found a negative correlation between depression and anxiety symptom severity, as well as level of symptomatic distress and the No-Think score [BDI: $R(36) = -0.343$, $p \leq 0.05$; SCL-90 depression index: $R(36) = -0.465$, $p \leq 0.01$; SCL-90 anxiety index: $R(36) = -0.445$, $p \leq 0.01$].

II.3. Discussion of the results

Our results provide novel evidence for the consequences of intermediate-term alcohol abstinence on memory retrieval and suppression. To the best of our knowledge, this was the first study to apply the TNT paradigm in AD to directly compare episodic memory performance and inhibition of retrieval. In accordance with our hypothesis, our current results demonstrated that there was no significant difference in baseline memory abilities between the two groups. However, it has to be noted that AD patients had a significantly higher demand for training in order to reach the same levels of accuracy as seen in the control group. The instruction to focus on retrieval improved episodic memory performance in both groups with no essential difference. Crucially, the instruction to try and suppress retrieval of NT items resulted in a significantly different pattern for the AD and HC group. Healthy control participants were able to suppress the previously related words in the NT condition supporting the critical effect of cognitive control processes over inhibition of retrieval.

Previous studies have confirmed that episodic memory performance can normalize over an approximately 6-month period of sustained abstinence. Our current findings are in accordance with the notion that deficits of episodic memory might either be mild or even improve in the course of abstinence in AD. Neuroimaging studies support the role of the mediofrontal gyrus (MFG) in inhibitory modulation of the hippocampus presuming that successful cognitive control over memory retrieval and cued recall is associated with an inhibitory effect of the MFG on the hippocampus. However, the assessment of inhibitory control mechanisms in AD still needs further exploration.

The close relationship between AD and mood disorders has been studied extensively and firmly established. Findings report a high level of comorbidity between AD and depression or anxiety. Notably, remitted or current AD represents a significantly increased risk for chronically persisting depressive and/or anxiety disorders. Anxiety in early abstinence was found to represent a great risk for relapse. Our current findings support the idea of a relevant effect of anxiodepressive symptoms on inhibitory control in intermediate-term alcohol abstinence. Thus, different mechanisms might be involved and alternative aspects might have to be considered for depression and/or anxiety in AD as compared to anxiety and depression alone.

III. The effect of reward contingencies and emotional valence on associative memory in major depression

III.1. Background

Primarily considered and classified as a mood disorder, changes in emotion are universally recognized as being inherent to major depression (MD). However, the cognitive impairment has become a relevant dimension of most psychiatric disorders, an aspect seriously affecting real-world functioning. Cognitive deficits have widely been reported in MD, e.g. working memory, mood-congruent memory deficit, and executive dysfunction. The severity of the cognitive deficit may change in remission, though some evidence contradicts it. The focus of our study was the assessment of associative or relational memory and the influence of reward contingencies and emotional information on it using an eye-tracking paradigm. Related to these processes, the role of mediotemporal structures, the limbic system and prefrontal brain regions is essential. Smaller hippocampal volumes and metabolic changes in MD have been specifically related to episodic memory dysfunction. Research evidence reported mild to moderate episodic

memory impairments in MD even proposing episodic memory performance as a potential pre-morbid marker of depression.

Patients suffering from MD might also exhibit disadvantageous behavioral responses to reward or loss/punishment. It is presumed that depressed patients are unable to modulate their behavior as a result of reward because of decreased dopaminergic signaling. Impairment in reward learning ability and in the modulation of behavior as a function of reward increases the risk for MD to persist.

Eye-movements are able to capture immediate access to stored information and may detect memory traces that do not even reach conscious stages, thus rapidly guiding to successful memory performance. The most commonly assessed eye-movements in MD are saccadic eye-movements and fixations. In MD psychomotor alterations have been detected regarding reaction time in prosaccade and anti-saccade tasks. Several previous studies have reported emotional memory alterations in MD and related affective disorders hypothesising that depression is associated with prolonged attention toward negative information. Importantly, eye-movements might serve as biomarkers to distinguish depressed and control participants and also to differentiate between unipolar and bipolar depression.

We established the following hypotheses:

- H1: MD patients show lower level of performance on an associative memory task measured explicitly and via eye-movements, with their performance improving after a 6 months' period of time.
- H2: MD patients present an altered pattern of fixation duration compared to HCs influenced by emotional valence and reward contingencies, showing a mood-congruent bias.
- H3: The associative memory performance measured explicitly and implicitly correlates with the severity of depressive symptoms.

III.2. Presentation of the study

28 patients from the Department of Psychiatry, University of Szeged, Hungary and 30 healthy controls (HC) were recruited in our study. The follow-up measurement took place approximately 6 months after baseline and only the patients were retested.

All participants completed an associative memory task. The task was built of two major parts: (1) during the three consecutive training phases participants were asked to memorize 36 pairs of backgrounds and facial emotional expressions (happy/sad/neutral). After each pair a virtual monetary reward or loss appeared briefly, with no associated instruction provided. (2) During testing 12 background scenes were presented serving as the cue. Subsequently three faces of different emotions appeared overlaid on the background. Half (six trials) of the test trials contained the face previously paired with the cue (Match trials). For Non-match trials (six trials) none of the three faces was associated with the scene during training. Participants were asked to try and recall the matching face and keep viewing it („implicit testing”). Explicit (behavioral) testing of relational memory by forced-choice recognition followed, where participants were instructed to press a button each rendered to the position of the face, or another button if neither face matched the scene. During the follow-up measurements, testing was performed using the same experimental paradigm entailing training, implicit and explicit memory examination.

Clinical symptoms were assessed using semi-structured interviews and self-report questionnaires. The Hamilton Depression Rating Scale (HDRS) was used to evaluate the severity of depression. The shortened version of Beck Hopelessness Scale symptoms was applied to assess feelings of hopelessness. The Hypomania Checklist (HCL-32) was administered as a screening tool to exclude hypomania or mania. National Adult Reading Test (NART) was applied to estimate premorbid IQ.

On the explicit memory task MD patients performed on a significantly lower level compared to healthy control (HCs) ($p \leq 0.001$). We found MD patients to fixate for a significantly shorter duration on correct faces during Match trials ($t = 4.711, p \leq 0.001$) as compared to the HC group. The two different approaches to measure associative memory performance correlated with each other ($R = 0.586, p \leq 0.003$). We found a significant interaction of group (MD vs. HC) by associative memory condition (Match and Non-match) by facial emotion (happy, sad, and neutral) and by monetary reward and loss ($F_{2,76} = 3.131, p \leq 0.049$). In the Match condition, the MD group viewed faces associated with monetary reward for a significantly longer duration than the HC group ($t_{48} = 2.501, p = 0.016$). However, patients fixated on the sad match faces associated with monetary reward for a significantly shorter duration than the HC group ($t_{48} = -3.637, p \leq 0.001$).

During baseline testing performance on both explicit and implicit memory testing correlated negatively with depressive symptom severity as measured by clinical rating scales (explicit measure: HDRS: $R = -0.501, p \leq 0.001$, Beck: $R = -0.505, p \leq 0.001$, implicit measure: HDRS: $R = -0.311, p \leq 0.022$, Beck: $R = -0.280, p \leq 0.040$).

In follow-up testing, explicit memory performance of the MD group did not improve significantly, despite the fact that depressive symptom severity reduced significantly based on HDRS compared to baseline ($t = 4.082, p \leq 0.004$). We found that fixation duration on rewarded faces in Match trials at baseline correlated negatively with symptom severity at follow-up based on total HDRS scores ($R = -0.399, p \leq 0.016$).

III.3. Discussion of the results

In accordance with our hypothesis MD patients showed an associative memory impairment detected during a recall phase, as revealed by abnormal eye-movement behavior and a deficit in explicit recognition. Episodic memory requires binding of an item to a particular context. This aspect of memory can be

assessed with tests of associative or relational memory, during which previously unrelated items are to be memorized in pairs. In MD episodic memory performance can be a potential pre-morbid marker of depression, which makes it a specially relevant issue. Here our purpose was to investigate relational memory performance in MD as indicated by eye-movements associated with explicit recognition measures. We used an approach found to be sensitive to relational memory deficits in patients with amnesia due to medial temporal lobe damage as well as schizophrenia.

We found a significant effect of facial emotion and virtual reward or loss on relational memory performance. This adds to the evidence that emotional processing is altered in MD and that difficulties may occur in modulation of responses related to reward contingencies. We hypothesized that a difference in interaction of these effects in the MD and HC group would presume the possibility of an alternate neuronal processing of the effects of facial emotion and virtual monetary reward or loss on relational recall. Surprisingly, we found MD patients to fixate on stimuli associated with virtual monetary reward for a longer duration and the effect of emotional type also proved relevant. We found that fixation duration on sad faces previously associated with monetary reward was significantly decreased during Match conditions for the MD group. This suggests an emotional bias interacting with the implied viewing preference for rewarded stimuli that potentially affects relational recall. In contrast to our hypothesis, we did not find a mood-congruent effect in the recollection phase. This seeming contradiction might be explained by individual variations in neuronal activation patterns, genetic variations, or by the enhancing effect of antidepressive on positive information processing.

A number of functional neuroimaging studies have emphasized the role of an emotional or motivational pathway impairment in the dysfunctional reward-related processing in MD, with the fronto-striatal circuit presumed to be involved. It has even been suggested that a disruption of this widely distributed network

associated with a disturbance of the reward circuitry might serve as a biomarker for depression. The fronto-limbic network and specifically amygdala is also known to be affected in MD. The dysfunction of these areas in episodic memory formation has been proposed as a neurocognitive trait or vulnerability factor for depression.

We did not detect any significant follow-up effects, the associative memory deficit persisted inspite of the reduction of depressive symptoms. It is in accordance with previous research findings which suggested that a distinct pattern of cognitive impairment involving memory aspects persists beside antidepressive medication.

IV. Short-term effect of transcranial magnetic stimulation on cognition in healthy participants

IV.1. Background

A recently emerging treatment option aiming to reduce depressive symptoms is the use of non-invasive brain stimulation methods. One of these methods is transcranial magnetic stimulation (TMS), a method working via the principle of electromagnetic induction. Repetitive transcranial magnetic stimulation is able to modulate the cortical excitability of a specific brain region, with the effect of TMS via GABAergic systems being presumed as an underlying mechanism.

The method of TMS has been proven to be effective in reducing depressive symptoms, though the rate of responders still shows a relatively high interpersonal variability. Several neuroimaging studies have reported increased neuronal activity of the right DLPFC and a decrease in left DLPFC function in MD. Thus, the most commonly investigated protocols aiming to reduce depressive symptoms involve the application of facilitating high-frequency rTMS over the

left DLPFC or the use of low-frequency TMS over the right DLPFC, or a bilateral stimulation combining these two.

A specialized pattern of repetitive TMS (rTMS) is theta-burst stimulation (TBS). Basically, two major patterns of TBS can be distinguished: the intermittent TBS (iTBS) and the continuous TBS (cTBS). Similarly to high and low frequency rTMS, these two subfacets of TBS seem to have reverse effects on cortical excitability: iTBS having a facilitating, while cTBS exerting inhibitory effect in the stimulated brain region.

Traditional rTMS or TBS can be used not only for modulating mood. Several studies have issued short-term or long-term effects of TMS on cognition. The most commonly targeted DLPFC contributes to memory processes and executive functioning apart from emotional regulation. Previous studies have revealed that a single session of high-frequency rTMS or iTBS can improve aspects of cognition in healthy participants for a certain period of time, especially attention, working memory, and even more complex control functions. In contrast, cTBS over DLPFC might elicit a temporary deterioration in these functions in the healthy. Left and right DLPFC might have different roles in these processes; though the exact lateralization effect of the stimulation shows contradictory results.

Our aim was to assess short-term effects of TBS on working memory, control of attention and saccadic eye-movements in healthy participants.

Our hypothesis was that healthy participants present enhanced working memory, saccade/antisaccade performance and conflict monitoring after a single session of iTBS, and impaired performance in these tasks after receiving a session of cTBS over their DLPFC.

IV.2. Presentation of the study

Thirty-six healthy participants were recruited in the study. The study consisted of four sessions: (1) cranial MRI for neuronavigation (2) motor threshold

measurement and administration of the safety questionnaire as part of the safety protocol, (3) completion of cognitive tests before and after 600 impulses of TBS, (4) session 4 was identical to session 3 except for the site of stimulation. One participant received either iTBS or cTBS during both session 3 and 4. The stimulated area was the left or right DLPFC. Stimulation was completed on a low intensity, which did not exceed 30 % of the maximum potential intensity.

Among the cognitive tests n-back task involves working memory and also the ability to maintain and manipulate pieces of information. In our study it consisted of three difficulty levels: 1-back, 2-back and 3-back. During the task, capital letter stimuli were presented serially on the screen. Participants were instructed to press the target key if they saw the letter that appeared one (1-back), two (2-back) or three letters (3-back) earlier. For evaluating the performance we used the d' value interpreted in the framework of the signal detection theory.

The Attention Network Test (ANT) operationalizes three relatively independent attentional networks: the alerting network, orienting network, and the executive control network. Regarding our hypothesis, our focus was assessing the executive control network, which is responsible for selective control and conflict monitoring. During the task, one or five arrows pointing leftwards or rightwards were presented either above or below a fixation cross. The participant's task was to respond by pressing the matching key according to the direction of the central arrow (left or right). Three conditions can be distinguished based on target stimuli: congruent (all arrows pointing in the same direction as the central target arrow), incongruent (the arrows pointing in the opposite direction as the target arrow), and neutral (no distracting arrows). The incongruent condition reflecting conflict effect is associated with longer reaction times.

The third task was a saccade/antisaccade task. After a fixation cross appeared in the center of the screen, a cross appeared either in the center, on the left or on the right side of the screen (at a 45° visual angle peripherally). There

were three conditions: cue stimuli either served as control, saccadic or anti-saccadic cues. In case of the control stimuli (blue dot), the participant's task was to fixate on the center of the screen without any voluntary eye movements (control condition). When the pro-saccadic cue was presented (green or red dot), the task was to look directly at the appearing cross (pro-saccadic condition). When the anti-saccadic appeared in the center of the screen (red or green), the subjects were asked to try and fixate in the opposite direction horizontally without looking at the cross (anti-saccadic condition).

In results of the n-back task there was a significant interaction between time of measurement (pre- or post-stimulation) and cognitive load (i.e. level of difficulty) ($F_{(2,33)} = 5.015$, $p < 0.013$), with significantly higher discriminability after stimulation in the two-back ($p < 0.032$) and three-back condition ($p < 0.021$). Another significant interaction between time of measurement, cognitive load and type of stimulation was found ($F_{(2,33)} = 3.864$, $p < 0.031$). Post-hoc analysis revealed that d' increased only in the iTBS group at two-back ($p < 0.001$) and three-back level ($p < 0.005$), but not for one-back ($p > 0.343$).

We found no effect of either type of stimulation on overall accuracy or on overall reaction time across participants in the ANT. According to our hypothesis, regarding Conflict effect in ANT, a significant interaction of time of measurement and stimulation type was revealed based on the original and corrected computations as well ($F_{(1,33)} = 5.240$, $p < 0.029$). Post-hoc analysis revealed that stimulating the right DLPFC resulted in a significant interaction of time of measurement and stimulation type (original: $F_{(1,33)} = 6.766$, $p < 0.014$, corrected: ($F_{(1,33)} = 5.465$, $p < 0.026$).

We investigated the effect of iTBS and cTBS on the performance of the saccade/antisaccade task and found a significant main effect of type of saccade (prosaccade or antisaccade) in the percentage of errors ($F_{(1,22)} = 4.521$, $p < 0.001$), with higher rate of errors in the antisaccade condition compared to the prosaccade condition ($p < 0.001$). A significant interaction of time of measurement and

stimulation type was revealed in the percentage of errors in the prosaccade condition only when stimulating the right DLPFC ($F_{(1,21)} = 4.521$, $p < 0.045$), but not the left DLPFC ($p > 0.05$). Intermittent TBS resulted in a lower rate of errors in the prosaccade task, while cTBS led to a higher rate of errors.

IV.3. Discussion of the results

We aimed to assess the acute effects of iTBS and cTBS applied at a low intensity over the left or right DLPFC on complex working memory, the executive component of attentional networks, and eye-movements including prosaccades and antisaccades. To our best knowledge, this is the first study to assess TBS effects on cognition at such a low intensity.

Our hypothesis was partly confirmed as we found the facilitating effect of iTBS on performance of the n-back task assessing complex working memory. This effect was independent of the stimulated hemisphere. No significant effect of cTBS was demonstrated with the n-back task. Previous research reported the deteriorating effect of cTBS on working memory; however, more evidence points towards the facilitating effect of iTBS on it. We found a significant influence of iTBS on the 2-back and 3-back conditions of the n-back task, which represent a higher cognitive demand. Presumably, the 1-back condition is not sensitive enough to detect differences in healthy participants when applying TBS.

DLPFC plays a crucial role not only in working memory processes via the episodic buffer, but also in the regulation of eye-movements. While we recognize the complexity of these attentional networks, here we focused on the executive control of attention based on our hypotheses. We found that iTBS and cTBS had an opposite influence on conflict effect both based on the original and the corrected calculation, but only when stimulating the right DLPFC with cTBS deteriorating conflict detection causing longer reaction times for incongruent stimuli, and iTBS resulting in an improvement reflected by shorter RTs. The importance of the right

prefrontal and parietal brain areas are well known in attentional control functions. Assessing saccadic eye-movements, iTBS and cTBS had significant and opposite effects on errors in prosaccades, with iTBS improving and cTBS disrupting the performance of healthy participants. This effect was found only when stimulating the right DLPFC. We presume that the lateralization effect of stimulation is explained by the neuronal network involved in attention control. In contrast to our hypothesis, no measurable effect of either stimulation could be detected on the performance of antisaccades. The low level of intensity used by us might have been insufficient to elicit a significant effect in antisaccade performance.

V. Summary of the results

- Supporting our hypothesis, AD patients were not able to suppress No-think items during recollection compared to healthy participants.
- As expected, AD patients had a significantly increased demand for training in order to reach the same levels of accuracy as the control group.
- The level of depressive and anxiety symptoms influenced negatively the patients' performance on the Think/No-think task as expected.
- MD patients could recall fewer items correctly in the associative memory test measured explicitly and also via eye-movements, supporting our hypothesis. However, their memory performance did not improve significantly during the follow-up phase.
- In accordance with our hypotheses, MD patients presented an altered pattern of fixation duration compared to HCs influenced by emotional valence and reward contingencies.
- Patients did not show a mood-congruent bias as we hypothesized; in the Match condition, the MD group viewed faces associated with monetary reward for a significantly longer duration, and they fixated on the sad match faces

associated with monetary reward for a significantly shorter duration than the HC group.

- In healthy participants, 600 impulses of iTBS performed over the DLPFC could exert a facilitating effect on complex working memory independently of the stimulated site.
- Stimulation of the right DLPFC with iTBS and cTBS exerted an opposite effect on conflict detection and performance in the prosaccade condition, with iTBS improving them, and cTBS deteriorating them temporarily.

VI. Brief summary

To sum up, a series of questions concerning the exact nature and underlying neuronal correlates of inhibitory control processes in AD along the process of abstinence still remain. However, by a thorough exploration of how current clinical signs affect executive cognitive control processes in the daily life of patients, caregivers might be able to target more specific therapeutic interventions. Above this, the ability to exert control over intrusive memories of potentially appealing cues might be of crucial importance in the long-term process of sustained abstinence.

Therapeutic implications involving crucial cognitive aspects of major depression might consider emphasizing the role of reward contingencies related to the affective etiology of MD. Eye tracking might yield new insights into the assessment of cognitive function in MD. Eye-tracking variables like errors in prosaccade tasks may serve as a biomarker in the assessment of major depression.

Neuromodulational technics like TMS can serve as a potential tool to reduce affective symptoms and the extent of cognitive deficit not only in major depression. TMS is a widely assessed method mainly involving depressed patients, but the treatment of AD patients via neuromodulation have also gained attention and might be a promising tool in maintaining abstinence.

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