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

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II. Németh VL, Kurgyis E, Csifcsák G, Maráz A, Almási DA, Drótos G, Szikszay P, Andó B, Janka Z, Must A.
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Gender-specific degeneration of dementia-related subcortical structures throughout the lifespan.
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III. Must A, Horváth S, **Németh VL**, Janka Z.
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Ven N, **Németh VL**, Csifcsák G, Harsányi SzG.
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Table of content

I. ABBREVIATIONS

AA	Alcoholics Anonymous
ACC	anterior cingulate cortex
AD	alcohol dependence
AMT	active motor threshold
APA	American Psychiatric Association
ANT	Attention Network Test
AUDIT	Alcohol Use Disorders Identification Test
B	Baseline
BA	Broadmann
BDI	Beck Depession Inventory
BIS	Barratt's Impulsivity Scale
cTBS	contiuous theta burst stimulation
DDT	Delayed Discount Task
DLPFC	dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	electroencephalography
ERP	event related potential
FEF	frontal eye-field
fMRI	functional magnetic resonance imaging
GABA	Gamma Amino Butyric Acid
HC	healthy control
HCL-32	Hypomania Checklist
HDRS	Hamilton Depression Rating Scale
iTBS	intermittent theta burst stimulation
LPFC	lateral prefrontal cortex
M	mean
MD	major depression
MFG	middle frontal gyrus
MRI	magnetic resonance imaging
MST	medial superior temporal area
MTL	medial temporal lobe
NART	National Adult Readint Test
NT	No-think
PEF	parietal eye-field
PFC	prefrontal cortex
RMT	resting motor threshold
SCID	Structural Clinical Interview for DMS disorders
SCL-90	Symptom Checklist-90
SD	standard deviation
SE	standard error
SEF	supplementary eye-field
T	Think
TBS	theta burst stimulation
TMS	transcranial magnetic stimulation
TNT	Think/No-think
VLPFC	ventrolateral prefrontal cortex
VTA	ventral tegmental area
WHO	World Health Organization
WM	Working memory

II. SCOPE AND AIM OF THIS WORK

Alcohol dependence (AD) and major depression (MD) are global health issues in society worldwide, particularly in some Northern and Eastern European countries. According to a recent retrospective study assessing 17 European countries, the highest rate of death caused by alcohol-related diseases was measured in Hungary. Regarding major depression, WHO ranked it the 4th leading cause of disability to work, and predicts it to become the 2nd by 2020 (Kessler and Bromet, 2013; Murray and Lopez, 1996). AD and MD both exert a severe burden not only for the patients, but for their families and relatives as well, significantly deterioirating 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.

III. BACKGROUND

1. Cognitive deficit in AD

Negative consequences of chronic alcohol comsumption have been an issue of interest for decades (Fitzhugh et al., 1960). If it reaches a certain level of severity, it can lead to alcohol dependence, which is a mental disorder defined by the APA in DSM-IV (APA, 2000). Based on a number of earlier studies, prolonged alcohol comsumption can cause damage not only to several organs of the cardiovascular system or the liver, but also to the brain (Charness, 1993; Pfefferbaum et al., 1995). Chronic alcohol consumption can result in the atrophy of neurons and the shrinkage of the brain (Hunt and Nixon, 1993). Additionally, it can alter the action of neurotransmitters, e. g. that of glutamate and GABA (Oscar-Berman et al., 1997). Crucially, there are certain brain areas which are more vulnerable to chronic alcohol comsumption. These areas include the limbic system (including the amygdala and especially the hippocampus), the diencepalon (including the hypothalamus and the thalamus), the cerebellum, and the cerebral cortex, especially the prefrontal cortex (Oscar-Berman et al., 1997). Lesions in these areas can be connected to the impairment of several cognitive functions.

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 (Fernandez-Serrano et al., 2010; Fernandez-Serrano et al., 2011). Deficits in these domains can significantly deteriorate the patient's performance at work, and their social and family relationships as well. Crucially, these deficits can prevent patients from sustaining abstinence. However, several studies confirmed the improvement of neurocognitive functions in AD after a certain period of abstinence (Claiborn and Greene, 1981; Fein et al., 1990; Kish et al., 1980). Findings indicates a remarkable improvement in most neurocognitive domains following several months of sustained abstinence (Fein et al., 2006; Munro et al., 2000; Sullivan et al., 2000). The course of improvement in cognitive functioning over the different phases of abstinence is summarized in Table 1. It needs to be emphasized that the severity of the deficit in certain cognitive functions such as decision-making and inhibition can influence the ability to maintain abstinence (Ando et al., 2012).

Affected cognitive domains	Short-term abstinence (48 hours - 1 month)	Intermediate-term abstinence (1-6 months)	Long-term abstinence (>6 months)
Decision-making	✓	✓	✓
Non-verbal short-term memory	✓	✓	✓
Visuospacial skills	✓	✓	✓
Cognitive flexibility	✓	✓	✓
Verbal learning skill	✓	✓	x
Verbal short-term memory	✓	✓	x
Semantic memory	✓	✓	x
Control of impulsivity	✓	✓	x
Planning	✓	x	x
Abstract thinking	✓	x	x
Fluency	✓	x	x
Working memory	✓	x	x
Episodic memory	✓	x	x

Table 1 – Cognitive deficits across different phases of abstinence (Fein et al., 1990; Fein et al., 2006; Fernandez-Serrano et al., 2010; Fernandez-Serrano et al., 2011).

As mentioned above, the media-temporal lobe (MTL) including the hippocampus is a brain area highly susceptible to chronic alcohol consumption. In accordance with this, deficits of learning and memory are considered to to be major issues within cognitive impariment in AD patients (Fein et al., 1990; Munro et al., 2000). An early study demonstrated that independently of the participants' age, AD patients showed lower performance in almost every task demanding verbal learning (Ryan and Butters, 1980). However, age can be a crucial factor during recovering from AD, according to Munro et al (2000) older AD patients show slower recovery pattern during abstinence, especially in cognitive functions closely related to hippocampus, e. g. episodic memory.

1.1 Episodic memory deficit in AD

Deficits of episodic memory in AD were reported in several earlier studies (Parker et al., 1974; Parker et al., 1976). Episodic memory includes encoding, storing and retrieving information and events associated with personal experience embedded into a specific context of space and time. This system enables a person to consciously recollect events from the past (Wheeler et al., 1997), and also includes autonoetic awareness allowing the person to mentally relive the past (Tulving, 2001). The impairment of episodic memory in AD is linked to reduced ability to learn and memorize new and complex pieces of information (Pitel et al., 2007a). Additionally, episodic memory impairment and deficits of working memory influence

procedural learning in short-term abstinence (Pitel et al., 2007b). The level of the deficit is supposed to correlate with the extent of hippocampal atrophy (Pitel et al., 2007a). However, episodic memory deficits parallel with other cognitive domains e. g. executive functions show improvement in intermediate-term abstinence and can even return to normal level (Pitel et al., 2009). Mattyassy et al. (2012) found that intermedie-term abstinent AD patients did not differ from healthy participants in learning fish-face associations; however, patients demonstrated an impaired performance during the transfer phase, when they had to generalize the learnt associations.

Studies investigating episodic memory in AD and confirming deficits used Weschler Memory Scale (Fama et al., 2004; Glenn and Parsons, 1992; Goldstein et al., 2004), learning name-face pairings (Beatty et al., 1995; Tivis et al., 1995), or word lists (Sherer et al., 1992). Though these results refer to a significant impairment in episodic memory in AD, the specific characteristics of the deficit still need to be clarified (e. g. the processes of encoding and retrieval). Some previous studies demonstrated a deficit in retrieval in AD (Weingartner et al., 1996; Zinn et al., 2004), especially during tasks when executive control is demanded on a higher level, e. g. during free recall (Weingartner et al., 1996). Controversially, preserved retrieval of information has also been found (Nixon et al., 1998).

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 (Pitel et al., 2012). During testing, a cue item is presented and the participant is instructed to recall the pair of that item. In AD several brain areas are affected taking part in the process of relational memory: the MTL, notably the hippocampus in connection with episodic memory (Dickerson and Eichenbaum, 2010), the prefrontal cortex (Fletcher and Henson, 2001) including the ventrolateral prefrontal cortex (VLPFC) being responsible for the selection of relevant stimuli, and the dorsolateral prefrontal cortex (DLPFC) taking part in forming associations among the active elements of memory, contributing to building long-term memory (Blumenfeld and Ranganath, 2006).

1.2 Impulsivity and inhibitory control deficit in AD

Another core feature of AD is the deficit of inhibitory control (Lawrence et al., 2009a; Lawrence et al., 2009b; Noel et al., 2013). Control of inhibition forms one of the three main components of executive functions (shifting, inhibition and updating) based on (Miyake et al., 2000). Dalley et al. (2011) described response inhibition as a top-down process involving the prefrontal cortex, the orbitofrontal cortex, subregions of the nucleus accumbens, limbic

structures, the anterior cingulate cortex and also the hippocampus. This top-down process may occur either directly or in an indirect way via cascade mechanisms of the striato-ventral tegmental area (VTA)-striatal circuitry (Haber et al., 2000). Evidence from previous studies support this form of top-down control over the striatal mechanisms: Pezze et al. (2009) found that elevated impulsive responding enhanced by medial PFC areas is attenuated by D2/3 receptor antagonist sulpiride infusion introduced into intra-accumbens regions. The regulation of inhibitory control mechanisms is modulated via the noradrenergic pathways of the locus coeruleus, dopaminergic pathways deriving from the midbrain, and serotonin systems of the dorsal raphe nucleus.

In addition to inhibitory control deficit, the relation of impaired response inhibition and impulsivity has been addressed in several studies (Bari and Robbins, 2013; Dalley et al., 2011; Logan et al., 1997). Impulsivity is considered to be the result of insufficient inhibitory control (Bari and Robbins, 2013), with the level of impulsivity showing correlation with the extent of response inhibition deficit (Enticott et al., 2006). A number of previous studies pointed out that patients with AD show a higher level of impulsivity as compared to healthy individuals ((Dick et al., 2010; Lawrence et al., 2009a; Lawrence et al., 2009b). In AD, the drinking behavior is composed of basically two cognitive systems confronting each other: a bottom-up impulsive process causing the urge to drink and a top-down reflexive process trying to limit alcohol intake by exerting executive control (Bernardin et al., 2014). The bottom-up component is considered to play a major role in automatic behavioral patterns and is based on implicit associational memory connecting incentive cue ingers to drinking behavior involving dopaminerg pathways of the amygdala-striatal circuit. The top-down reflective system works via executive functions to overcome the impulsive bottom-up system, related to elevated activity in several frontal regions, the striatum and the insula. As mentioned above, chronic excessive alcohol consumption also deteriorates these frontal cortical areas and networks (Lawrence et al., 2009a; Lawrence et al., 2009b). The control deficit related to the damage of these areas and connections may lead to increased level of impulsivity (Crews and Boettiger, 2009). According to Crews and Boettiger (2009), sustained abstinence may exert its beneficial effect via the improvement of executive functions and the decrease of impulsivity. Therefore, reducing the level of impulsivity might have a major role in relapse prevention.

However, the level of impulsivity and the severity of inhibitory control deficit show a relatively great extent of intrapersonal variability in AD patients (Dick et al., 2010). One of the potential influencing factors is genetic predisposition. Previous studied assessing first-level relatives of AD patients revealed that non-alcohol-addicted first-level relatives presented a

significantly higher level of impulsivity based on behavioral measurements compared to healthy control subjects, indicating that alcohol addiction may be related to an impulsivity endophenotype. The heterogeneity of measured impulsivity may also derive from the method of measurement (i. e. behavioural or questionnaire testing), which raises the possibility that impulsivity is composed of several subfacets, with certain studies reporting correlatetion between them, whereas others show little correlation (Dick et al., 2010). Regarding the interpersonal heterogeneity of inhibitory control in AD. Oberauer (2009) separates two relatively distinct components of inhibitory control: overcoming dominant, prepotent response and repressing proactive interference from the memory. Previous research focused predominantly on the control exerted over prepotent, but irrelevant or inappropriate responses. However, much less is known about relevant aspects of cognitive control suppressing interference from memory.

One option to investigate inhibition of retrieval is the Think/No-think (TNT) paradigm designed by Anderson and Green (Anderson and Green, 2001). The TNT 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 (Depue and Banich, 2012). 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 (Depue and Banich, 2012; Depue et al., 2007). The research group of Depue pointed out that memories with emotional content are suppressed via two steps of neural mechanism differentiated in time (2007). First, mainly through the right inferior frontal gyrus an initial suppression occurs over areas related to sensory elements of memory representation (e.g. visual cortical areas, thalamus). Consecutively, the right medial frontal gyrus exerts control over areas of emotional and multimodal elements of memory representation (e.g. hippocampus, amygdala). All of the above regions are mediated by fronto-polar areas. These results elicit the process of memory suppression and the role of prefrontal regions in its control.

2. Cognitive deficit in major depression

Primarily considered and classified as a mood disorder, changes in emotion are universally recognized as being inherent to MD (APA, 2013). However, the way we feel and the way we process these emotions greatly interacts with cognitive aspects, i.e., the way we

perceive and know the world around us (Dolcos et al., 2011). Research in the past few decades has focused on the significant impairment in cognitive function in MD patients. It is now becoming evident, that cognitive disturbances are not merely a consequence of symptoms of affect (Hammar and Ardal, 2009). Moreover, the cognitive impairment has become a relevant dimension of most psychiatric disorders, an aspect seriously affecting real-world functioning (Millan et al., 2012). Cognitive deficits have widely been reported in MD, e.g., working memory and decision-making impairment in unmedicated MD patients, executive dysfunction in young adults with MD (Castaneda et al., 2008; Taylor Tavares et al., 2007). Various aspects of cognitive disturbance have been reported in the acute phase of the illness, e.g., executive dysfunction, including updating, shifting and inhibition processes (Harvey et al., 2004; Rogers et al., 2004). Cognitive deficits, e.g., mood-congruent memory retrieval impairment, has also been described in untreated, mild depression (Li et al., 2016b). Findings also indicate that an improvement in the cognitive status is not always in accordance with the remission of a depressive episode (Kennedy et al., 2007). Nevertheless, the cognitive deficit plays a crucial role in functional recovery from depression, whereas a persistent cognitive impairment might be an important factor associated with long-lasting disability in everyday functioning (Jaeger et al., 2006).

2.1 Memory disturbances in MD

Among the various cognitive aspects associated with MD, memory disturbances have gained growing interest. Based on the emerging evidence of smaller hippocampal volumes, MD has become a potential risk factor for poor clinical outcome and consequent Alzheimer's disease (MacQueen and Frodl, 2011). The smaller hippocampal volumes and metabolic changes in MD have been specifically related to episodic memory dysfunction (Mervaala et al., 2000), since episodic memory mechanisms are believed to be supported by the hippocampus (Althoff and Cohen, 1999; Bird and Burgess, 2008; Cohen and Eichenbaum, 1993; Eichenbaum et al., 1994; Konkel and Cohen, 2009). As mentioned above, 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. Research evidence reported mild to moderate episodic memory impairments in MD even proposing episodic memory performance as a potential pre-morbid marker of depression (Airaksinen et al., 2004; Airaksinen et al., 2007). Strikingly, the remission of depressive symptoms was typically not accompanied by improved episodic memory performance (Airaksinen et al., 2006; Bierman et al., 2005). Evidence has been reported that patients with MD have increased difficulty to exclude negative information – even

if irrelevant – while performing a memory task (Levens and Gotlib, 2009). Complementary, the recall of positive or rewarding information is also impaired (Brittlebank et al., 1993; Levens and Gotlib, 2009). A recent study by Wimmer and Shohamy (2012) has extended the role of the hippocampus beyond its role in associative memory formation to the ability to transfer and spread value between items. It has been suggested that the hippocampus contributes to an automatic assessment of value and to decision-making processes not necessarily driven by conscious awareness.

2.2 Reward processing in MD

Patients suffering from MD might exhibit disadvantageous behavioral responses to reward or loss/punishment (Eshel and Roiser, 2010; Must et al., 2013; Must et al., 2006). However, MD patients were found to be influenced by immediate large reward in a decision-making task, with reward having a greater influence on related response patterns (Must et al., 2006). More depressive symptoms have been related to perseveration in selecting options that led to overall gains (Byrne et al., 2016).

However, it is crucial to point out that the processing of reward is not a homogenous construct; it involves different aspects like motivation, pleasure, satiety, and the salience or anticipation of the stimuli (Whitton et al., 2015). In MD, decreased processing of incentive salience, motivation and reinforcement-based learning can be detected. This might result in dysfunction of reward-related decison-making and in attention allocation towards reward-related stimuli. Impairment in reward learning ability and in the modulation of behavior as a function of reward increases the risk for MD to persist after 8 weeks of adequate treatment (Pizzagalli et al., 2008; Vrieze et al., 2013), and can predict the recurrence of depressive episodes even when administering antidepressive therapy (Pechtel et al., 2013). This decreased reward responsiveness can be revealed also in healthy individuals, if phasic dopaminerg signaling is suppressed with the help of medication. It is presumed that depressed patients are unable to modulate their behavior as a result of reward because of decreased dopaminergic signaling (Whitton et al., 2015). Mesocortical limbic pathways (including dorsal and ventral striatal areas) play a crucial role in reinforcement-based learning, which is presumed to be impaired in MD. During reward anticipation reduced level of activation can be detected in the putamen, nucleus accumbens and in the anterior cingulate. In association with the impairment in these areas, patients with MD also tend to exert lower level of physical effort in order to achieve a larger reward (Treadway and Zald, 2011). In addition, decreased activation in the ventral striatal area is considered a risk factor for MD.

These results indicate that reward might have a more complex and implicit effect on cognitive function and modulating behavior in MD.

2.3 Eye-tracking in MD

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 (Althoff and Cohen, 1999; Hannula and Ranganath, 2009; Hannula et al., 2007). Above this, eye-movements might be able to add insight into processes found to be altered when investigating reaction time differences in the context of emotional stimuli in MD (Naudin et al., 2014). To assess cognitive processess in major depression, a variety of eye-tracking paradigms can be used, most commonly prosaccade or antisaccade tasks, free viewing tasks, and visual searching tasks, in parallel with assessing pupil dilation (Carvalho et al., 2015).

Several types of eye-movements can be distinguished, such as saccadic eye-movements, smooth pursuit eye-movements, vergence eye-movements or vestibulo-ocular eye-movements (Purves et al., 2001). The most commonly assessed eye-movements in MD are saccadic eye-movements and fixations. TMS and neuroimaging studies have demonstrated that the brain network contributing to adequate eye-movements includes the frontal eye-field (FEF), parietal eye-field (PEF), supplementary eye-field (SEF), prefrontal eye-field (SEF) in the DLPFC, medial superior temporal area (MST), and the precuneal region (Pierrot-Deseilligny et al., 2004). These areas have rich neural connections to other parts of the brain, such as the cerebellum, the brainstem, the oculomotor system, and the thalamus. Eye-fields participate not only in eye-movements but also in decision-making processes, modulation of attention or memory (Pierrot-Deseilligny et al., 2004).

Considering saccadic eye movements, intentional saccades and antisaccades need to be defined. An intentional saccade or voluntary prosaccade refers to perfoming a quick, saccadic eye-movement purpousfully (also referred to as prosaccades), while antisaccades are eye-movements carried out when the instruction is to look into the opposite direction of a suddenly appearing stimulus. In MD psychomotor alterations have been detected regarding reaction time in prosaccade and anti-saccade tasks (Carvalho et al., 2015). Several previous studies have reported emotinal memory alterations in MD and related affective disorders hypothesising that depression is associated with prolonged attention toward negative information. Certain eye-tracking studies have also found that dysphoric participants showed a significantly greater bias to maintain gaze longer on negative pictures compared to control pictures, without evidence for an initial shift of orienting towards negative cues (e.g. (Caseras et al., 2007). However, results

are still somewhat contradictory related to remitted patients. Some studies report a persisting attentional bias to sad faces in remitted MD (Soltani et al., 2015), while others found no significant difference as compared to healthy controls regarding sad faces, but a decreased attentional bias toward happy faces (Li et al., 2016a). In addtion, it is important to note that age can also modify mood-related eye-movement patterns of patients with MD (Carvalho et al., 2015).

Overall, eye movement analysis has been proposed as a promising new avenue in MD. They might serve as biomarkers to distinguish depressed and control participants and also to differentiate between unipolar and bipolar depression (Carvalho et al., 2015).

3. Transcranial magnetic stimulation in MD

3.1 Background mechanisms of TMS

A recently emerging treatment option aiming to reduce depressive symptoms is the use of non-invasive brain stimulation methods (for a review, see Nemeth et al., 2016). One of these methods is transcranial magnetic stimulation (TMS), working via the principle of electromagnetic induction (George and Belmaker, 2000). The device consists of an electric coil placed tangentially over the scalp above the brain area to be stimulated, and a condensator working as a pulse generator connected to the coil. During stimulation a rapid, brief change of magnetic field occurs, inducing electric current in the underlying tissue that can cause the depolarization of neurons in the targeted brain area. The effect exerted on the neurons is related to neuronal mechanisms analogue with long-term potentiation and long-term depression (Di Lazzaro et al., 2005; Wassermann et al., 1998). Repetitive transcranial magnetic stimulation is able to modulate the cortical excitability of a specific brain region (Rossi et al., 2009), with the effect of TMS via GABAergic systems being presumed as an underlying mechanism (Luborzewski et al., 2007; Yue et al., 2009). Depending on the frequency of the stimulation, rTMS can exert inhibitory (≤ 1 Hz) or facilitating effects (≥5 Hz) on the neuronal excitability of the stimulated brain area (Hallett, 2007; Wassermann and Zimmermann, 2012). A specialized pattern of rTMS is the theta-burst stimulation (TBS) first described by (Huang et al., 2005) as an alternative rTMS protocol with shorter stimulation periods, resulting in seemingly longer-lasting effects. The higher efficacy of TBS is based on the assumption that it mimics more closely the neurons' natural firing rate than the standard repetitive protocol. Basically, two major patterns of TBS can be distinguished: the intermittent TBS (iTBS) with repeated gamma frequency trains applied at theta rhythm, and the continuous TBS (cTBS) with an uninterrupted train of bursts. Similarly to high and low frequency rTMS, these two subfacets

of TBS seem to have reverse effects on cortical excitability: iTBS having a facilitating (Di Lazzaro et al., 2008), while cTBS exerting inhibitory effect in the stimulated brain region (Di Lazzaro et al., 2005).

The application of TMS is considered to be a safe method (Grossheinrich et al., 2009). Numerous previous studies deliver proof that TMS causes no permanent harmful effect (Rossi et al., 2009). Mild headache and local pain are reported as the most common adverse effects, and in extremely rare cases, syncope or epileptiform seizure can occur (Janicak and Dokucu, 2015). The use of TBS over the DLPFC has been found to be safe at lower intensities and potential side effects have been evaluated in subjects with low motor threshold (MT) (Grossheinrich et al., 2009). In the vast majority of studies involving stimulation of the DLPFC, intensity is typically set according to the measured MT. However, a recent study reported that MT – serving as an indicator of safe intensity – might be overestimated especially if determined by visual observation of motor reactions only (Westin et al., 2014). This further raises the importance of using lower stimulation intensities. It should be noted that some evidence indicates that MT does not correlate with the excitability of non-motor cortical areas (Boroojerdi et al., 2002).

Though the effects transcranial magnetic stimulation protocols were tested on the human motor cortex in the first place, its impact on the prefrontal area is also intensively studied, mainly related to its potential antidepressive effect (for a review, see Lefaucher et al., 2014). Several neuroimaging studies report increased neuronal activity of the right DLPFC and a decrease in left DLPFC function in MD (e.g. Fitzgerald et al., 2006). 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. In accordance with a protocol approved by the Federal Drug Administration (FDA) in 2008, high frequency rTMS applied over the left DLPFC for 4-8 weeks has a significant antidepressive effect even in treatment-restistance major depression (Baeken et al., 2011; George et al., 2013; Lefaucheur et al., 2014; Pascual-Leone et al., 1996). These results are based on sham-controlled trials, where sham stimulation was performed using either a tilted coil, or a special sham coil. The use of TBS to reduce depressive symptoms has also been investigated (Chung et al., 2015). These resuls indicate that 50 % of depressed patients were responders following cTBS over the right DLPFC. (Li et al., 2014) found a significant decrease in depressive symptoms based on HDRS scores following a two-week procedure of bilateral stimulation (applying iTBS over the left DLPFC and cTBS over the right DLPFC), and the rate of responders reached 57.9 %.

3.2 Modulating cognition using TMS

While stimulating the prefrontal cortex can cause mood improvement in affective disorders (Allan et al., 2011), it is also able to modulate cognitive performance (Guse et al., 2010). The most commonly stimulated area is the DLPFC (situated in BA 9 and 46 [Broadmann, 1909]), a crucial neural substrate in cognitive control involved in adaptation to the changing environment by the dynamic selection of the goal-relevant behavior when automatic responses are not effective or conflicting (Mansouri et al., 2009). In addition, several neuroimaging and electrophysiological studies have emphasized the role of DLPFC in memory processes, especially episodic and working memory (Balconi, 2013). DLPFC plays a fundamental role in working memory processes primarly being responsible for the maintaining of attentional selection. This process can be described as a controlling operation by selecting the elements in the short-term storage to be in the focus of the attention and to be manipulated (Curtis and D'Esposito, 2003). Consequently, individual working memory capacity is closely related to the ability of controlling attention (Redick and Engle, 2006). Furthermore, increased activation of DLPFC can be detected during conflict resolution testing, such as the anti-saccade task (Ford et al., 2005) and during working memory tasks as well (Curtis and D'Esposito, 2003).

These results suggest that one essential role of the DLPFC is cognitive control of actions in terms of different cognitive abilities. However, the effect of TMS on cognition targeting the DLPFC still needs to be clarified as the results are not consistent when assessing healthy individuals. (Bagherzadeh et al., 2016) found that stimulating the left DLPFC using a high-frequency rTMS protocol results in improved working memory (WM) performance measured with the verbal digit span test and the 2-back test. An in vivo fMRI study revealed that applying low-frequency TMS on the right DLPFC has no measurable effect on WM performance using n-back task; however, it elicited a significant decrease in functional connectivity but not resting-state connectivity between the right DLPFC and the left hippocampus during WM processes (Bilek et al., 2013). Previous studies have revealed that rTMS exerts an eminent effect on executive functions when applied over the DLPFC (Hamidi et al., 2009), which is a core area for controlling a range of higher cognitive functions as part of the frontoparietal network (Duncan and Owen, 2000; Niendam et al., 2012). When using TBS instead of the traditional repetitive TMS protocol, a facilitating effect of iTBS on working memory was found in a sham-controlled study, with the enhancing effect lasting approximately 40 minutes following the stimulation (Hoy et al., 2016). The beneficial effect of iTBS on cognition was confirmed by

Demeter (2016) as well. In contrast, cTBS was found to impair 2-back but not 0-back or 3-back performance in healthy participants when applying over left DLPFC (Schicktanz et al., 2015).

Regarding MD studies, a recent review found 8 from 13 studies assessing the effect of rTMS not only on mood but also on cognition, to report significant improvement in cognitive function, mainly in the area of verbal memory, psychomotor speed and concentration (Demirtas-Tatlidede et al., 2013). Addressing the effect of TBS on cognition apart from its antidepressive action, (Martin et al., 2016) found that depressed patients showed a significant improvement in working memory using the n-back test as a result of iTBS. In addition to this, (Chung et al., 2015) revealed that TBS can also improve executive function, with the improvement being dissociable from the antidepressive effects. When assessing the influence of rTMS on eye-movements, (Crevits et al., 2005) demonstrated that 10 sessions of high frequency TMS applied over the left DLPFC caused a decrease in latency of antisaccades in MD patients. Additionally, ten sessions of iTBS can also shorten latency of antisaccades in patients with bipolar disorder in the depressed phase (Beynel et al., 2014).

Based on previous studies and experiences, 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.

H3: 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.

H4: MD patients present an altered pattern of fixation duration compared to HCs influenced by emotional valence and reward contingencies, showing a mood-congruent bias.

H5: 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. METHODS AND MATERIALS

In each study a written informed consent was obtained from all participants prior to the assessments. Participation was completely voluntary, all participants had the opportunity to quit at any phase of the assessment. Study protocols were approved in each case by the local Ethics Committee. All data were stored and used anonimously. The assessments were carried out according to the Helsinki Declaration.

The patient groups were recruited from two healthcare institutions: AD patients were recruited from the Hospital of Szigetvár, Szigetvár, Hungary and MD patients were enrolled from the Department of Psychiatry, Albert Szent-Györgyi Health Center, University of Szeged, Hungary. In each case, highly trained professionals specialized in psychiatry verified the inclusion and exclusion criteria in an interview phase prior to further assessments. AD and MD patients were diagnosed based on DSM-IV (APA, 2000) by trained physicians. In Study I and II, AD and MD groups were closely matched for age, gender and level of education to their healthy control groups. Patients with a psychiatric disorder other than AD in Study I and MD in Study II were excluded. History of drug dependence, severe head injury or major neurological disorder were listed as exlusion criteria in both Study I and II. The exclusion and inclusion criteria were verified in all cases based on the patients medical records. In all three studies, healthy controls were required to have no current or former psychiatric or neurological disorder, and a history of significant head injury. All participants had a normal or corrected-to-normal (20/20) visual acuity.

1. STUDY I

1.1 Participants

In the first study, 72 participants were enrolled (a total of 43 males and 29 females), including 36 patients (ADs; age: 21-61 years, M = 42.81 ± 8.96), and 36 healthy controls (HCs; age: 24-63 years, M= 40.39 ± 10.04). Demographic characteristics of all participants are illustrated in Table 1. The p value exceeding 0.05 for all variables supports that the AD and HC group are comparable in age, years of education and errors in the National Adult Reading Test (NART). Chi-square tests showed no significant differences in gender (Chi-square = 0.921, df = 1; Table 2).

	HC group Mean (SD) *N = 36*	**AD group Mean (SD) *N = 36***	**Statistics[a]**
Gender (male/ female)	21/15	22/14	F(1,70) = 0.056, p = 0.813
Age	40.39 (10.04)	42.81 (8.96)	F(1,70) = 1.162, p = 0.285
Education (years)	13.10 (2.84)	12.67 (2.66)	F(1,70) = 0.654, p = 0.421
NART (errors)	8.77 (7.81)	12.083 (10.50)	F(1,70) = 2.263, p = 0.137

NART: National Adult Reading Test.
[a]Analysis of variance (ANOVA)

Table 2 – Demographic characteristics of AD and HC groups

AD patients were recruited from the Hospital of Szigetvár which follows the Minnesota Model. This inpatient addiction unit is considered to be a unique healthcare facility for AD patients. Patients take part in a complex, comprehensive program lasting 6 months, during which the first steps of the 12-step-program in connection with AA (Alcoholics Anonymous) groups are involved. The average duration of abstinence in the AD group was 14.61 weeks (SD = 9.60). Patients were not taking any psychotropic substance at the time of the study. Additionally, they were not administered any medication for alcohol addiction and dependence. An exclusion criteria was the presence of withdrawal symptoms. Two patients were diagnosed with a primary psychiatric disorder present at the time of the study, therefore they were excluded.

All participants were assessed using the Hungarian version of the National Adult Reading Test (NART) constructed to predict premorbid IQ measures (Nelson and Willison, 1991). All patients were requested to complete the Alcohol Use Disorders Identification Test (AUDIT) for demographic and alcohol consumption-related variables (Babor et al., 2001). The Beck Depression Inventory (BDI) was performed to quantify depressive symptoms (Beck et al., 1961). Additionally, the Derogatis' Symptom Checklist-90 (SCL-90) was administered to evaluate clinical symptoms referring to psychological distress (Derogatis, 1977). The Delayed Discounting Test (Richards et al., 1999) and the Barratt Impulsiveness Scale were completed to objectively measure the level of impulsivity (Barratt and White, 1969; Patton et al., 1995). All interviews were conducted by two trained psychologists specialized in clinical psychology under the supervision of a board certified psychiatrist.

1.2 Experimental paradigm

A Hungarian version of the Think/No-think task (Anderson and Green, 2001) was administered for the assessment of associative memory and inhibition of retrieval. The task

involves the computerized presentation of 30 non-related, neutral picture-word pairings (Figure 1). Stimuli were presented in each case on a 17-inch colored display connected to a Windows-based computer, using the Presentation Software (version 16.5; Neurobehavioral Systems, Albany, CA, USA; http://www.neurobs.com/presentation). Pictures were randomly paired with words. All words were written in Hungarian and were balanced for frequency based on a pilot assessment prior to the study. During each trial, a colored image and a word written with white letters were presented simultaneously on a black background for a period of 3.5 s. The experimental paradigm consisted of three major phases. The instructions were similar to the test instructions applied by Anderson and his collegues in their original experiment (Anderson and Green, 2001). Participants were asked to try and memorize the associated pairs for a final recognition test. Consecutively, participants were instructed to name the related word following the appearence of the image serving as a cue. The answers were recorded by the experimenter. Training blocks of all picture-word pairings were presented randomly and were repeated until the participant reached a level of at least 80% of correct identification of pairings (i.e. 24 words of the total 30). This level of accuracy was defined based on previous studies using this paradigm. Participants were allowed to take breaks if needed. Immediately after completing the training blocks, all pairings were randomly assigned into three groups: Baseline (B), Think (T), and No-think (NT). Classification was randomly rotated across participants to ensure that each stimulus pairing is assigned to each condition equally often. During the subsequent phase, only the cue item (i.e. the picture) was presented and subjects were requested to either recall (i. e. „think") or suppress (i. e. „not think") the target word previously paired with the cue stimulus (20 pairs in total). In case of the ten „Think' (T) items surrounded by a green colored frame when presented, participants were instructed to try to recall and name the related word. In contrast to this, participants were asked to try and suppress the words previously presented with the pictures and now presented with a red colored frame. These cases were the „No-think" (NT) items (10 pairings). Cue images were presented eight times in a random order for testing inhibition over associative memory retrieval. In the final test, all 30 images were presented originally studied during the training phase. Participants were asked to try and explicitly recall the word associated with the image during the initial training block. Items presented in the training phase only and not repeated subsequently served as the „Baseline" (B) condition to measure baseline memory. Cued recall accuracy of T and NT items were measured compared to B accuracy.

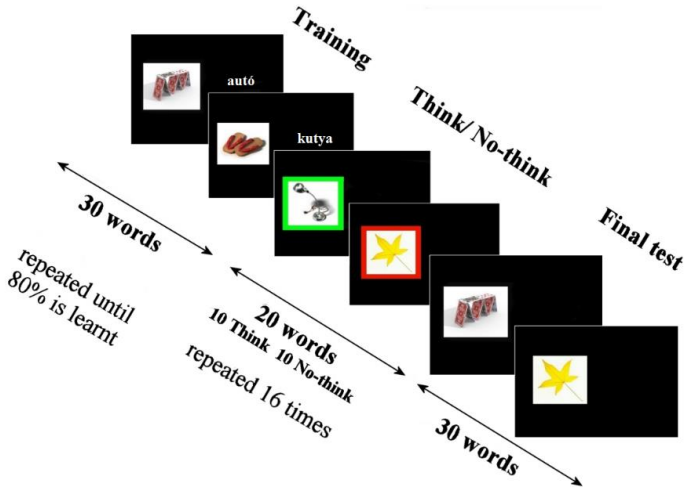

Figure 1 – The Think/No-think computerized task. During each trial a full-colored image and a word were presented simultaneously for a period of 3.5 s. The experimental paradigm included three major phases. During the initial training block participants viewed the 30 image–word pairs. Training blocks consisting of the randomized presentation of all stimulus pairings were repeated until the participant succeeded to correctly identify at least 24 (i.e., 80% of the 30 pairs). 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" or suppress, i.e., "not think" of the target stimulus previously paired with the cue. Words previously studied with pictures now surrounded by a green colored frame, i.e., the T items, were asked to be recalled and named. In contrast to this, participants had to try to suppress the words which have been paired with images now presented with a red frame, these were the NT items. The final test consisted of the presentation of all 30 images originally studied.

1.3 Statistical analysis

Statistical analysis was carried out using the statistical software SPSS (version 15.0; IBM Corp., Chicago, IL, USA, 2006). To examine the differences in demographic characteristics between the AD and HC group an analysis of variance (ANOVA) was performed. The relationships between clinical variables and the number of recalled items were assessed using Pearson's coefficient. To determine the number of errors in NART, Spearman's Rho was calculated. Independent Samples Kruskal-Wallis Test was carried out to assess the distribution of variables across the two groups. Group differences in TNT performance across T, NT and B conditions were assessed using a general linear model, with the condition as the within-subject factor and group as the between-subject factor (AD vs HC). Age was entered in the model as a covariate considering its possible effect on episodic memory and inhibition over retrieval (Anderson et al., 2011). Additionally, two novel variables were computed (T-B and NT-B) to measure group differences for effects of practice and inhibition on retrieval. Group differences in the number

of repetitions during the initial training phase serving to reach the predefined level were assessed using Mann-Whitney U-probes. Statistical differences characterized by a p value below 0.05 were considered to be significant.

2. STUDY II

2.1 Participants

Written informed consent was obtained from 28 patients (age: M = 49.33 ± 10.88 years) diagnosed with MD based on DSM-IV criteria and 30 healthy controls (HC, age: 46.83 ± 10.85 years) after approval of the study protocol by the local Ethics Committee (Ref. no.: 49/3-11/20144k). Patients were recruited from the Department of Psychiatry, Albert Szent-Györgyi Health Center, University of Szeged, Hungary. Prior to the enrollment in the study, patients were going through a clinical interview based on SCID-I (APA, 2000) and were diagnosed by clinical professionals specialized in psychiatry. Two control subjects reported to have currently taken antidepressive medications and were excluded therefore. Table 3 shows the demographic and clinical characteristics of the MD and HC group.

	N	**MD** **Mean (SD)**	**HC** **Mean (SD)**	**Statistics**
Age	58	49.22 (10.88)	46.83 (10.85)	t=0.723, p=0.474
Gender (male/ female)	58	5/ 23	10/ 18	χ=2.276, p=0.131
Years of education	58	12.15 (2.77)	13.61 (2.73)	t=-1.753, p=0.088
Weeks between baseline and follow-up	14	24.07	-	-
HDRS $_{\text{baseline}}$	28	18.15 (5.21)	-	}t=4.082,
HDRS $_{\text{follow-up}}$	14	8.00 (6.28)	-	p=0.004*
Beck $_{\text{baseline}}$	28	6.00 (3.58)	-	}t=1.269, p=0.245
Beck $_{\text{follow-up}}$	14	3.13 (3.23)	-	

HDRS $_{\text{baseline}}$ and HDRS $_{\text{follow-up}}$: Total scores in Hamilton Depression Rating Scale at baseline and follow-up measurement, Beck$_{\text{baseline}}$and Beck$_{\text{follow-up}}$= Total scores in shortened version of Beck Hopelessness Scale at baseline and follow-up measurement.

*significant at $p<0.05$

Table 3 - Demographic and clinical characteristics

Clinical symptoms were assessed using semi-structured interviews and self-report questionnaires. The Hamilton Depression Rating Scale (HDRS, also known as Hamilton Rating Scale for Depression) (Hamilton, 1960) is a clinically widely used semi-structured interview evaluating the severity of depression from two aspects: somatic symptoms and mood. The HDRS includes 17 items scaled from 0 to 4 for measuring the severity of depression and 4 additional items to assess the characteristics of depression. The shortened version of Beck Hopelessness Scale symptoms (Beck et al., 1974; Perczel Forintos et al., 2013) was applied to assess feelings of hopelessness using 4 statements scaled from 0 to 3. The Hypomania Checklist (HCL-32, Angst et al., 2005) was administered as a screening tool to exclude hypomania or mania. National Adult Reading Test (NART) (Nelson and Willison, 1991) was applied to estimate premorbid IQ. Associative memory was assessed via eye-movements measuring fixation duration as well as a forced-choice testing.

2.2 Experimental paradigm

The eye-tracking paradigm applied here to assess associative memory implicitly was a modified version of the task used by (Hannula et al., 2007; Williams et al., 2010). In the original version participants viewed three consecutive, randomized study blocks consisting of the same 36 face-background scene pairs during the training phase. The test phase followed immediately after completion of training and included 12 trials, each composed of three faces overlaid on one scene image. During the six Match trials, one of the three faces had been paired with the scene during the training phase, whereas in the six Non-Match trials none of the faces had been paired with that scene during training.

In the current study, fixation duration and eye-movements were recorded with iView X™ Hi-Speed SMI eye-tracker (SensoMotoric Instruments, Teltow, Germany, http://smivision.com/). Stable and consistent position of participants' head was assured with a chin rest (distance from display: 90 cm/approximately 36 inches). Stimuli were presented on a 17" CRT monitor (refresh rate: 100 Hz) controled by Windows using the iView X Experimental software.

Two types of stimuli were presented: neutral background images (colored scenes, sized 1024 x 768 pixels) and faces of three different emotions: happy, sad, and neutral (314 x 384 pixels). One face stimulus appeared in only one emotional expression. Stimuli of faces consisted of 18 male and 18 female face images obtained from the NimStim database (Tottenham et al., 2009), balanced for type of emotional expressions.

The eye-tracking task consisted of two major parts: (1) during three consecutive training phases participants were asked to memorize a total of 36 pairs of backgrounds and facial emotional expressions (happy/sad/neutral). After each pairing, a virtual monetary reward or loss appeared briefly, with no associated instruction provided. (2) During the testing phase, 12 background scenes were presented serving as a cue. Subsequently three faces of different emotions appeared overlaid on the background. Half of the test trials (6 trials) contained the face previously paired with the cue (Match trials). During Non-match trials (6 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. In this phase, participants were instructed to indicate by button-press the position of the matching face (upper left, upper right, middle-bottom) if present, or to press the space key 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 (Figure 2).

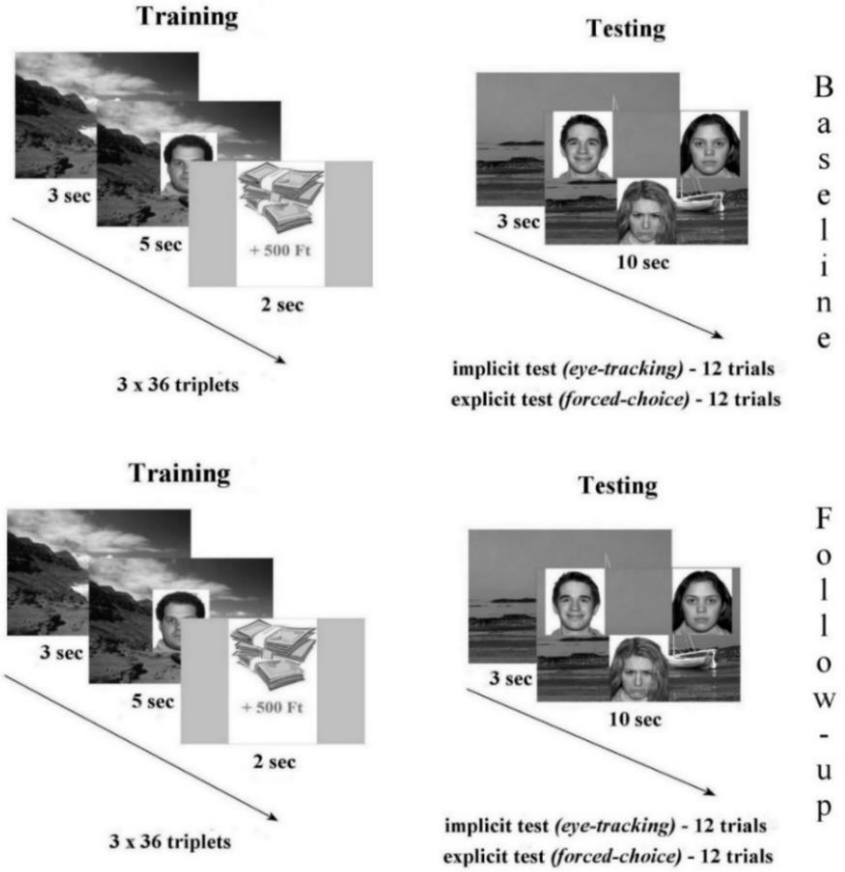

Figure 2 – The relational memory task was built of two major parts: (1) during the three consecutive training phases participants were asked to memorize a total of 36 pairs of backgrounds and facial emotional expressions (happy/sad/neutral). After each pair a virtual monetary reward or loss appeared 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. In this phase, participants were instructed to press a button each rendered to the position of the face (upper left, upper right, and middle-bottom), 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.

2.3 Stimulus presentation

The eye-tracking procedure was applied under consistent lighting conditions with subjects sitting exactly 90 cm from the monitor, in a stable position throughout the task. SMI eye-tracker uses the registration of pupil and corneal reflection to calibrate the position of the eye by an infrared camera. After a 9-point calibration, all participants were asked to read the written instructions presented on the monitor. Sufficient time was provided for participants to raise questions as needed. All subjects were instructed to try and memorize the background-face pairings for a subsequent recall.

In each of the three consecutive training phases, stimulus presentation started with a fixation cross for all 36 trials. A background scene appeared for 3 s, with an image of a facial expression being then overlaid on the backgroung for 5 s. After each pair a virtual monetary reward of a smaller (500 Hungarian currency, HUF, approximately 1.6 Euro) or a larger amount (2000 HUF, approximately 6.5 Euro); or a virtual monetary loss of a smaller (500 Hungarian currency, HUF, approximately 1.6 Euro) or a larger amount (2000 HUF, approximately 6.5 Euro) was presented for 2 s. These fixed triplets were presented in a semi-random order during each training session. Participants were allowed to take breaks between the sessions.

During the „implicit" test phase a background scene appeared for 3 s with three faces being overlaid for another 10 s with eye-movements being recorded. Participants were instructed to search with their eyes and try to recall which of the three faces had been paired with the background scene during training, without giving an explicit response. Participants were asked to keep their eyes focused on the computer screen, even if no matching face was detected. On Match trials, the matching face was assigned equally often in each of the three different spatial locations (upper left, upper right, and middle-bottom position). Lists of stimuli were rotated and counterbalanced across participants to ensure that each scene was paired

equally often with each face across the study. Virtual monetary reward or loss has also been rotated and counterbalanced across participants to ensure a balanced distribution of the four different monetary stimuli with the three different facial emotional expressions and sufficient power for subsequent statistical testing. It has been assured that each participant is exposed to different stimuli associations during the baseline and follow-up measurements to exclude any intrusion effects.

To assess explicit recognition of the face-scene pairings, we administered a subsequent four-alternative forced choice memory test after the implicit eye-movement phase was completed. Eye-movements were no longer recorded in this phase. Participants viewed the 12 test displays in the same order and with the exact same background scene and face stimuli as during the preceding implicit test phase. Participants were asked to indicate mathing face by pressing a computer key corresponding to its position on the display or pressing the space bar if they thought none of the faces had been paired with that scene during training.

2.4 Follow-up phase

Participants were invited to participate in a follow-up testing approximately 6 months after the initial, baseline measurements have been completed. Stimulus presentation has been performed similar to initial testing. Clinical data has been recorded and the experimental paradigm has been administered in the same design, i.e., relational memory assessment with three training phases on the background – emotional facial expression – virtual monetary reward or loss stimulus triplets followed by the implicit testing phase with eye-movement being recorded. The explicit memory assessment followed subsequently. Fourteen out of the 28 initial patients were available and agreed to participate in the follow-up phase.

2.5 Statistical analysis of eye-movement and behavioral data

Data analysis was performed offline. Preprocessing of the data was carried out using the software of the SMI eye-tracker and this was followed by statistical analysis. We compared demographic parameters between the HC and MD group at baseline using independent samples t-tests. Clinical characteristics were addressed comparing the MD group at baseline and at follow-up using paired-sample t-tests. Explicit memory performance was compared between groups with two-tailed, independent-samples t-tests. Results (t) were compared with the corresponding value of the Student’s distribution at the appropriate degree of freedom. We

assessed the effect of the different levels of virtual monetary reward and loss using repeated measured ANOVA, paired post hoc comparisons were Bonferroni corrected.

Group differences in overall viewing patterns were tested using a repeated measures analysis of variance (ANOVA) for fixation duration including relational memory condition (Match and Non-match), facial emotion type (happy, sad, and neutral) and virtual monetary effect (reward and loss) as within-subject factors and group (HC and MD) as between-subject factor. Interactions between conditions were further analyzed using paired-sample t-tests, and Bonferroni post hoc testing was used to assess the effect of facial emotion.

Pearson correlation was used to assess an association between viewing duration on the correctly matched face during Match trials and explicit memory performance. In order to perform this analysis, we first extracted viewing duration on the matching face for all Match trials which where subsequently explicitly identified as correct and correlated the obtained fixation times with explicit memory performance. This analysis aimed to detect the relationship between the two approaches of relational memory investigation. We performed repeated-measures ANOVA to compare fixation duration at baseline and follow-up for MD patients for the relational memory condition (Match and Non-match), emotional expression (happy, sad, and neutral) and monetary reward or loss. A potential association of viewing duration on the correctly matched face during Match trials as an implicit measure of relational memory, as well as between explicit behavioral performance and clinical data was assessed with Pearson correlation. Results were considered significant if type I error remained below 0.05.

3. STUDY III

3.1 Participants

Thirty-six healthy volunteers (22 males and 14 females), aged between 20 and 37 years (M = 25.111 years, SD = 3.387) were recruited to participate in Study III (Table 4). All participants were required to have no history of any psychiatric or neurologic disorder. Subjects were screened for symptoms of depression based on BDI scores (Beck et al., 1961). Participant with a BDI score higher than 9 were excluded. Having a pacemaker, any ferromagnetic methal implant, migraine, or epilepsy were listed as exclusion criteria. Medications taken and other present disorders were recorded that could influence or contraindicate transcranial magnetic stimulation. Out of all participants, 35 subject were right-handed and 1 subjects was left-handed based on the Edinburgh Handedness Inventory (Oldfield, 1971).

	iTBS group Mean (SD) *N = 18*	cTBS group Mean (SD) *N = 18*	Statistics
Gender (male/ female)	10/8	12/6	χ=0.494, p=0.131
Age	25.28 (2.65)	24.94 (4.07)	t=0.291, p=0.773
Level of education	13.10 (2.84)	12.67 (2.66)	
Elementary	0	0	χ=0.494, p=0.733
Secondary	6	8	
College	12	10	

Table 4 – Demographic characteristics of the iTBS and cTBS group

3.2 Experimental paradigm

The experimental paradigm consisted of four sessions (see Figure 3). First, a T1-weighted cranial MRI scan was performed using a 1.5 T Siemens MRI device. The second session included the recording of demographic data, and the administration of clinical scales if it was indicated: BDI was completed if any mood disorder was suspected. The TMS safety questionnaire and the Edinburgh Handedness Inventory were completed prior to the motor threshold measurement. During the third and fourth session, participants completed the Attention Network Test (ANT), the n-back task with 3 levels of difficulty, and two types of anti-saccade tasks before and after receiving 600 pulses of either continuous or intermittent theta burst stimulation. The order of the tasks was counterbalanced across participants, but each participant completed the tasks in the same order in both TBS sessions. In the first session, either the participants' right or left dorsolateral prefrontal cortex was stimulated, and the other side of DLPFC on the second session, respectively. The order of the stimulated hemispheres was counterbalanced across participants. Two groups were formed: 18 out of the 36 participants were given iTBS, and 18 participants received cTBS. Participants were randomly assigned to the groups and were naïve to the stimulation type. The experiment protocol was the same in both groups, except for the type of the stimulation.

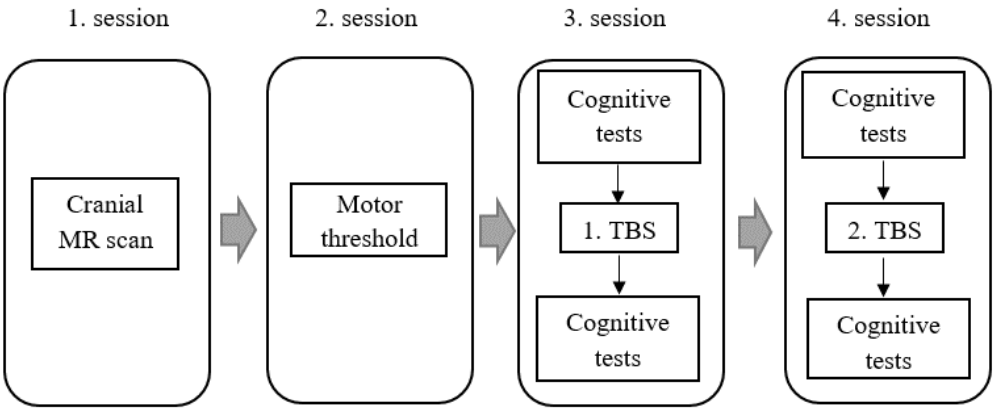

Figure 3 – Experimental design of Study III containing 4 phases: (1) Cranial MRI scan, (2) Motor threshold measurement along with completing the safety inventory and demographic tests, (3) Completing the n-back test, ANT and the saccade/antisaccad test before and after 600 impulses of either iTBS or cTBS, (4) minimum 2 weeks later a second TBS session followed identical to the first, except for stimulation site.

3.2.1 N-back task

The n-back task involves working memory and also the ability to maintain and manipulate pieces of information (Owen et al., 2005). The version we used was programmed in Python and was presented using PsychoPy (version: v1.82.01) based on previous research in the field (Peirce, 2007). During the 1-back task, 100 randomized capital letter stimuli (A, C, E, I, K, L, S, O, R, T, U) were presented serially on the screen, each of them for 1500 ms with an interstimulus period of 500 ms. Participants were instructed to press the 'Space' key if the current letter on the screen was the same as presented one stimulus earlier. During 2-back task, participants were asked to press the target key if the currently seen letter is the same as presented 2 letters earlier, and during 3-back task subjects had to press the key if the currently presented letter was the same as presented 3 stimuli earlier. The frequency of target stimuli was set to 20%. Participants were allowed to take a rest once within the block and also between the blocks of different levels. RTs and the number of hits, correct rejection, false alarms and misses were recorded.

3.2.2 Attention Network Test

The Attention Network Test (ANT) operationalizes three relatively independent attentionat networks: the alerting network, orienting network, and the executive control network (Fan et al., 2002). The alerting network is related mostly to the reticular system in the brainstem and noradrenergic projections derived from the locus coeruleus (Coull et al., 1996b; Marrocco et al., 1994). This network is responsible for increasing vigilance to an anticipated stimulus

(Fan et al., 2009). The orienting network is related to processing facets of attention that contribute to select a certain information from numerous inputs. This system is closely linked to FEF, superior colliculus, the pulvinar and the thalamus and to the functioning of cholinergic systems (Corbetta et al., 2000; Corbetta and Shulman, 2002; Posner, 1980). Both the alerting and orienting system shows a right lateralization. The executive control of attention is responsible for more complex mental operations like detecting and resolving conflict occurring between certain brain areas (Botvinick et al., 2001; Bush et al., 2000). It is also linked to selective attention and the cognitive control of conflicts. This action involves mostly the anterior cingulate cortex (ACC), the lateral prefrontal cortex (PFC) (Matsumoto and Tanaka, 2004), both being parts of the dopamine system of VTA (Benes, 2000). Recently two subdivisions have been distinguished: the fronto-parietal network carries out corrections in real time, while the cingulo-opercular system provides a steady background for performing throughout the task via saving relevant information.

Parameters of the ANT were the same as in the original paradigm used by (Fan et al., 2002). Each trial began with a fixation cross displayed in the center of the screen for a random period between 400 and 1600 ms. A consecutive warning cue appeared for 100 ms followed by a 400 ms fixation period. The target stimulus or stimuli (one or five arrows pointing leftwards or rightwards) were presented either above or below the fixation cross. The participant's task was to respond by pressing the matching key as fast and accurately as possible according to the direction of the central arrow (left or right). The target disappeared immediately after the response, then the next trial followed. The task consisted of three consecutive blocks, proceeded by a practicing block containing 24 trials. Each block included 96 trials, thus the participants completed a total of 312 trials.

There were four different cues, and three different flanker types throughout the task. The cue configurations were the following: no cue (there was no cue prior to the target), double cue (an asterisk was presented both above and below the fixation cross), spatial cue (an asterisk appeared either above or below the fixation cross), center cue (the asterisk was displayed at the fixation cross's exact location). The flankers were either 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) or neutral (no distracting arrows were present). Thus, three conditions can be distinguished based on target stimuli: neutral, congruent and incongruent (Fig 4). The different cues and flankers were equally presented throughout the three blocks, and the order of the presentation was randomized for each participant. Accuracy and reaction times (RT) were recorded during each trial.

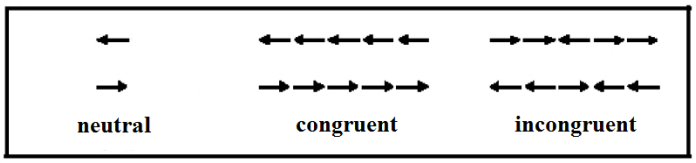

Figure 4 – Conditions in the Attention Network Task according to the type of target stimuli (Fan et al., 2002). The flankers were either congruent (all arrows pointing in the same direction as the central target arrow), incongruent (the arrows pointing in the opposite direction as the target arrow) or neutral (no distracting arrows were present).

3.3.3 Saccade/Antisaccade task

Eye-movements were recorded using a Tobii TX300 Eye Tracker device (Tobii Technology AB, Stockholm, Sweden). Following a five-point calibration process, subjects were instructed to fixate at the center of screen with the resolution being 1024 * 768 pixels, and the refresh rate 60 Hz. Throughout the task, a centrally positioned colored dot (sized 20 pixels) was presented on the screen serving as a cue for recording 125/50/200 data point with a sampling interval of 0.004 (125*0.004 for the cue stimulus, 50*0.004 for fixation and 200*0.004 for targeting). Consequtively, after a 1 ms long interstimulus interval, a cross (sized 15 pixels) 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, respectively), the subjects were asked to try and fixate in the oppositve direction horizontally without looking at the cross (anti-saccadic condition). The control cue was a blue dot in every case, while the color of the pro-saccadic and the anti-saccadic cues (red and green colors) were altered across participants. 72 trials were presented with equally balanced conditions throughout the task.

3.2.4 Theta-burst stimulation protocol

TBS was generated by a Magstim Rapid^2 stimulator connected with a figure-eight coil (The Magstim Company Ltd, Whitland, Wales, UK). According to previous research and also considering international guidelines (Lefaucheur et al., 2014), right and left DLPFC were chosen to be the target of stimulation. The target area has been identified based on our previous MRI results as endpoints of the paths originating in the subgenual anterior cingulate cortex to the DLPFC, as a result of which the target area could be characterized with the following

coordinates: X= -27.75, Y = 19.25, Z = 55.0.5 for the left, and X = 29.7, Y = 19.8, Z = 54.13 for the right DLPFC. The neuromodulation of this specific area has already been associated with decrease in depressive symptoms (Mayberg et al., 2005). The structural T1-weighted cranial MRI-scan was used to achieve a more precise localization of the target on the participant scalp using a Zebris TMS Neuronavigator (Brain Innovation, Maastricht, the Netherlands) with the ultrasound CMS20 Measuring System (Zebris GmbH, Tübingen, Germany). This system allowed us to visualize the relative position of the coil and the target area in situ.

CTBS and the iTBS patterns were established based on (Huang et al., 2005) protocol (see Figure 5). The cTBS pattern consisted of 3 pulses given at 50 Hz (gamma frequency) in every 200 ms (theta frequency intervals of 5 Hz) for 40 s. For the iTBS stimulation, a 2 s train was repeated every 10 s for 190 s in total. Three pulses were given in a row at 50 Hz. Thus, a total of 600 pulses were given to each participant in both the cTBS and the iTBS group.

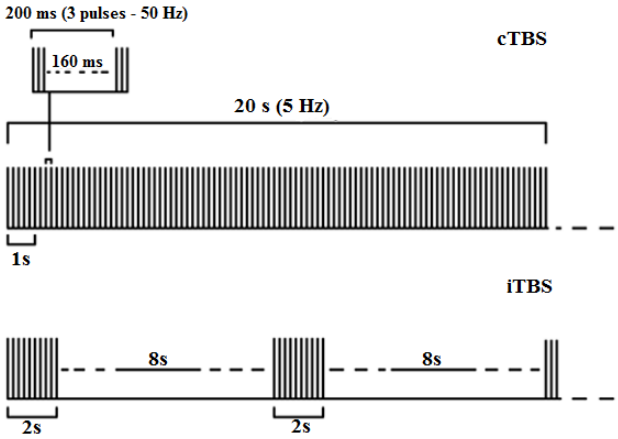

Figure 5 – Patterns of continous theta burst stimulation (cTBS) and intermittend theta burst stimulation (iTBS) based on (Rossi et al., 2009). The cTBS pattern consisted of 3 pulses given at 50 Hz (gamma frequency) in every 200 ms (theta frequency intervals of 5 Hz) for 40 s. For the iTBS stimulation, a 2 s train was repeated every 10 s for 190 s in total. Three pulses were given in a row at 50 Hz.

Stimulation intensity was kept at 30% of the maximum capacity of the Magstim Rapid^2 stimulator for both groups due to safety considerations (Grossheinrich et al., 2009). Before the experiment, the resting motor threshold (RMT) was determined. It was defined as the lowest level of stimulation intensity induced over the right primary motor cortex that would result in a visible contraction of the left abductor pollicis brevis muscle in at least 3 out of 6 stimulations. In one case RMT proved to be lower than 40%, so intensity was reduced to 80% of active motor threshold (AMT) (where AMT was defined as 80% of RMT). The mean RMT did not differ between the two groups (M_{itbs} = 60.556%, SD=12.580, M_{ctbs} = 61.333%, SD = 12.848, t(34) = -0.184, p = 0.855).

3.3 Statistical analyses

The n-back performance was assessed using the discriminability index (d'), interpreted in the framework of the signal detection theory (Stanislaw and Todorov, 1999). according to this theory, there are four types of answers: hits (correctly detected targets), misses (targets wrongly identified as non-targets), false alarms (non-targets wrongly identified as targets) and correct rejections (correctly deteced non-targets). D' is a sensitive statistical index considering both the ability to maximize hits and minimizing false alarms. It is computed from the standard deviation of signal and noise distribution, with higher scores representing more readily detected signals, therefore greater discriminability (Haatveit et al., 2010). D' scores were calculated for each participant as follows:

$$d' = Z(\text{hit rate}) - Z(\text{false alarm rate}).$$

We analyzed d' scores using a 3 × 2 × 2 repeated-measures ANOVA with cognitive load (1-back, 2-back or 3-back), time of administration (pre- or post-stimulation), and side of stimulation (right or left DLPFC) as within subject factors, and stimulation type (iTBS or cTBS) as between subject factor. Pairwise comparisons of means were used for the assessment of significant interactions.

For the analysis of ANT performance, three main variables can be computed crucial for the attention network: orienting effect, alerting effect and conflict effect (Fan et al., 2002). These variables are considered relatively independent from each other. Focusing on executive functioning regarding the context of the thesis and out hypothesis, here we present the analysis of the conflict effect in detail. Based on the original publication, conflict effect can be computed as following: $\text{Conflict effect} = RT_{\text{incongruent target stimuli}} - RT_{\text{congurent target stimuli}}$

We excluded RTs within 200 ms in the upper and lower section of the provided time frame based on Xu et al. (2015). Corrected indicators for the efficiency of cognitive control were computed as follows (Xu et al., 2016):

$$\text{Corrected conflict effect} = \text{Conflict effect} / \text{RT (s)}$$

The above correction is explained by the generally high level of performance of healthy, young participants, where even smaller RT differences can have great importance. Medians were used instead of means based on Xu et al. (2015), considered more robust and providing valid information even for outliers.

Two 3 × 2 × 2 repeated-measures ANOVA designs were used with conflict effect (and Corrected conflict effect in the other design), time of administration (pre- or post-stimulation), and side of stimulation (right or left DLPFC) as within subject factors, and stimulation type

(iTBS or cTBS) as between subject factor. Pairwise comparisons of means were applied for the assessment of significant interactions.

Data analysis of the oculomotor performance in the saccade/antisaccade task was carried out with a custom written application in MATLAB. Latency and decision accuracy were investigated. Saccades can be defined based on three thresholds: velocity (30◦/s), acceleration (8000◦/s^2), and saccadic motion (0.15◦) (Beynel et al., 2014). Latency was determined as the first significant deviation of eye movement from the mean deviation (i.e. from the noise). Decision error was defined as the deviation from the predicted direction. A 3 × 2 × 2 repeated-measures ANOVA design was used with prosaccade and antisaccade errors (percentage) and latency (ms), time of administration (pre- or post-stimulation), and side of stimulation (right or left DLPFC) as within subject factors, and stimulation type (iTBS or cTBS) as between subject factor.

V. RESULTS

1. STUDY I

1.1 TNT performance

The means of correctly recalled trials across TNT conditions are presented in Figure 6. We found a significant main effect of group (HC vs. AD) x condition (T, NT, and B) [Greenhouse-Geisser $F(1.568,108.198) = 5.408$, $p \leq 0.01$, observed power 0.767] after correcting for the potentially confounding effect of age. There were no significant group differences between AD and HC group when comparing each testing individually: Baseline $F(1,70) = 2.707$, $p = 0.104$, Think $F(1,70) = 0.807$, $p = 0.372$, No-Think $F(1,70) = 2.037$, $p = 0.156$. In addition to this, we compared the two newly computed variables between the two groups and found a significant difference for NT-B [$F(1,70) = 6.400$, $p \leq 0.01$]. In contrast to this T-B was not significantly different between the two groups [$F(1,70) = 1.521$, $p = 0.222$]. We believe that these results support the idea that there is a significantly different pattern of performance for AD and HC when assessing the effect of inhibition on retrieval. While the two groups did not differ essentially in their baseline memory ability as well as effect of practice on retrieval, the ability to inhibit memory retrieval seems altered in the AD group. The mean NT-B score for HC group was negative, reflecting the effect of the instruction to suppress the retrieval of NT items. As opposed to this, mean NT-B scores for AD patients remained positive, indicating that the instruction to inhibit retrieval did not lead to a significant decline in recall.

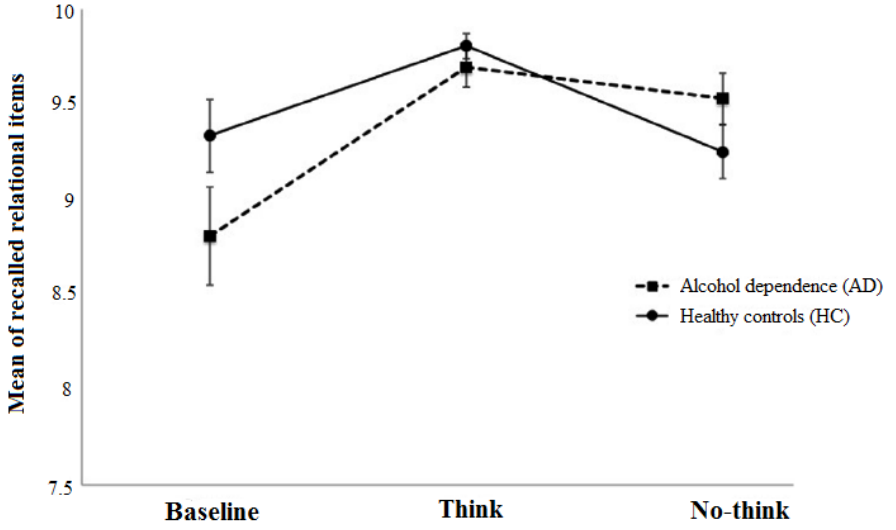

Figure 6 – Means of correctly recalled trials across TNT conditions. We found a significantly different pattern of performance for AD and HC when assessing the effect of inhibition on retrieval. At the same time the two groups did not differ significantly in their baseline memory ability as well as effect 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 a significantly increased demand for training in order to reach the same levels of accuracy as the control group [$U(72) = 518.15$, $p < 0.05$].

1.2 Correlations within the AD group

The descriptive statistics of self-report measures registered in the patient group are presented in Table 5.

	Minimum	Maximum	Mean	Standard deviation
AUDIT total score	19.00	40.00	31.10	6.12
BDI total score	1.00	28.00	10.98	7.10
BIS total score	50.00	94.00	68.54	9.61
DDT	0	0.94	0.08	0.17
SCL-90 somatization index	0	2.33	0.76	0.64
SCL-90 compulsive index	0.11	3.22	1.29	0.73
SCL-90 interpersonal sensitivity index	0	3.22	1.06	0.87
SCL-90 depression index	0.08	3.54	1.35	0.99
SCL-90 anxiety index	0	3.10	1.05	0.77
SCL-90 hostility index	0	2.17	0.65	0.60
SCL-90 phobic anxiety index	0	1.71	0.68	0.52
SCL-90 paranoid ideation index	0	3.17	0.92	0.76
SCL-90 psychoticism index	0	2.00	0.71	0.58
SCL-90 global severity index	0	0.20	0.09	0.06
SCL-90 positive symptom total	4.00	76.00	45.92	20.11
SCL-90 positive symptom distress total	1.00	3.12	1.80	0.60

AUDIT: Alcohol Use Disorders Identification Test; BDI: Beck Depression Inventory; BIS: Barratt Impulsiveness Scale; DDT: Delayed Discounting Task; SCL-90: Symptom Checklist-90.

Table 5 – Descriptive clinical measures of the alcohol-dependent group

Several clinical symptom measures correlated with performance achieved on the TNT task (see Table 6). Measures of Delayed Discounting Task (DDT) 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 NT 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: $R(36) = -0.445$, $p \leq 0.01$].

	Number of repetitions in learning phase	**Number of recalled words**				
		Training phase	Final test	Baseline	Think	No-think
Pearson coefficient (*R*)						
DDT	0.311	**-0.405***	-0.206	-0.313	0.221	-0.020
BIS total score	-0.196	**-0.335**	-0.078	-0.098	-0.043	-0.002
SCL-90 compulsive index	0.040	-0.125	-0.197	-0.082	-0.055	**-0.359***
SCL-90 interpersonal sensitivity index	0.159	**-0.415***	**-0.377***	-0.334	-0.097	**-0.356***
SLC-90 depression index	0.134	**-0.312**	**-0.350***	-0.269	-0.015	**-0.465****
SCL-90 anxiety index	0.231	**-0.346***	**-0.393***	**-0.361***	0.019	**-0.438****
SCL-90 hostility index	0.057	**-0.350***	-0.074	-0.082	0.065	-0.101
SCL-90 phobic index	-0.033	**-0.459****	-0.213	-0.299	-0.031	-0.010
SCL-90 paranoid ideation index	0.183	**-0.388***	-0.269	-0.283	0.076	-0.282
SCL-90 global severity index	0.107	**-0.411***	**-0.339***	-0.288	-0.040	**-0.380***
SCL-90 positive symptom distress total	0.115	**-0.377***	-0.327	-0.256	0.010	**-0.445****

*Correlation is significant at the 0.05 level; **Correlation is significant at the 0.01 level.

DDT: Delayed Discounting Task; BIS: Barratt Impulsiveness Scale; SCL-90: Symptom Checklist-90

Table 6 – Correlations between clinical measues and performance on the Think/No-think task in the AD group.

2. STUDY II

2.1 Clinical characteristics

The MD and HC groups were closely matched for age, gender and level of education (Table 3). Total HDRS scores at follow-up revealed a significant improvement in depressive symptom severity as compared to the first measurement ($t = 4.082$, $p \leq 0.004$). Scores on Beck Hopelessness Scale also decreased, but the difference from baseline scores remained below

statistical significance (t = 1.269, p = 0.245). All MD patients were treated with antidepressive medication and remained on the same schedule during the follow-up period.

2.2 Baseline testing

2.2.1 Explicit memory testing (MD > HC)

On the explicit memory task MD patients performed on a significantly lower level compared to HCs (M_{MD} = 56.743% ± 27.865, M_{HC} = 78.205% ± 16.707, p ≤ 0.001) (Figure 7A).

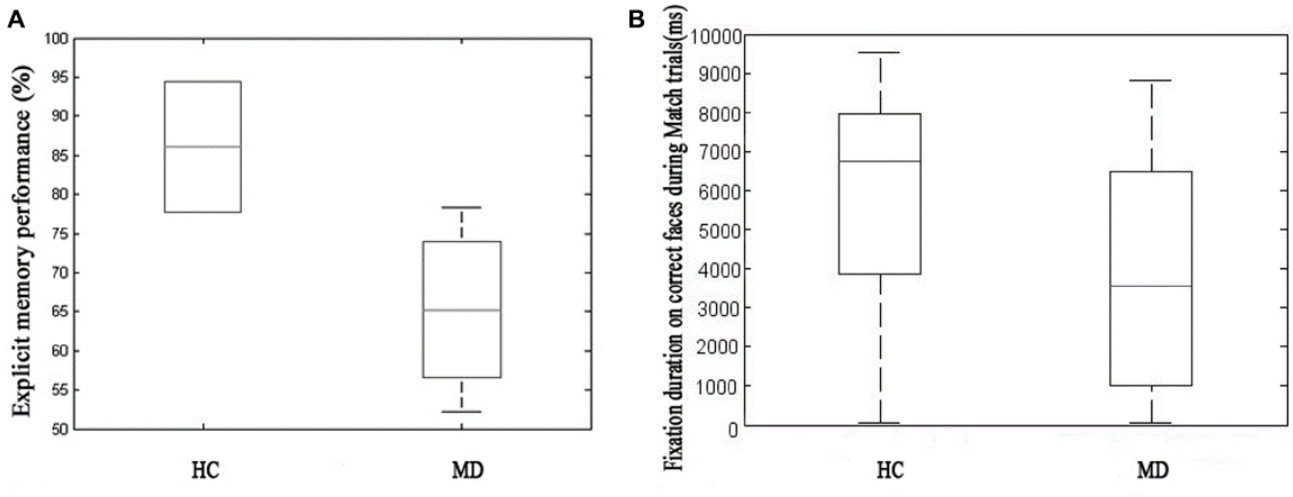

Figure 7 – Explicit memory performance during behavioral (forced choice button-press) testing on the left side of the figure (A) and fixation duration on faces correctly identified as a Match on the right (B) comparing the healthy control (HC) and major depression (MD) group. On the explicit memory task MD patients performed on a significantly lower level compared to healthy control (HCs) (the HC group showed low variability, M_{MD} = 56.743% ± 27.865, M_{HC} = 78.205% ± 16.707, $p \leq 0.001$). We found MD patients to fixate for a significantly shorter duration on correct faces (i.e., subsequently correctly identified as a matching face) during Match trials which contained relational memory information (M_{HC} = 5741.60 ± 2893.50, M_{MD} = 3795.30 ± 2899.00, t = 4.711, $p \leq 0.001$) as compared to the HC group. The two different approaches to measure relational memory performance correlated with each other (R = 0.586, p ≤ 0.003).

2.2.2 Implicit memory testing, the effect of facial emotion and the level of monetary reward loss (MD > HC)

We found MD patients to fixate for a significantly shorter duration on correct faces during Match trials (M_{HC} = 5741.60 ± 2893.50 ms, M_{MD} = 3795.30 ± 2899.00 ms, t = 4.711, p ≤ 0.001) as compared to HC (Figure 7B). Performance on implicit (eye-tracking) and explicit (forced-choice button-press) testing correlated significantly with each other (R = 0.586, p ≤ 0.003).

We investigated the effect of the different levels of virtual monetary reward or loss on the performance of the two groups. The repeated measures ANOVA did not detect a significant effect, thus we decided to analyze the two levels of reward and loss jointly. The repeated measures ANOVA of fixation duration revealed a significant main effect of relational memory condition (Match vs. Non-match) ($F_{1\text{-}38} = 23.728$, $p \leq 0.001$), a significant main effect of facial emotion ($F_{2\text{-}76} = 7.287$, $p \leq 0.001$) as well as a significant main effect of monetary reward or loss ($F_{1\text{-}38} = 42.705$, $p \leq 0.001$). Importantly, we found a significant interaction of group (MD vs. HC) by relational memory condition (Match and Non-match) by facial emotion (happy, sad, and neutral) by monetary reward and loss ($F_{2\text{-}76} = 3.131$, $p \leq 0.049$). The interaction testing of all factors revealed that, in the Match condition, the MD group viewed faces associated with monetary reward for a significantly longer duration (M = 3489.05 ± 1382.788 ms) than the HC group ($t_{48} = 2.501$, $p = 0.016$) (Figure 8). However, the MD patients fixated on the sad match faces associated with monetary reward for a significantly shorter duration (M = 2292.124 ± 1304.498 ms) than the HC group ($t_{48} = -3.637$, $p \leq 0.001$) (Figure 9).

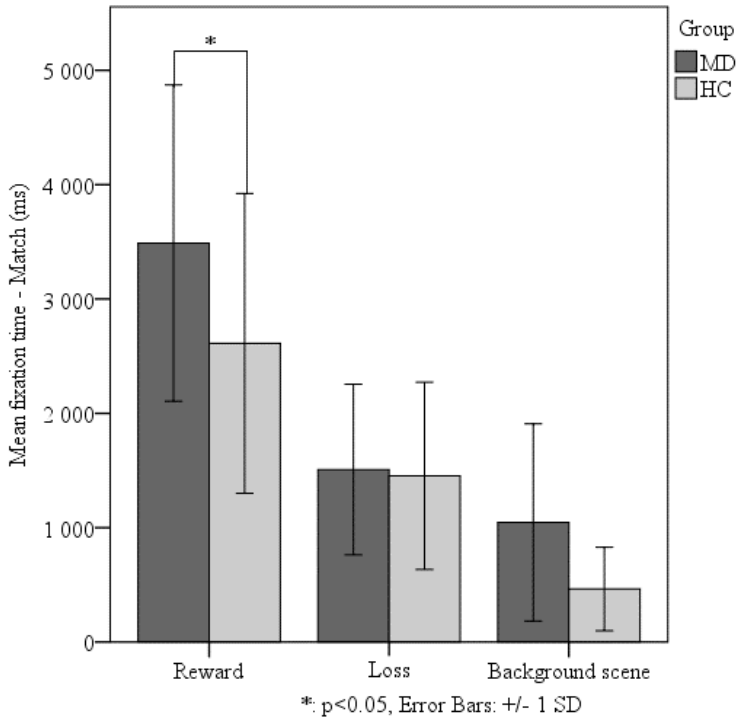

Figure 8 – Effect of virtual monetary reward or loss on fixation durations comparing the MD and HC groups. In the Match condition – when relational memory information was present –we found MD patients to view faces associated with monetary reward for a significantly longer duration (M = 3489.05 ± 1382.788) than the HC group ($t_{48} = 2.501$, $p \leq 0.016$). This analysis was justified by higher order statistical analysis examining main effects of facial emotion and virtual reward or loss on relational memory performance.

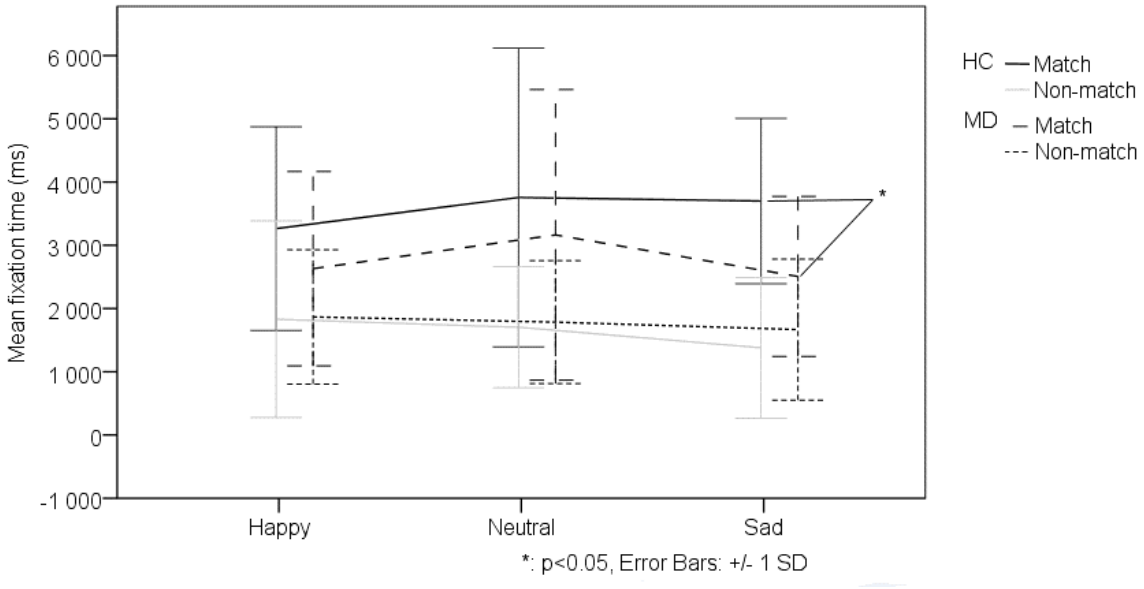

Figure 9 – Effect of facial emotion on viewing patterns comparing the MD and HC groups in trials associated with monetary reward. MD patients fixated on the sad match faces associated with monetary reward for a significantly shorter duration (M = 2291.124 ± 1304.498) than the HCgroup (t_{48} = -3,637, $p \leq$ 0,001).

2.2.3 Correlation of implicit and explicit memory performance with clinical symptom severity (MD only)

Performance on both explicit and implicit memory testing correlated negatively with depressive symptom severity as measured by clinical rating scales (explicit measure: $HDRS_{baseline}$: R = -0.501, p ≤ 0.001, $Beck_{baseline}$: R = -0.505, p ≤ 0.001, implicit measure: $HDRS_{baseline}$: R = -0.311, p ≤ 0.022, $Beck_{baseline}$: R = -0.280, p ≤ 0.040). This implies an association between better relational memory performance and lower scores on clinical rating scales, i.e. less severe symptomatology.

2.3 Baseline > Follow-up testing

2.3.1 Explicit and implicit memory testing

Explicit memory performance of the MD group did not improve significantly. No significant follow-up effect in viewing durations could be detected when comparing baseline and follow-up measurements in the MD group in a repeated measures ANOVA design including relational memory condition (Match and Non-match), emotional expression (happy, sad, and neutral) and monetary reward or loss. Nevertheless, we found a correlation between performance of the MD follow-up group on implicit and explicit memory testing (R = 0.749, p ≤ 0.02).

2.3.2 Correlation of implicit and explicit memory performance with clinical symptom severity (MD only)

We found a negative correlation between severity of depressive symptoms based on HDRS scores and memory performance of the MD group at follow-up (explicit testing: $R = -0.465$, $p \leq 0.045$, implicit testing: $R = -0.428$, $p \leq 0.067$). However, we did not find a significant correlation with Beck scores ($p > 0.05$).

2.3.3 Correlation of significant differences in viewing patterns (MD > HC) at baseline with MD clinical symptoms at follow-up

While implicit and explicit memory performance at baseline showed no correlations with symptom severity at follow-up ($p > 0.05$), 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 ($R = -0.399$, $p \leq 0.016$). However, no significant correlation with Beck scores was found ($p > 0.05$).

3. STUDY III

3.1 Discriminability performance on the n-back test

Means and standard deviations of d' according to cognitive load, stimulation side and stimulation type are presented in Table 7.

	1-back				2-back				3-back			
	Left		Right		Left		Right		Left		Right	
d'	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
pre iTBS	4.431	0.081	4.253	0.273	3.474	0.637	3.327	0.729	2.033	0.777	2.091	0.765
post iTBS	4.213	0.360	4.373	0.158	3.715	0.581	3.747	0.662	2.386	0.854	2.304	0.784
pre cTBS	4.376	0.133	4.325	0.225	3.535	0.764	3.503	0.661	1.981	1.001	2.188	0.889
post cTBS	4.328	0.237	4.413	0.101	3.492	0.683	3.565	0.717	2.012	0.757	2.346	0.972

Table 7 – Means and stantard deviations of d' values according to cognitive load, stimulation side and stimulation type.

We found a significant main effect of time of measurement (pre- or post-stimulation) ($F_{(1,34)} = 9.571$, $p < 0.004$) with higher d' scores after stimulation. A significant main effect of cognitive load was revealed as well ($F_{(2,33)} = 157.909$, $p < 0.001$, with the highest d' scores for one-back condition ($p < 0.001$ over two-back condition), and the lowest d' scores for three-

back condition (p < 001 over two-back condition). This indicates that signal detection deteriorates with the increasing cognitive demand. A significant interaction between time of measurement and cognitive load was also detected ($F_{(2,33)} = 5.015$, $p < 0.013$), with significantly higher discriminability after stimulation in the two-back ($p < 0.032$) and three-back condition ($p < 0.021$,), and with no difference for one-back condition ($p > 0.625$) according to the post-hoc analysis. A 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 ($p > 0.343$) (Figure 10). No significant change occured considering time of measurement in the cTBS group at any level of the n-back task (one-back: $p > 0.665$, two-back: $p > 0.946$, three-back: $p > 0.501$). The side of the stimulation did not affect any of the measured variables (all $p > 0.05$).

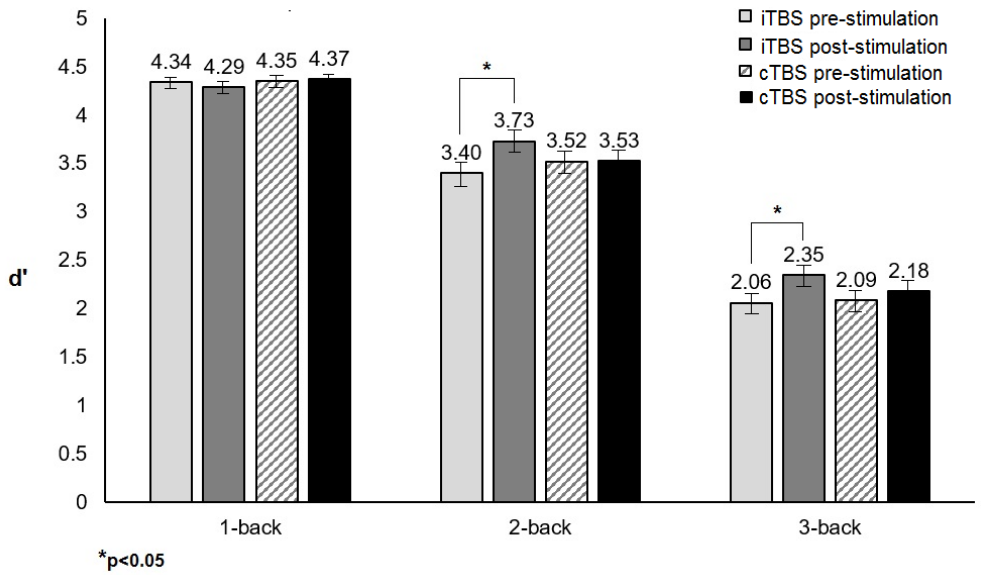

Figure 10. Effects of stimulation on d' at 1-back, 2-back, and 3-back level. Error bars:+/- 1 SD A significant interaction between time of measurement, cognitive load and type of stimulation was found ($F_{(2,33)} = 3.864$, $p < 0.031$). Post-hoc analysis revealed that d' increased only in the iTBS group at two-back ($p < 0.001$) and three-back level ($p < 0.005$), but not for one-back ($p > 0.343$).

3.2 Performance on the Attention Network Test

We found no effect of either type of stimulation on overall accuracy ($p > 0.591$) or on overall reaction time ($p > 0.347$) across participants on the ANT. According to our hypothesis, we focused on the effect of iTBS and cTBS on variables related to executive functioning. Means of medians, standard deviations and standard errors of corrected conflict effects and conflict effects without correction are presented in Table 8. Regarding Conflict effect with its median computed according to the original methods, a significant interaction of time of measurement

and stimulation type was revealed ($F_{(1,33)} = 5.240$, $p < 0.029$). Post-hoc analysis revealed that stimulating the right DLPFC resulted in a significant interaction of time of measurement and stimulation type ($F_{(1,33)} = 6.766$, $p < 0.014$). This did not occur for the stimulation of the left DLPFC ($p > 0.05$). Intermittent TBS resulted in the decrease of conflict effect, while cTBS had an opposite effect, causing an increase. Similar results were found when applying the corrected formula: a significant interaction of time of measurement and stimulation type was found for conflict effect ($F_{(1,33)} = 4.855$, $p < 0.035$). Furthermore, similar to the results of the original computation, post-hoc analysis also revealed that stimulating the right DLPFC resulted in a significant interaction of time of measurement and stimulation type ($F_{(1,33)} = 5.465$, $p < 0.026$, see Figure 11). This was again not present for the stimulation of the left DLPFC ($p > 0.466$). The analysis of variables of conflict effect revealed a significant interaction of time of measurement and stimulation type on median RTs of incongurent stimuli, for the right DLPFC ($F_{(1,33)} = 5.416$, $p < 0.026$), but not for the left DLPFC ($p > 0.841$).

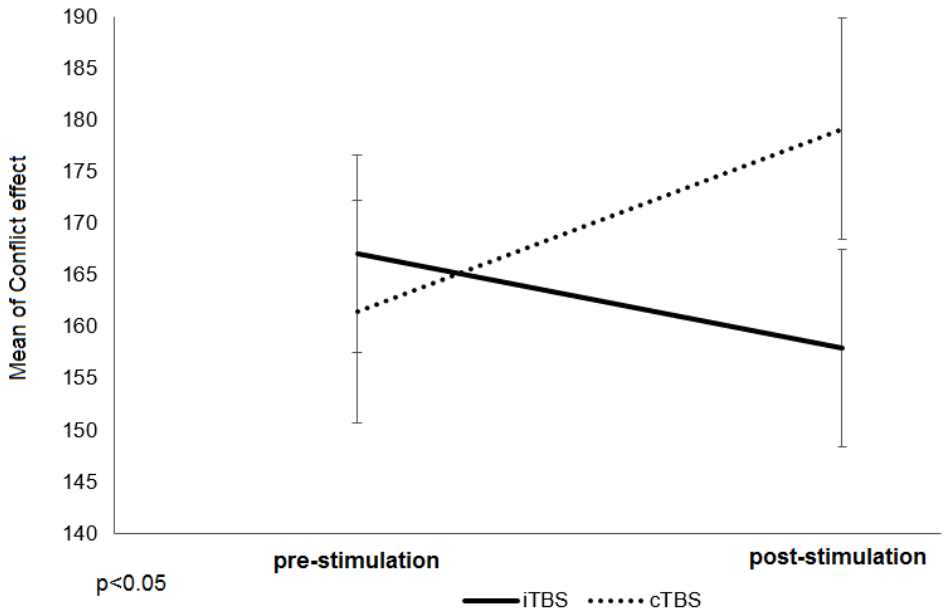

Figure 11 – Means of corrected conflict effect measures in the iTBS and cTBS groups before and after stimulation. Error bars: +/- 1 SE. a significant interaction of time of measurement and stimulation type was found for conflict effect ($F_{(1,33)} = 4.855$, $p < 0.035$). Post-hoc analysis also revealed that stimulating the right DLPFC resulted in a significant interaction of time of measurement and stimulation type ($F_{(1,33)} = 5.465$, $p < 0.026$).

		Corrected conflict effect			Conflict effect without correction		
		Mean	SD	SE	Mean	SD	SE
cTBs	Left DLPFC pre stim.	170.054	170.054	11.738	101.028	25.739	6.067
	Left DLPFC post stim.	158.864	158.864	13.474	100.417	23.209	5.470
	Right DLPFC pre stim.	167.100	167.100	10.751	91.611	23.364	5.507
	Right DLPFC post stim.	157.919	157.919	10.022	103.333	23.239	5.478
iTBS	Left DLPFC pre stim.	174.707	174.707	10.560	101.583	29.239	6.892
	Left DLPFC post stim.	172.258	172.256	10.184	96.583	37.301	8.792
	Right DLPFC pre stim.	161.495	161.495	10.160	100.500	34.216	8.299
	Right DLPFC post stim.	179.153	179.153	9.526	93.500	29.144	7.068

Table 8 – Means, standard deviations and standard errors of corrected conflict effect and conflict effect without correction in the iTBS and cTBS group before and after stimulation.

3.3 Saccade/antisaccade task

Means and stantard deviations of saccade/antisaccade variables are presented in Table 9. We investigated the effect of iTBS and cTBS on the perfomance 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 ($p < 0.001$).

Furthermore, we found a significant interaction of time of measurement and stimulation type 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 ($p > 0.786$). Intermittent TBS resulted in a lower rate of errors in the prosaccade task, while the cTBS lead to a higher rate of errors. No significant difference or interaction was detected between the groups in the percentage of errors in the antisaccade task ($p > 0.516$), or in the total latency of saccades and antisaccades ($p > 0.802$).

	Total latency (sec)				Errors in prosaccades (%)				Errors in antisaccades (%)			
	Left		Right		Left		Right		Left		Right	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
pre iTBS	0.287	0.457	0.290	0.031	10.632	21.713	14.317	17.160	23.490	22.513	23.174	24.014
post iTBS	0.282	0.411	0.280	0.375	9.671	14.586	7.698	7.583	27.836	20.375	19.724	23.584
pre cTBS	0.283	0.054	0.272	0.029	6.212	7.510	3.138	4.288	25.066	14.799	24.470	14.562
post cTBS	0.267	0.030	0.266	0.039	4.558	7.957	5.570	5.995	21.090	10.524	24.444	17.705

Table 9 – Means and standard deviations of total latency, errors in prosaccades and errors in antisaccades in the iTBS and cTBS group before and after stimulation.

VI. DISCUSSION

While MD and AD constitute distinguished disorder categories defined by specific criteria, physiopathology and characteristics, in real life they often accompany each other, and one might facilitate the development of the other. Strikingly, evidence even indicates a genetic predisposition to a phenotype of MD comorbid with AD linked to chromosome 1 (Nurnberger et al., 2002). Several brain areas are affected in both MD and AD, such as the MTL including the hippocampus, prefrontal areas or the limbic cycle (Miguel-Hidalgo and Rajkowska, 2003). These alterations are associated with functional neurocognitive changes affecting learning skills, memory processes and executive functions, among others. Cognitive deficits, especially executive function impairment are linked to remarkably decreased quality of life (Green et al., 2000), maladaptive social skills (Kurtz et al., 2005) and poorer treatment outcomes (Czuchry and Dansereau, 2003), which all indicate the importance of this question.

The close relationship between AD and mood disorders has been studied extensively and firmly established (Grant and Harford, 1995; Helzer and Pryzbeck, 1988; Regier et al., 1990; Ross et al., 1988). Findings report a high level of comorbidity between AD and depression or anxiety (Boschloo et al., 2011; de Graaf et al., 2002). Notably, remitted or current AD represents a significantly increased risk for chronically persisting depressive and/or anxiety disorders (Boschloo et al., 2012). Trait anxiety present after 3 weeks of abstinence was found to represent a great risk for relapse (Driessen et al., 2001). While the relevant literature consistently indicates that patients diagnosed with depression have difficulties with memory inhibition (Cottencin et al., 2008; Hertel and Mahan, 2008) it is unclear whether AD patients with co-morbid depression and anxiety resemble patients suffering from anxio-depressive disorders alone. Sjoerds et al. (2014) did not find AD patients to be more impulsive than patients with depression and anxiety symptoms solely, but they did reveal impairments of inhibition in the AD group which correlated with increased disorder severity. Our current findings support the idea of a relevant effect of anxio-depressive 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.

Our results also 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. Examining AD patients in intermediate term abstinence

allowed us to investigate the consequences of chronic alcohol consumption on the ability to retrieve or suppress previously learned memory associations without the interfering effect of current alcohol use or symptoms of withdrawal. 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 previoustly related words in the NT condition supporting the critical effect of cognitive control processes over inhibition of retrieval. While the pattern of results was statistically comparable across groups for the B and T conditions, it was reversed for the critical NT items. The ability to suppress retrieval was found to be impaired in AD patients in this condition as we expected.

Previous studies have confirmed that episodic memory performance can normalize over an approximately 6-month period of sustained abstinence (Fein et al., 2006; Munro et al., 2000). In contrast to this, AD patients who relapsed showed more severely impaired memory related cognitive performance that could not be accounted for by a general executive dysfunction (Pitel et al., 2009). In addition, Pitel et al. (2010) found AD patients to present only mild to moderate deficits of explicit memory capacities. 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. Based on our results the baseline relational memory performance of AD patients was not significantly worse compared to the control group. Strikingly, repeated training on retrieval and the instruction to try and remember certain items had a beneficial effect on TNT performance in the T condition.

Decreased performance compared to baseline in the NT condition suggest that cognitive control exerted over inhibition of retrieval actually reduces accuracy and depletes memory processes. This is supported by our results deriving from the HC group. As opposed to this, NT scores in the AD group increased. Intermediate-term abstinent patients with AD have been reported to present pronounced dysfunctions in the generalization of associations (Mattyassy et al., 2012). This impairment might be indicative of decreased episodic memory performance and relate to the dysfunction of MTL structures. Functionally relevant microstructural changes in brain regions contributing to episodic memory functions have been reported in AD patients (Chanraud et al., 2009). Neuroanatomical correlates of relational encoding, as well as cognitive

control over associative memory processes and inhibition of retrieval have been assessed taking advantages of a combination of the behavioral approach and neuroimaging methods. Results based on functional magnetic resonance imaging (fMRI) as well as event related potential (ERP) electroencephalography (EEG) studies confirm the role of interaction between the lateral prefrontal cortex (LPFC) involving the middle frontal gyrus (MFG) and MTL structures including the hippocampus (Bergstrom et al., 2007; Detre et al., 2013; Waldhauser et al., 2012). Findings from fMRI studies signify increased activation of the MFG and adjacent areas for the NT condition whereas the hippocampus showed decreased overall activity during cued recall testing. Strikingly, actually forgotten items of the NT condition evoked an increase in hippocampal activation as compared to all other trials but solely in the first part of the experiment. Conversely, the initial increase was followed by the largest deplete in activation during the final phase. In view of this pattern a potential explanation might be that inhibition of retrieval derived from the MFG induces a complex mechanism commencing with the association of inhibitory processes to the to-be-forgotten NT stimuli. Meta-analysis of findings from neuroimaging studies support the role of MFG in the 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 (Depue and Banich, 2012). Whereas the vast majority of the TNT literature supports the notion that intentional cognitive control improves inhibition of retrieval, it has to be stated that some studies did not replicate these results (Dieler et al., 2010; Mecklinger et al., 2009). Furthermore, instructions given to participants (Racsmany et al., 2012), demand on cognitive processes, and especially working memory as well as strategy might significantly influence behavioral results on the TNT task, which need further clarifying (Festini and Reuter-Lorenz, 2013; Raaijmakers and Jakab, 2012).

In AD the PFC and its subregions seem particularly vulnerable to chronic ethanol consumption (for a review see Moselhy et al., 2001). Findings also indicate that disturbances in PFC function play a crucial role in recovery difficulties and increased relapse risk (Seo et al., 2013). Recent evidence based on animal studies indicate that abstinence from alcohol in rats with a history of significant alcohol intake produced dysregulation of the medial PFC resulting in an impairment of executive control processes. Notably, the deficit typically occurred during acute (first days of abstinence) but not prolonged (16–68 days) abstinence suggesting the potential of improvement with the length of abstinence (George et al., 2012).

Facets of impulsivity have frequently been associated woth the mechanism of inhibitory control (Dalley et al., 2011; de Wit, 2009). A number of studies provide evidence for the

impairment of inhibitory processes in AD (Li et al., 2009; Noel et al., 2001). Additionally, measures of inhibitory control were raised as predictors of problem drinking in adolescents at risk for AD (Nigg et al., 2006). Here we found higher levels of impulsivity to be associated with impaired relational encoding in AD patients.

In contrast with this, MD patients showed a different pattern of relational memory deficit. Our study provides novel evidence for a relational memory deficit in MD. We were able to demonstrate this deficit by studying eye-movements as an indirect measure of relational memory and by supporting our findings with explicit, forced-choice recognition of the previously associated stimulus pairs. According to our results a deficit in retrieval of relational representations may well be presumed in MD as indicated by a significantly impaired match face recall during explicit testing accompanied by significantly shorter viewing durations on the matching face during eye-tracking. Episodic memory disturbances have been raised as a potential pre-morbid marker of depression (Airaksinen et al., 2004; Airaksinen et al., 2007). 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. The relatively small number of test trials has to be noted as a limitation, although this paradigm can be compared to previous assessments of relational memory (Titone et al., 2004; Williams et al., 2010).

With our experimental design we aimed to detect the effect of facial emotion and monetary reward or loss on relational memory. However, we intended to separate the effect of virtual monetary reward or loss from social reward represented by faces with positive emotional valence or negative social stimuli, respectively, by not cueing former with the background scene, but merely establishing an implicit link between the facial emotion and the virtual monetary reward or loss. 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.

However, the viewing preference for previously rewarded stimuli and the decreased fixation duration on sad facial expressions was quite unexpected.

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 (Blood et al., 2010; Zhang et al., 2013). Reward learning mechanisms are known to be linked to the striatum (Schultz, 2006). However, more recently, the ability to transfer value between stimuli thus biasing decisions not driven by conscious awareness has been attributed to the hippocampus (Wimmer and Shohamy, 2012). Here we aimed to manipulate associative encoding and retrieval by value representations and assess potential, more implicit effects on hippocampal mechanisms of action. Our analysis revealed that facial emotion and virtual monetary reward or loss had a significant influence on relational memory condition. We found that the MD group viewed faces previously associated with virtual monetary reward for a significantly longer duration during trials containing relational memory information, i.e., during Match trials. Our previous results also indicated a greater influence of reward in MD (Must et al., 2006). This seeming contradiction might be explained by individual variations in neuronal activation patterns (Misaki et al., 2016), genetic variations and personality traits (Byrne et al., 2016; Must et al., 2007) or false recollection affecting the cognitive evaluation of rewarding stimuli (Davidson et al., 2002). Antidepressive therapy has also been found to have an enhancing effect on positive information processing (Wells et al., 2014). In the neural background of an altered attentional focus on reward contingencies in depression the fronto-striatal circuit is presumed to be involved. Converging evidence shows that depressed patients demonstrate abnormal behavioral responses to reward contingencies corresponding to abnormal function in fronto-striatal systems (Eshel and Roiser, 2010). 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 (Ma et al., 2012).

Previous studies reported emotional memory deficits in MD and related disorders assuming that depression is associated with prolonged attention on negative information. Indeed, eye-movement studies revealed that dysphoric patients showed a significantly greater bias to maintain gaze longer on negative pictures, relative to control pictures with no evidence for an initial shift of orienting to negative cues (Caseras et al., 2007). Taking into consideration that depressed patients are characterized by decreased maintenance of gaze on positive stimuli and increased maintenance of gaze on dysphoric stimuli, one might presume that a maintained attentional preference also leads to a mood-congruent memory bias (Armstrong and Olatunji, 2012). However, results remained contradictory. Despite an impaired memory performance for

emotional stimuli in depression and dysphoria, no mood-congruent memory bias could be identified for dysphoric or previously depressed patients (Sears et al., 2011; Williams et al., 1997; Yiend, 2010). Relational memory for negative emotional stimuli was found to activate the hippocampus and related areas both during encoding and retrieval. However, hippocampal activity and memory performance were not enhanced by negative emotionality (Onoda et al., 2009). Results on the effect of emotional faces on attentional bias in MD further contribute to the complexity of interpretations. Symptom severity has been found to correlate both with an attentional bias for sad and happy faces (Duque and Vazquez, 2015) Some studies report a persisting attentional bias to sad faces in remitted MD (Soltani et al., 2015), while others found no significant difference as compared to controls concerning sad faces, but a decreased attentional bias toward happy faces (Li et al., 2016a).

It has been pointed out that the neuropathophysiology of depression also involves a limbic-thalamo-cortical circuit that includes the amygdala, striatum, medio-dorsal thalamus, and areas of the ventral and medial prefrontal cortex (Drevets, 2003). Reductions in hippocampal size and enlargement of the amygdala in MD were revealed as potential predictors of emotional memory functions (Weniger et al., 2006). Increased activity of the fronto-limbic network and specifically amygdala involvement in episodic memory formation in first episode MD patients has been proposed as a neurocognitive trait or vulnerability factor for depression (van Eijndhoven et al., 2011). The level of the over-recruitment of a neuronal network involved in emotional relational memory was also found to be related to the severity of clinical symptomatology (Hamilton and Gotlib, 2008). Strikingly, an eventual control of amygdala over-recruitment might serve as a novel therapeutic approach for the treatment of depressive symptoms (Young et al., 2014). Amygdala activation has reliably been found in response to both positive and aversive emotional stimuli (Ball et al., 2009). The role of amygdala has become evident in triggering responses and consequent decision-making processes to emotional stimuli, including facial emotions as well as monetary reward or loss (for a comprehensive review see Gupta et al., 2011).

Regarding cognitive deficits in remitted patients, episodic memory impairment previously described in MD has been found to persist after the remission of clinical symptomatology (Airaksinen et al., 2006; Bierman et al., 2005). Here we found preferential viewing of the matching face subsequently recognized as correct as well as behavioral measures of relational memory to correlate negatively with symptom severity. Therefore, better relational memory performance implies less severe clinical symptomatology. However, implicit and explicit memory performance at follow-up did not improve significantly as compared to

baseline. Again, preferential viewing of the matching face correlated positively with the explicit choice and negatively with symptom severity. Viewing patterns of MD patients were found to be similar to controls for Non-match displays, which contained no relational memory information. Converging scientific evidence supports the clinical notion that cognitive impairment may remain and persist residually in the remitted state of MD (Hasselbalch et al., 2011). Mood congruent information-processing biases also presumed to have a crucial role as vulnerability factors for the development, maintenance (Everaert et al., 2015) and even recurrence of depression (Gotlib and Joormann, 2010; Kellough et al., 2008; Mannie et al., 2015). Specifically, persistent emotional memory impairment has been linked to distinct neural mechanisms mainly involving the frontal cortical neuronal networks (van Wingen et al., 2010). Strikingly, impaired responsiveness to reward related to the fronto-striatal network has also been reported in remitted MD suggesting this to be a trait marker for depression (Dichter et al., 2012).

With the follow-up examination carried out 6 months after the first testing, we aimed to examine whether specific facets of relational memory impairments in MD would potentially predict the patients' clinical outcome. We did not detect any significant follow-up effects, the relational memory deficit persisted. We found that longer fixation duration for faces associated with virtual reward in Match trials at baseline was associated with a less severe clinical symptomatology and a better outcome at follow-up. Nevertheless, we remain critical and aim to further extend our investigations considering the low number of patients examined at follow-up. Here we also need to note that all patients were treated with antidepressive medication at the time of investigation. However, all patients remained on the same medication during the follow-up period. Previous research findings have suggested a distinct pattern of cognitive impairment involving memory aspects persisting beside antidepressive medication (Luo et al., 2013).

We believe that our current results provide novel insight into the complex pattern of cognitive deficit present in AD and MD. According to the TNT paradigm, AD patients seem to have impaired learning skills when associating two unrelated items, and they also presented deficits in inhibition of control over suppressing memories. Our results also suggest that AD patients have deficits in the ability to modulate behavior based on reward and punishment contingencies. MD patients had impaired associative memory performance based on a forced-choice recognition test and eye-tracking measures. Their responses were influenced by emotional stimuli and reward/ punishment contingencies. According to the literature, MD patients show problems with reward and punishment processing and have distortions in

emotional information processing, which may be captured by tracking eye-movements. The notion has been raised, that the above cognitive deficits may contribute to the recurrence of depressive episodes.

Age and gender are modulating factors of crucial importance recommended to be considered when investigating cognition in any psychiatric condition, such as MD or AD (Ganguli, 2009). In the elderly, symptoms of depression along with different levels of cognitive impairment can be a sign of dementia (e.g. vascular dementia or AD) (Morimoto et al., 2014). It is important to distinguish these clinical manifestations from pseudodementia associated with a current depressive episode which may show a similar pattern of cognitive impairment (Alexopoulos et al., 1993). In addition, late-life depression has specific symptomatic characteristics that require distinct treatment approaches. Depressed mood as well as chronic alcohol consumption are both considered major risk factors for dementia (Devanand et al., 1996; Letenneur, 2004; Ownby et al., 2006; Topiwala et al., 2017). The MTL including the hippocampus, especially its C1 subregion, the amygdala, the parahippocampal gyrus and the thalamus are all particularly vulnerable to chronic ethanol consumption and aging (Yang et al., 2012). In combination with aging, gender might also greatly influence the individual cognitive reserve capacity altering functionality (for a review, see Nemeth et al., 2017).

Converging research evidence supports the key role of cognition in social functions in AD, MD and several other neuropsychiatric disoders (Fernandez-Serrano et al., 2010; Hammar and Ardal, 2009; Stuchlik and Sumiyoshi, 2014). Thus, several therapeutic approaches aim to improve cognition in AD and MD, such as cognitive behavior therapy, antidepressive treatment and AA groups (Petersen and Zettle, 2009). Among treatment measures, TMS has recently gained increasing attention not only as serving as a novel method to treat depressive symptoms and modulating cognition, but also to treat AD (Gorelick et al., 2014; Grall-Bronnec and Sauvaget, 2014; Hoppner et al., 2011). The effect of TMS on cognition remains a question of debate, and the enrollment of healthy participants might yield further useful insight into the somewhat controversial findings of TMS related to cognitive function. More recently, a growing body of research supports the beneficial effect of rTMS and TBS on cognition in healthy individuals (Bagherzadeh et al., 2016; Demeter, 2016; Guse et al., 2010).

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 working memory. This effect was independent of the stimulated hemisphere. In contrast, no significant effect of cTBS was demonstrated with the n-back task. Previous research reported the deteriorating effect of cTBS on working memory (Schicktanz et al., 2015); however, more evidence points towards the facilitating effect of iTBS on it (Bagherzadeh et al., 2016; Demeter, 2016; Hoy et al., 2016). 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. In addition, we did not detect any hemispheric lateralization effects of TBS.

When explaining memory processes, Moscovitch (1992) raised a model with four major components: (1) a non-frontal component including neocortical areas mediating item-specific completion of implicit memory tasks; (2) a modular medial temporal or hippocampal component dealing with encoding, storage and retrieval of episodic memory tests involving associative items; (3) a basal ganglia component mediating procedural tasks of memory; (4) a central system component involving frontal areas mediating performance on explicit memory tests when the use of cognitive strategies is required. Previous neuropsychological and neuroimaging studies have underlined the importance of frontal areas in memory processes. The PFC, especially the DLPFC seems to have a crucial role in both WM and episodic memory processes (Curtis and D'Esposito, 2003), implicating a connection or interaction between them. This link could be the episodic buffer defined as a multimodal loop supporting the storage of new material in long-term memory (Baddeley, 2000), in which the DLPFC has a special role in organizing WM (Blumenfeld and Ranganath, 2006).

The laterality of activities in brain areas involved in WM proceses is still a debated issue. Some models emphasize hemispheric asymmetry in activity during encoding and retrieval like the HERA (hemispheric encoding/ retrieval asymmetry) (Tulving, 1984) or the CARA (cortical asymmetry of reflective activity) (Nolde et al., 1998) model. On the other hand, other studies support the bilaterality of both encoding (Fan et al., 2002; Sandrini et al., 2003; Schmidt et al., 2002) and retrieval. We did not find any differences in n-back performance related to the side of the stimulation. We presume that both the right and left DLPFC contribute to successful encoding and retrieval. Nevertheless, it has to be noted that we did not apply the stimulation during the assumed time period of encoding or retrieval, but before and after the task has been performed, thus only measuring potential effects on overall performance.

We found no significant effect of stimulation on overall accuracy or reaction time on the ANT. These variables might be too robust in young, healthy participants for them to be influenced significantly by one session of TBS. We also analyzed the influence of TBS on attentional networks. Fan et al. (2002) demonstrated that three major attentional networks can be distinguished which operate relatively independently from each other: the orienting system, the alerting system and executive attention. 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. CTBS appeared to exert a deteriorationg effect on conflict detection causing longer reactions times for incongruent stimuli, while iTBS resulted in an improvement reflected by shorter RTs. These results are consistent with data from Xu et al. (2013)Xu et al., 2013, suggesting cTBS to cause an increase in conflict effect when stimulating the right DLPFC. (Yan et al., 2009) also supported the role of right DLPFC in attention control processes, as only stimulation of the right DLPFC was associated with significant changes. The importance of the right prefrontal and parietal brain areas are well known in attentional control functions (Cabeza et al., 2008; Coull et al., 1998; Coull et al., 1996a). A recent meta-analysis drew attention to the role of the right anterior insula and inferior frontal junction in supervisory attentional control over the importance of PFC (Cieslik et al., 2015). The authors presume that PFC has a rather indirect role by selecting the goal-relevant stimuli. In addition to this, DLPFC in itself is a highly complex brain area that might not act homogenously when contributing to control functions. According to Cieslik et al. (2013), the right DLPFC can be divided into two subregions: an anterior-ventral and a posterior dorsal subregion, based on their activation patterns and connections throughout the brain as yielded by neuroimaging studies. In the light of the ANT specifically, executive control is linked to complex mental operations like detecting and resolving conflict occurring between certain brain areas (Botvinick et al., 2001; Bush et al., 2000), which involves mostly the ACC, and the LPFC (Matsumoto and Tanaka, 2004), both being parts of the dopamine system of the VTA (Benes, 2000). Xiao et al. (2016) found that executive control can be associated not only with areas of the dorsolateral superior frontal gyrus, but also the thalamus and parahippocampal gyrus.

We also aimed to assess the immediate effect ot iTBS and cTBS on prosaccades and antisaccade performance. The role of DLPFC in organizing eye-movements and in decision-making processes related to eye-movements have been broadly supported (e.g. Pierrot-Deseilligny, 2004; Purves, 2001). 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. It is also possible that the smaller impact of the stimulation was compensated by the contralateral hemisphere through interhemispheric inhibition. However, 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. Yan et al. (2009) assessed the functional connectivity of the DLPFC and ACC and detected a stronger association in the righ DLPFC. We presume that the lateralization effect of stimulation is explained by the neuronal network involved in attention control (Wang et al., 2010).

VII. CONCLUSIONS

In summary, our first study provides novel evidence for a deficit to exert inhibition of retrieval by applying the TNT paradigm in AD. Relational encoding showed a significantly different pattern in the two groups with an increased demand for training in AD. However, associative recall ability in intermediate-term abstinence was not found to be significantly impaired when compared to HCs. Crucially, the instruction to try and suppress retrieval did not reach the level of the HC group for AD patients in intermediate-term abstinence.

While AD patients had a decreased performance in learning the associations to be memorized, they did not differ from healthy participants in the recall rate of previously associated items. In contrast to this, in accordance with our hypothesis MD patients showed a relational memory impairment detected during a recall phase, as revealed by abnormal eye-movement behavior and a deficit in explicit recognition. 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.

Similarly, AD patients have also been characterized by reward/punishment processing deficiencies, showing a preference for immediate higher reward even if this is disadventogous on the long-term. This manifestation of a response inhibition deficit is linked to a top-down process involving the prefrontal cortex, the orbitofrontal cortex, subregions of the nucleus accumbens, limbic structures, the anterior cingulate cortex and also the hippocampus, brain areas which are commonly affected in both AD and MD.

As for MD patients, implicit (i.e. fixation duration) and explicit measures of relational memory correlated with each other and with clinical symptoms as we expected. However, we

could not detect a significant improvement in relational memory performance at 6 months follow-up. Viewing patterns associated with reward at baseline in conditions when relational memory information was present suggested better clinical symptomatology and outcome.

Assessing the impact of TMS on cognition in healthy subjects may improve understanding and predicting the effects on patients with neuropsychiatric disorders. Our results support the notion that iTBS exerts a facilitating effect on WM, while cTBS was not associated with deterioration of WM. We found that stimulating the right DLPFC may lead to opposite effects of iTBS and cTBS on conflict detection in the executive control of attention. When assessing eye-movements, we found TBS to influence only the performance of voluntary saccades, but not antisaccades.

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.

Another possibility for embracing these results could be developing attentional trainings for patients to help them correcting negative cognitive distortions and preventing relapse. Apart from this, neurmodulational 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 asssessed 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.

VIII. FUTURE PERSPECTIVES

Our results provide evidence that even one session of TBS with low intensity can cause short-term changes in working memory and saccade performance in healthy participants.

Extending our studies from the immediate consequences of a single session of TBS on cognitive functions in healthy individuals, we aim to examine the long-term effects of repeated bilateral TBS in MD patients. We have established an experimental paradigm consisting of 10 sessions of bilateral TBS applied over the DLPFC. Prior to and after the 10 sessions a complex cognitive and affective evaluation is performed. The active and sham groups are currenty being extened with a 3-months follow-up planned to be performed. Based on the preliminary results, depressive symptoms improve significantly and cognitive aspects are being addressed. We hope to contribute to the currently used TMS paradigms in MD also aiming to identify potential factors contributing to cognitive reserve capacity.

IX. LIMITATIONS

In our constant effort to improve study design, it is extremely important to note the limitations of the studies included in the dissertation. Certainly, a higher number of participants would have improved statistical power and the robustness of our findings. It may have been useful to perform a follow-up measurement of AD patients to obtain a longitudinal picture and to measure level of impulsivity and state of mood in the healthy control group also, for comparison. A higher rate of patients participating in the follow-up phase of the MD study would have served identification of potential contributing factors to the reduction of depressive symptoms and the improvement of memory function. It may have been beneficial to include less variables in the eye-tracking task to be able to draw more straghtforward conclusions. In the TMS study involving healthy participants, it would be interesting to recruit elderly participants to address the effect of age and gender.

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