Investigation of variables influencing cognitive inhibition: from the behavioral to the molecular level

Untersuchung der Einflussgrößen kognitiver Unterdrückung: Vom verhaltensorientierten zum molekularen Ansatz

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0. Abstract

English

The present work investigated the neural mechanisms underlying cognitive inhibition/thought suppression in Anderson's and Green's Think/No-Think paradigm (TNT), as well as different variables influencing these mechanisms at the cognitive, the neurophysiological, the electrophysiological and the molecular level.

Neurophysiological data collected with fNIRS and fMRI have added up to the existing evidence of a fronto-hippocampal network interacting during the inhibition of unwanted thoughts. Some evidence has been presented suggesting that by means of external stimulation of the right dlPFC through iTBS thought suppression might be improved, providing further evidence for an implication of this region in the TNT. A combination of fNIRS with ERP has delivered evidence of a dissociation of early condition-independent attentional and later suppression-specific processes within the dlPFC, both contributing to suppression performance.

Due to inconsistencies in the previous literature it was considered how stimulus valence would influence thought suppression by manipulating the emotional content of the to-be-suppressed stimuli. Findings of the current work regarding the ability to suppress negative word or picture stimuli have, however, been inconclusive as well. It has been hypothesized that performance in the TNT might depend on the combination of valence conditions included in the paradigm. Alternatively, it has been suggested that inconsistent findings regarding the suppression of negative stimuli or suppression at all might be due to certain personality traits and/or genetic variables, found in the present work to contribute to thought inhibition in the TNT. Rumination has been shown to be a valid predictor of thought suppression performance. Increased ruminative tendencies led to worse suppression performance which, in the present work, has been linked to less effective recruitment of the dlPFC and in turn less effective down-regulation of hippocampal activity during suppression trials. Trait anxiety has also been shown to interrupt thought suppression despite higher, however, inefficient recruitment of the dlPFC. Complementing the findings regarding ruminative tendencies and decreased thought inhibition a functional polymorphism in the KCNJ6 gene, encompassing a G-to-A transition, has been shown to disrupt thought suppression despite increased activation of the dlPFC.

Through the investigation of thought suppression at different levels, the current work adds further evidence to the idea that the TNT reflects an executive control mechanism, which is sensitive to alterations in stimulus valence to some extent, neurophysiological functioning

as indicated by its sensitivity to iTBS, functional modulations at the molecular level and personality traits, such as rumination and trait anxiety.

Deutsch

Diese Arbeit befasste sich mit der Untersuchung der neuronalen Grundlagen kognitiver Inhibition /Gedankenunterdrückung in Anderson's und Green's 'Think/No-Think' Paradigma (TNT), sowie der Erfassung verschiedener Einflussgrößen auf der kognitiven, der neurophysiologischen, der elektrophysiologischen und der molekularen Ebene.

Mit fNIRS und fMRT durchgeführte neurophysiologische Studien haben die Annahme der Beteiligung eines Fronto-Hippocampalen Netzwerkes an der Unterdrückung unerwünschter Gedanken bekräftigt. Hinweise auf eine Verbesserung der Unterdrückungsleistung mittels externer Manipulation der neuronalen Aktivität durch iTBS unterstützen die Annahme einer Beteiligung des dlPFC an den Mechanismen innerhalb des TNT weiter. Durch die Kombination von fNIRS und ERP wurde eine Dissoziation zwischen frühen bedingungsunabhängigen Aufmerksamkeits- und späteren unterdrückungsspezifischen Prozessen innerhalb des dlPFC aufgezeigt.

Vor dem Hintergrund widersprüchlicher Resultate bezüglich des Einflusses der Stimulus-Valenz auf die kognitive Inhibition in der vorhandenen Literatur wurde dieser Aspekt auch in der vorliegenden Arbeit berücksichtigt. Auch in dieser Arbeit aufgetretene widersprüchliche Ergebnisse bezüglich der Unterdrückung negativer Stimuli führten zu der Hypothese, dass die Unterdrückungsleistung in dem TNT in Abhängigkeit der Valenz der weiteren eingeschlossenen Stimuli erfolgt. Alternativ wurde eine Abhängigkeit von Persönlichkeitsmerkmalen und/oder genetischen Variablen vorgeschlagen, welche in der vorliegenden Arbeit als Einflussgrößen nachgewiesen wurden. So konnte gezeigt werden, dass die Erhebung ruminativer Tendenzen eine zuverlässige Vorhersage der Unterdrückungsleistung zulässt. Höhere ruminative Tendenzen führten zu signifikant verschlechterter Unterdrückungsleistung. Dies konnte auf eine ineffektive Rekrutierung des dlPFC gefolgt von ungenügender Aktivierungsabnahme im Hippocampus während der Gedankeninhibition zurückgeführt werden. Darüber hinaus konnte gezeigt werden, dass mit der Zunahme ängstlicher Persönlichkeitsmerkmale die Unterdrückungsleistung trotz erhöhter Aktivität im dlPFC abnimmt. In Ergänzung zu den Ergebnissen bezüglich ruminativer Tendenzen und gestörter kognitiver Inhibition konnte ein störender Einfluss eines funktionellen genetischen Polymorphismus im KCNJ6 Gen unter Einbeziehung einer Punktmutation (G-A Transition) nachgewiesen werden.

Durch die Untersuchung der Gedankenunterdrückung auf unterschiedlichen Ebenen, konnte die vorliegende Arbeit weitere Hinweise dafür liefern, dass mit dem TNT exekutive Kontrollfunktionen abgegriffen werden, welche durch Stimulusvalenz, neurophysiologische

Prozesse (durch eine die iTBS betreffende Sensitivität angezeigt), funktionelle Modulationen auf der molekularen Ebene, sowie Persönlichkeitsmerkmale wie ruminative Tendenzen und Ängstlichkeit beeinflussbar sind.

1. Introduction and Theory

1.1. Introduction to Cognitive Inhibition and Memory Suppression

Cognitive inhibition is defined as "the stopping or overriding of a mental process, in whole or in part, with or without intention" (MacLeod 2007; p.5), in terms of the suppression of previously activated cognitive contents of processes, the clearing of irrelevant actions or attention from consciousness, and resistance to interference from potentially attention-capturing processes or contents (Harnishfeger 1995), or more specific as "reducing the activation level for a given response, preventing it from achieving threshold […] and by doing so [enabling] weaker but more appropriate responses [to be] expressed" (Anderson 2006; p. 329). The term cognitive inhibition has been used to explain a variety of phenomena in different domains of research, ranging from developmental psychology in explaining children's performance in the false belief task to the inhibition of stereotypical behavior investigated in social psychology or the investigation of certain personality traits influencing behavior as well as inhibitory processes as an important topic in personality psychology (for a brief overview see MacLeod 2007). Most growth in the investigation of cognitive inhibition has, however, occurred in the field of memory research. In the past most studies have focussed on facilitatory mechanisms that enable or enhance memory and its function (e.g. Anderson 1999; Russell 1971; Squire & Zola-Morgan 1991). Inhibition, however, is a vital process to its proper functioning as well and has in the last decade increasingly been recognized as one of the core concepts in memory research (Dudai, Roediger III & Tulving 2007).

In the field of memory research inhibition resulting in forgetting might seem undesirable at first, given the negative association of memory impairment with diseases such as Alzheimer's or dementia. However, cognitive control over unwanted thoughts, is adaptive in a number of situations ranging from everyday experiences such as the need to ensure that the most current knowledge is assessed (e.g. today's parking spot, not yesterday's or the changed address of a friend) to situations baring more serious implications, such as the need to suppress reminders of unpleasant events such as memories of trauma, the loss of a loved one, embarrassment or anxiety (Anderson 2007). In the field of motor inhibition, paradigms such as the Go/Nogo task, in which subjects are asked to respond for example with a button press whenever they see a letter, except when the letter is a 'B', which indicates that no response is required/wanted, are used to investigate underlying processes warranting the

stopping of a response. Since the majority of the trials require a button press, subjects experience difficulties withholding a response when it is needed. The problem of being presented with a situation triggering a pre-potent response (i.e. in this case a button press) in the face of the need for a weaker but contextually more appropriate response (i.e. withholding the button press when seeing a 'B') requires so-called response-override. Various studies so far have shown response-override situations, such as in the Go/Nogo, to trigger executive processes exerting control over down-stream motor responses (e.g. Casey, Trainor, Orendi, Schubert, Nystrom, Giedd et al 1997; Garavan, Ross & Stein 1999). A decade ago, Anderson and Green (2001) hypothesized that parallel executive control mechanisms might be at work during the suppression of cognitive processes, such as memories. Analogue to the inhibition of motor responses, paradigms, such as the retrieval-induced forgetting, directed forgetting or Think/No-Think paradigm (TNT) have been developed making the investigation of thought/memory inhibition possible (for a review of the three methods see e.g. Anderson 2005, 2006). The TNT has been described as best targeting the active control mechanisms recruited to stop/inhibit memories and thoughts from occurring and therefore as being best suited to investigate processes involved in the suppression of memories and thoughts (e.g. Anderson 2007; Depue, Banich & Curran 2006). The paradigm and the current status of research are described in the next paragraph.

1.2. The Think/No-Think Paradigm (TNT)

1.2.1. Development of the TNT by Anderson and Green

The TNT has been developed by Anderson and Green (2001) to investigate executive control processes recruited in order to inhibit thoughts from entering awareness. The paradigm is derived from the well-established Go/Nogo paradigm, which is used to study top-down control over motor responses. Analogous to the Go/Nogo task subjects are instructed to respond (i.e. 'think') when presented with some previously learned stimuli (e.g. words, pictures) while asked to withhold the response to others (i.e. 'no-think'); in other words the TNT requires the recall of some stimuli and to stop recall of others when presented with an initially learned associated cue. If stopping retrieval of an unwanted stimulus or thought is achieved by recruiting inhibitory control mechanisms its later retention should be impaired, compared to retrieved items or even baseline items, which are learned but neither suppressed nor retrieved, resulting in a pattern of below-baseline recall of suppressed stimuli in a post-experimental cued-recall test. Figure 1 outlines the procedure of the TNT established by Anderson & Green (2001). During the study phase, subjects are trained on the link between

previously non-associated word pairs. In the subsequent TNT phase they are presented with one of the words (i.e. cue) and instructed to either recall or inhibit recall of the previously learned partner word, indicated by the color of the cue (e.g. green for 'think' and red for 'no-think'). Following the TNT phase, subjects are presented with a list of all cues and asked to recall all partner words (same probe recall test).

Think/No-Think Paradigm

			Test Phase	
	Study/Training	Think/No-Think Phase	Same Probe	Independent Probe
Suppression	Ordeal-Roach	Ordeal	Ordeal	Insect r___
Respond	Steam-Train	Steam	Steam	Vehicle t___
Baseline	Jaw-Gum		Jaw	Candy g___

***Figure 1**: The Think/No-Think paradigm as developed by Anderson and Green (2001). Adapted from Anderson, Ochsner, Kuhl, Cooper, Robertson, Gabrieli et al. (2004).*

As hypothesized, recall of no-think trials was impaired to a below-baseline level after repeated attempts to control awareness of the stimuli (Anderson & Green 2001), suggesting the existence of an executive control process that is recruited during voluntary attempts to inhibit unwanted thoughts from entering consciousness. It was, however argued, that alternative mechanisms such as a newly formed association between the cue and a divisionary thought or a simple degradation of the association between cue and partner word could have led to impaired recall as well (Anderson & Green 2001). Therefore, in a second experiment Anderson and Green (2001) tested recall of no-think words with the independent probe method (Anderson & Spellman 1995), in which subjects are cued with a semantic category and the initial letter of the partner word (see Figure 1). The same pattern of below-baseline recall of no-think words emerged as obtained by cueing subjects with the original cue, ruling out interference by a newly formed association or simple unlearning and further supporting the idea of the existence of executive control mechanisms, which adapt patterns of thoughts internally (Anderson & Green 2001).

1.2.2. Behavioral Studies: The TNT at the Behavioral Level

Since the original work by Anderson and Green (2001), various studies have been conducted trying to replicate their findings of below-baseline suppression in the final recall test on a behavioral level. The attempt to fully replicate the original findings has, however, been only partially successful (see Table 1). In addition to the attempt to replicate Anderson's

and Green's (2001) results, investigation of variables potentially influencing TNT performance has been the aim of consecutive studies. Most have focussed on the investigation of the effect of stimulus valence (Depue et al 2006; Lambert, Good & Kirk 2010; Marx, Marshall & Castro 2008) or the effect of mood (dysphoria/depression: Hertel & Gerstle 2003; Hertel & Mahan 2008; Joormann, Hertel, Brozovich & Gotlib 2005; anxiety: Waldhauser, Johansson, Backstrom & Mecklinger 2010) on the cognitive control process examined in the TNT. Other factors investigated were certain psychiatric disorders associated with deficient cognitive control such as attention deficit hyperactivity disorder (ADHD; Depue, Burgess, Willcutt, Ruzic & Banich 2010) schizophrenia (Salame & Danion 2007) or Borderline Personality Disorder (Sala, Caverzasi, Marraffini, De Vidovich, Lazzaretti, d'Allio et al 2008). Other studies have focussed on certain personality characteristics such as working memory capacity (Waldhauser et al 2010), proneness to dissociative experiences (Wessel, Wetzels, Jelicic & Merckelbach 2005), or suppression strategies (Bergström, de Fockert & Richardson-Klavehn 2009b; Hertel & Calcaterra 2005). In the remainder of this paragraph these studies will be described in more detail[1].

Bulevich, Roediger, Balota and Butler (2006) conducted three experiments carefully following Anderson's and Green's (2001) original procedure. None of these experiments delivered evidence for impaired recall of no-think stimuli relative to baseline, questioning the reliability of the TNT as a measure of cognitive control.

Depue et al. (2006) replicated the original findings by Anderson and Green (2001) of lower final recall of no-think than baseline stimuli. In two experiments using two different sets of stimuli (words and pictures), they could furthermore show that negative stimuli were recalled better in the think condition and suppressed more effectively in the no-think condition relative to neutral stimuli (Depue et al 2006). In a recent study impaired recall of negative information in comparison to no suppression of positive information in a same probe and independent probe recall test was shown in two experiments performed by Lambert and colleagues (2010). The authors suggest that this reflects that negative information might be more accessible to cognitive control processes, corresponding partly to findings of a neuroimaging study showing that distinct neural systems seem responsible for encoding negative and neutral information, reflecting greater salience and therefore better encoding and consolidation of emotional material (Kensinger & Corkin 2004). These findings furthermore propose that cognitive control processes are mediated by the emotional content of the

[1] Only findings regarding the suppression effect (i.e. lower recall of no-think than baseline items) are discussed, unless mentioned otherwise

***Table 1**: Summary of the current literature using the TNT to investigate cognitive inhibition*

Study	Sample	Stimulus material	Cue	Target	Suppression effect (NT < Base) SP	IP
Anderson and Green (2001)	HC	nouns	neu	neu	**yes** (16)	**yes** (16)
Anderson et al. (2004)	HC	nouns	neu	neu	**yes** (16)	**yes**
Bergström et al. (2007)	HC	words	neu	neu	no	n.a.
Bergström et al. (2009a)	HC	words	neu	neu	no	n.a.
Bergström et al. (2009b)	HC (thought substitution vs. unaided)	words	neu	neu	subst: **yes** (16) unaided: **yes**	**yes** no
Bulevich et al. (2006)	HC	nouns	neu	neu	no	no
Depue et al. (2006)	HC	words & pictures	neu	neu/neg	**yes**	n.a.
Depue et al. (2007)	HC	pictures	neu face	neg	**yes** (12)	n.a.
Depue et al. (2010)	ADHD patients	pictures	neu face	neg	pat: no HC: **yes** (12)	n.a.
Hanslmayr et al. (2009)	HC	words	neu face	neu	**yes** (10)	n.a.
Hanslmayr et al. (2010)	HC	nouns	neu face	neu	**yes** (10)	n.a.
Hertel and Gerstle (2003)	Dysphoric students	nouns	pos/neg adjectives	neu	pats: no HC - pos: **yes** (16)	n.a.
Hertel and Calcaterra (2005)	HC (thought substitution vs. unaided)	nouns	neu adjectives	neu	subst: **yes** (12) unaided: no	n.a.
Hertel & Mahan (2008)	Dysphoric students	words (related/unrelated)	neu	neu	no	n.a.
Joormann et al. (2005)	Depressed patients	nouns	neu	pos/neg	pat - neg: **yes** (12) - pos: no HC: no	n.a.
Lambert et al. (2010)	HC	nouns	pos/neg	neu	neg: **yes** (16) pos: no	neg: **yes** pos: no
Marx et al. (2008)	HC	words	neu	pos/neg (low/high arousal)	n.a. (no baseline condition)	n.a.
Mecklinger et al. (2008)	HC	words	neu	neu	no	**yes**
Meier et al. (2011)	HC	words	neu	neu	no	no
Sala et al. (2008)	Borderline patients	nouns	neu	neu	pat: no HC: no	pat: no HC: no
Salame and Danion (2007)	Schizophrenic patients				pat: **yes** HC: no	n.a.
Waldhauser et al. (2010)	HC	nouns	neu	neu	no	n.a.
Wessel et al. (2005)	HC (high/low dissociation)	words	neu	neu	**yes** (16; no difference between groups)	no

manipulated stimuli, enhancing or reducing memory traces of items presented during the TNT phase, depending on the control condition (i.e. think or no-think).

Investigation of differences in the suppression of emotional material was extended by Marx et al. (2008), who took not only valence, but also the arousal level of the target words into account (i.e. resulting in four different conditions: low arousing positive, high arousing positive, low arousing negative, high arousing negative words). Unfortunately, the authors did not include a baseline condition, so the results only indicated lower recall of no-think than think words. In a free recall task the group could show that effective suppression occurred only for the positive words, and that the most pronounced suppression effect (in this case no-think < think) was for the high arousing positive words. No suppression was found for the negative words. These findings clearly contradict results obtained by Depue et al. (2006) and Lambert et al. (2010). Testing recall with a same probe test they could show suppression of negative and positive words, although the effect again was larger for the positive words. No interaction with arousal, however, was obtained in the same probe test (Marx et al 2008). Contrary to the hypothesis of facilitated cognitive control over emotionally negative information supported by Depue et al. (2006) and Lambert et al. (2010) findings by Marx et al. (2008) support the hypothesis that negative information is elaborated to a greater extent during memory processes (Kensinger & Corkin 2004), resulting in less effective suppression when compared to positive material. The effect of greater cognitive control over high arousing than low arousing positive words is discussed in the light of studies showing that while highly arousing information might facilitate encoding, non-arousing information may be less likely to be elaborated upon during encoding, resulting in lowered recall performance relative to negative non-arousing information (Kensinger 2004). In other words, highly arousing positive information might be most easily intentionally suppressed since they are least elaborately encoded in memory. Following this line of thought, it is suggested that processes elaborated on during encoding might play a more prominent role in memory inhibition than previously assumed by Anderson (2005).

In an experiment comparing TNT performance between a group of dysphoric students and control subjects using positive and negative words cueing a semantically related neutral word, Hertel and Gerstle (2003) found below-baseline suppression only following positive cues and only in the control group. Interestingly, recall for no-think words was even found to be improved in the dysphoric group regardless of valence, thereby not supporting the well-established mood-incongruent-forgetting hypothesis (i.e. better memory of negative items and worse memory of positive items), often reported in research using thought intrusion

paradigms for the investigation of mood-related memory and cognitive control effects (e.g. Howell & Conway 1992; Roemer & Borkovec 1994). In an additional correlation analysis Hertel and Gerstle (2003) interestingly could show that a ruminative response style, as measured by the Ruminative Response Scale of the Response Style Questionnaire measuring coping with depressive moods (RSS; Kühner, Huffziger & Nolen-Hoeksema 2007) predicted suppression performance regardless of mood status; in other words, subjects with high scores on the RSS, regardless of group status, showed impaired suppression, thus higher recall rates of no-think words than low scorers, therefore suggesting the presence of a general deficit in exerting cognitive control over unwanted thoughts. A later study by the same group compared the suppression of neutral words semantically related or unrelated to the cue word, again contrasting performance in a dysphoric and non-dysphoric student sample. No suppression effect was found in any of the conditions in the dysphoric or the non-dysphoric group. Comparing suppression of positive and negative words cued by neutral words in clinically diagnosed depressed subjects and healthy control subjects, Joormann and colleagues (2005)[1] could show that compared to healthy control subjects, who showed below-baseline suppression[2] of no-think words regardless of valence, depressed individuals exhibited better suppression of negative than positive words, and better suppression than the healthy controls. These results are clearly contradicting previous research investigating cognitive control over emotional information in depression for example using the directed forgetting paradigm (Power, Dalgleish, Claudio, Tata & Kentish 2000), which has shown better recall of to-be-forgotten negative than positive and to-be-remembered negative words consistent with the mood-incongruent forgetting hypothesis. Results from the Joormann et al. study (2005) furthermore are not in line with the study by Hertel and Gerstle (2003), which had found improved recall of no-think words in a group of dysphoric students, thereby replicating the directed-forgetting findings by Power et al. (2000), using the TNT paradigm. In addition to the observation of improved suppression of negative no-think words, Joormann et al. (2005) found that depressed subjects in the suppress-negative-respond-positive group exhibited poorer recall of unpracticed baseline words, which was neither observed in the suppress-positive-respond negative subsample of the depressed group nor in the healthy control group. This finding is discussed in the light of a study by Hertel and Calcaterra (2005), which has

[1] One half of the sample practiced suppression of negative words and recall of positive words (i.e. suppress-negative-respond positive), while the other half of the depressed subjects performed suppression on positive and recall on negative words (i.e. suppress-positive-respond-negative).
[2] After controlling for compliance with the instructions using a Strategies Questionnaire developed by Hertel and Calcaterra (2005)

shown that suppression performance in the TNT was significantly improved when subjects used a thought substitution strategy during the no-think phase. Together with research showing that depressed subjects tend to distract themselves from their ruminative thoughts about negative events by using other negative thoughts (Wenzlaff, Wegner & Roper 1988), the authors suggest that impaired recall of baseline words following suppression of negative words might reflect an enhancing effect of thought substitution strategies concerning negative relative to positive words in the depressed sample (Joormann et al 2005). Wessel et al. (2005) compared memory suppression of neutral words between healthy controls scoring high or low on the Dissociative Experience Scale. Dissociative coping styles, which encompass the mental disengagement from current events and are assumed to be used as a defense mechanisms against trauma (e.g. Gershuny & Thayer 1999), are hypothesized to interfere with successful suppression of unwanted thoughts, especially when they are negative in content (Wessel et al 2005). Although, they were able to replicate below-baseline suppression of no-think words in the same probe recall test (but not in the independent probe recall test), contrary to their prediction of better suppression performance in individuals displaying a high amount of dissociative experiences, they found no difference in memory impairment between the two groups. They claimed, however, that the prediction was based on studies showing a larger Stroop effect in high dissociators (DePrince & Freyd 1999; Freyd, Martorello, Alvarado, Hayes & Christman 1998) and the assumption that the same processes underlie inhibition of a pre-potent response in the Stroop Color Naming Test and the TNT. Given, however, recent findings that the Stroop and the TNT effect might reflect different concepts of interference, the results by Wessel et al. (2005) are not surprising. Friedman and Miyake (2004) have shown that Stroop performance relies on a variable reflecting control over response-distractor interference[1], while pro-active interference[2], which is thought to underlie the TNT, was unrelated to response-distractor interference. Another, point remarked by the authors is the possibility that differences in the ability to suppress might not surface when using neutral stimuli, but when using negative material, taking into account the original idea that dissociative strategies emerge in traumatic situations (Wessel et al 2005). In a study by Salamé and Danion (2007) individuals diagnosed with schizophrenia displayed a solid suppression effect in the same probe recall test while in the control group no such effect was

[1] The ability to ignore irrelevant pre-potent responses (e.g. to ignore the content of a word in the Stroop Color Naming Test)
[2] The extent to which people are able to ignore interference from memory (e.g. the previously learned association between the target word when presented with the cue in the no-think condition of the TNT)

observed[1]. Other clinical samples investigated were patients with Borderline Personality Disorder and ADHD, both disorders associated with deficient inhibitory control and dysfunctions in the neural circuitry associated with memory inhibition, which will be discussed in the next paragraph (e.g. Gomez 2003; Schachar, Tannock, Marriott & Logan 1995; Silbersweig, Clarkin, Goldstein, Kernberg, Tuescher, Levy et al 2007). The group around Sala (2008) was not able to show suppression in both the Borderline patients and the healthy control group, while in a very recent study Depue and colleagues (2010) showed successful memory suppression of negative pictures in the healthy control group but not in patients with ADHD in a same probe recall test. Both studies provide further evidence of impaired cognitive control processes in patient groups previously being shown to display deficient control over certain cognitive and especially control over memory processes. In another very recent study a group around Waldhauser (2010), although not able to show an overall suppression effect, could show a significant moderation of suppression performance by trait anxiety scores in a sample of healthy control subjects; better suppression was significantly predicted by lower scores on the trait subscale State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch & Lushene 1970). No correlation with working memory span was found. The authors discuss this finding in relation to deficient executive functioning during states of intense anxiety. Eysenck, Derakshan, Santos and Calvo (2007) claim that effective inhibition is disrupted indirectly by decreased processing efficiency in tasks involving inhibitory control during the experience of anxiety. Studies have been conducted, showing similar task accuracy, but longer processing times in highly anxious individuals (Derakshan, Ansari, Hansard, Shoker & Eysenck 2009; Derakshan & Eysenck 1998), as well as a correlation between anxiety and the amount of intrusions of unwanted thoughts in everyday life (Barnier, Levin & Maher 2004; Erskine, Kvavilashvili & Kornbrot 2007).

An important finding was obtained in a study by Hanslmayr, Leipold and Bäuml (2010), which could show that memory suppression is significantly improved by presenting the think/no-think instruction one second prior to presentation of the cue relative to the classical non-anticipatory presentation of the instruction to think or not think about the target simultaneously with the cue. This is in line with, among others, neuroimaging studies investigating memory formation (e.g. Adcock, Thangavel, Whitfield-Gabrieli, Knutson & Gabrieli 2006; Otten, Quayle, Akram, Ditewig & Rugg 2006) or cognitive control processes in other domains such as task switching (e.g. Dreisbach, Haider & Kluwe 2002; Lavric,

[1] Based on findings of deficient executive control mechanisms in schizophrenia (Fossati, Amar, Raoux, Ergis & Allilaire, 1999), the authors predicted effective memory suppression in the control group but not in the patients

Mizon & Monsell 2008) showing anticipatory activation of relevant neural networks (see paragraph 1.2.3.). The interpretation of these findings, however, appears problematic in the light of a study by Lee, Lee, and Tsai (2007) using the directed forgetting paradigm, in which evidence was presented that the temporal pattern of cue presentation may be playing a role in mediating forgetting. The group varied presentation time of the (Chinese) cue words and found that a clear suppression effect was present when cues were presented for a relatively brief period (3 seconds) but not when they were presented for a longer period (5 seconds)[1]. Due to methodological reasons, Hanslmayr et al. (2010) used different presentation times of the cue (i.e. 4 seconds in the anticipatory condition and 5 seconds in the classical condition), somehow limiting the value of the interpretation of the effect in favor of an anticipatory facilitation of the cognitive control process exerted when suppressing unwanted thoughts as during the no-think instruction.

Although it has been argued by some authors that the TNT is at least to some degree a laboratory analogue of Freud's repression mechanism (e.g. Anderson & Green 2001; Anderson et al 2004), only one very recent study investigated the longevity of the suppression effect elicited by repeated attempts to inhibit thinking about a thought. Meier, König, Parak and Henke (2011) not only tested recall of think and no-think items in a same probe and independent probe recall test immediately following the TNT phase but repeated both recall tests one week later. In their first experiment, they could not show below-baseline suppression in any of the recall tests. Interestingly, however, recall of no-think words, one week after the initial experiment was significantly improved relative to baseline words in the same probe test, suggesting that thought suppression had a reversed long-term effect. In a second experiment they manipulated task instructions by providing one half of their subjects with the instruction to substitute the target in response to the cue with an alternative word to achieve suppression (i.e. Substitution group) while giving the classical TNT instruction to the other half (i.e. Suppression group). Within each group half of the subjects performed the recall tests immediately after the experiment, while the other half was tested one week later. Again, no below-baseline suppression was observed and as in experiment 1 recall of no-think items had improved above baseline after one week in the Suppression Group, while they were recalled evenly well in the Substitute group. The authors interpret this, in line with Hertel and Calcaterra (2005), as indicating a beneficial effect of thought substitution for subsequent forgetting of no-think items. This effect, however, is discussed as most likely reflecting retroactive interference (Meier et al 2011) and not an actual disruption of the memory trace by

[1] Note that presentation time in the classical Anderson and Green (2001) study was 4 seconds

voluntary thought suppression as intended by Anderson and Green (2001). The lack of finding a long-term suppression effect is arguing against the original claim by Anderson and Green (2001) that the TNT represents a laboratory analogue of Freud's repression mechanisms. However, the value of the TNT as a measure of cognitive control is nonetheless undisputable.

1.2.3. Functional Imaging and Electrophysiological Studies: The Neural Representation of the TNT

Already in their original work, Anderson and Green (2001), hypothesized on the neural representation of thought inhibition in the TNT. They proposed the dorsolateral prefrontal cortex (dlPFC) as one important key structure, since it has been shown to be reliably activated in the Go/Nogo task during the inhibition of responses (e.g. Casey et al 1997; de Zubicaray, Andrew, Zelaya, Williams & Dumanoir 2000; Garavan et al 1999), the on-line manipulation of information currently stored in working memory (D'Esposito, Aguirre, Zarahn, Ballard, Shin & Lease 1998) as well as overcoming interference from competing working memory representations (Smith & Jonides 1999) or selection of one specific item to guide a certain response (Rowe, Toni, Josephs, Frackowiak & Passingham 2000). Another structure thought to be implicated is the hippocampus, which has long been known to be essentially involved in the formation of memory traces (e.g. see Bliss & Collingridge 1993; Squire 1992) and is anatomically connected to the dlPFC via the fornix and the retrosplenial cortex (Morris, Pandya & Petrides 1999; Petrides & Pandya 2006).

Various functional imaging and electrophysiological studies have been conducted since the initial behavioral study by Anderson and Green (2001) investigating the neural basis underlying thought suppression in the TNT. The discussion of the results in these studies has focussed on processes found to be related to the suppression effect and not so much to processes related to memory retrieval.

The first functional magnetic resonance imaging (fMRI) study was conducted by Anderson et al. himself (2004) and in addition to replicating below-baseline recall of no-think words in the same and independent probe recall test, as predicted they found a network of brain regions, including the lateral PFC, to be more active during no-think than during think trials. In turn, activation in the hippocampus was reduced during the suppression of words, indicating successfully stopped attempts to retrieve a memory during the no-think trials. To strengthen this claim and to rule out other explanations such as the simple disengagement of hippocampal activation due to a termination of the retrieval mode during the no-think condition, Anderson et al. (2004) performed further analyses investigating whether signal

change in the hippocampus would predict subsequent memory inhibition in the recall tests. They found different patterns of right hippocampal recruitment during suppression and simple forgetting (i.e. as indicated by activation during non-remembered think items). Additionally, they reported that later forgotten no-think words yielded more activation in the right hippocampus than no-think items that were subsequently remembered. Furthermore, the group could show a significant positive correlation between hippocampal activation during forgotten no-think relative to remembered no-think words and the amount of memory impairment. In the light of greater hippocampal activation during remembered think words than during forgotten think words, Anderson et al. (2004) assumed that greater activation during forgotten no-think words may "reflect greater intrusions of forgotten no-think items during suppression trials […] which may have triggered greater executive control to override retrieval and, in turn, greater memory inhibition" (p. 234). As an alternative explanation, the authors suggested that increased hippocampal activation might also reflect retrieval of diversionary thoughts that inhibit the to-be-suppressed memory trace. This interpretation would be in line with studies showing an enhanced suppression effect in subjects applying though substitution strategies as discussed in the previous paragraph (Hertel & Calcaterra 2005). Finally, the authors could show a positive correlation between greater activation during forgotten than during remembered no-think words in the dlPFC and the right hippocampus, suggesting an interaction of the two structures in the facilitation of cognitive control over unwanted thoughts. Depue, Curran, and Banich (2007), using negative pictures as stimuli, also isolated the dlPFC and hippocampus as two key structures involved in exerting cognitive control over unwanted thoughts. In addition they found decreased activation of the amygdala during no-think relative to think trials. This is not particularly surprising given the negative content of their stimulus material and is discussed as reflecting the suppression of processes found to be implicated in emotional learning (Hamann 2001; Phelps 2004). In consecutive analyses the authors tried to clarify the temporal pattern of the cognitive control processes called upon during no-think trials. In behavioral experiments it was shown that memory impairment for no-think items decreases as a function of the number of times cognitive control is exerted. By means of analysing activation of the previously isolated brain regions throughout the time course of the experiment, Depue et al. (2007) could show a complex pattern of prefrontal activation early in the experiment, which is accompanied by increased activation in the hippocampus and amygdala. Only later, after several no-think attempts significantly decreased activation below baseline in the two latter structures was observed. This decrease, in turn, was predicted by the amount of activation in the prefrontal cortex early

in the experiment. Taking only the last few no-think trials into account, the authors could show a linear decrease in hippocampal recruitment during think-trials that were subsequently remembered, to forgotten think trials, remembered no-think trials and forgotten no-think trials, while only forgotten no-think trials showed a significant drop of activation below the baseline activation level. The lower activity for forgotten no-think trials than for forgotten think trials is interpreted as further supporting the idea of the TNT measuring an active suppression mechanism (Depue et al 2007). The importance of the prefrontal cortex and the hippocampus in this active suppression mechanism is further corroborated by a significant correlation between greater memory impairment and heightened prefrontal as well as lower hippocampal[1] activation obtained in this study. Investigating the TNT at the neural level in a sample of patients diagnosed with ADHD, Depue et al. (2010) further investigated the idea that suppression of thoughts is achieved by executive control processes recruited in situation requiring response-override[2]. Patients with ADHD have been shown to display deficient inhibitory control in paradigms such as the Go/Nogo or the Stop Signal Reaction Time Task (SSRT; e.g. Aron & Poldrack 2005; Rubia, Overmeyer, Taylor, Brammer, Williams, Simmons et al 1999; Rubia, Smith, Brammer & Taylor 2003) accompanied by altered neural responses in areas critically related to performance in these tasks and the TNT (see above; Booth, Burman, Meyer, Lei, Trommer, Davenport et al 2005; Rubia et al 2003). Significant group-related activation differences in the prefrontal and subcortical structures (i.e. hippocampus and amygdala), shown in their previous study (Depue et al 2007), were found during no-think attempts relative to baseline (Depue et al 2010). Patients with ADHD did not show any increased activation in the dlPFC, however, significantly activated the hippocampus and the amygdala during no-think trials relative to baseline, possibly reflecting uncontrolled intrusion of the target associated with the cue. Control subjects showed the pattern of increased right dlPFC and decreased bilateral hippocampal/amygdaloid activation previously observed by the group (Depue et al 2007). As already shown in their earlier study, signal changes in these regions correlated significantly with each other in the control group but not in patients with ADHD. Furthermore, only the control group exhibited the previously reported correlation between the strength of the suppression effect in the behavioral recall test and increased activation in the right dlPFC. Finally, correlating brain activation and behavioral measures of inattention and hyperactivity as well as performance in a SSRT, the group could show that especially inattentive symptomatology was linked with the correlation between

[1] When taking only the last few no-think trials into consideration
[2] Behavioral patterns have been described in the previous paragraph (p. 19)

prefrontal cortex, hippocampus and amygdala. Moreover, higher levels of both inattentive and hyperactive symptomatology and poorer SSRT performance were shown to correlate with poorer inhibition over emotional retrieval[1]. These results show the benefit of studying patients with deficits in the domain of inhibitory control over cognitive processes to further outline the neural network underlying thought suppression and strengthening the claim that the TNT constitutes a well-suited laboratory test of cognitive control processes occurring naturally during the exertion of inhibiting unwanted thoughts from entering awareness and resulting in impaired memory of these thoughts. In sum, increased activation of prefrontal regions during suppression of memory relative to retrieval supports the view that suppression is an active process recruiting brain regions known to be important for executive control functions, such as the stopping of pre-potent motor responses in situations of response-override (e.g. Garavan et al 1999; Menon, Adleman, White, Glover & Reiss 2001).

In the first event-related potential (ERP) study investigating the electrophysiological correlates of the TNT, Bergström, Velmans, de Fockert and Richardson-Klavehn (2007), although not being able to replicate the classical suppression effect, could show a dissociation of an early frontally and parietally distributed negative and positive ERP component respectively, reflecting task-related strategic processes and a later (around 500 ms) positive left parietally distributed ERP component reflecting item-specific conscious recollection versus avoidance of recollection. The latter showed a significant reduction in amplitude during no-think trials, a fact discussed by the authors as reflecting the physiological correlate of the fMRI results by Anderson et al. (2004) and adding up to the evidence for the ability of voluntary thought suppression. Additionally, the data indicates, that even in the presence of physiological evidence of successful voluntary avoidance of recollection at the neural level in the TNT, subsequent forgetting might not occur (Bergström et al 2007). In a follow-up study Bergström, de Fockert and Richardson-Klavehn (2009a), addressed the claim that an alternative explanation might account for the lower amplitude in the late positivity reported earlier as indicating successful suppression of recollection in the TNT. They propose that successful avoidance of recollection in the TNT, might simply reflect that "the default state […] is to not recollect, that is, that the cues fail to elicit automatic recollection" and that "the memories that participants are asked to recall require the involvement of intentional control

[1] Note, however, that brain activation during the SSRT was found to be mainly in the right inferior frontal gyrus and pulvinar cortex, indicating the possibility that the SSRT and the TNT might present two different forms of inhibition (compare Friedman's & Miyake's (2004) distinction between pro-active interference and response-distractor interference; see p.18)

processes to achieve successful retrieval, and that successfully avoiding recall requires no voluntary control" (p. 1282; Bergström et al 2009a). By this means, the authors manipulated the strength and flexibility of the control processes tested in the TNT by switching the think and no-think condition after the first half of the experiment for some of the cue items. They could replicate their finding of reduced amplitudes of the late positive component during no-think relative to think trials in the first half of the experiment, and in addition an even larger and more reliable effect in the second half of the experiment for items with altered instructions (i.e. think to no-think and no-think to think from the first to the second half). Even in the absence of a behavioral suppression effect, this result indicates that practice of avoiding recollection is more crucial to the ability to successfully exert control over unwanted thoughts than the actual number of times a particular item had been avoided. This partly corresponds to findings by Depue et al. (2007), which had shown hippocampal disengagement to be largest in the last quartile of the experiment (i.e. after a certain amount of no-think trials). In a third experiment Bergström and her colleagues (2009b) investigated the influence of suppression strategies on the electrophysiological underpinnings of cognitive control processes over unwanted thoughts. They provided half of their subjects with the instruction to substitute the target word with another word during no-think trials to accomplish thought suppression (i.e. Substitute group), while the other half were given no instruction how to accomplish not thinking about the target (i.e. Suppression group). Contrary to findings by Hertel and Calcaterra (2005) presented in the previous paragraph only the Suppression group showed below-baseline recall of no-think words in the same and independent probe recall test. As in their earlier studies reduced amplitudes were observed in a late positive component during no-think trials. This effect, however, was only present in the Suppression group. Furthermore, the group isolated an N2-like component, which showed higher amplitudes for no-think than think trials in both groups, larger, however, in the Suppression group and which predicted subsequent forgetting of no-think words in the behavioral recall test. The N2 has consistently been shown to be associated with the stopping of pre-potent motor responses in the Go/Nogo paradigm (Kok 1986; Kopp, Mattler, Goertz & Rist 1996; Van Veen & Carter 2002). In line with hypotheses linking the N2 found in response to Nogo-trials to conflict monitoring in the face of the detection of a conflict between a pre-potent response and the presentation with a cue to stop this response (Van Veen & Carter 2002), the authors proposed that the higher negativity in the N2 during no-think trials reflects the detection of conflict and the beginning of a process accomplishing the detected need for cognitive control (Bergström et al 2009a). Another group around Mecklinger also isolated an N2 which showed

suppression-related modulations in amplitude (Mecklinger, Parra & Waldhauser 2009). In addition, in a second experiment the same subjects performed a Stop Signal task using the same stimulus material as in the TNT to investigate the relationship between cognitive control and motor stopping. A significant positive correlation between amplitudes elicited by no-think trials and the successfully inhibited motor response in the Stop Signal task was found for the N2, suggesting that similar neural processes are recruited by the two tasks. This claim is supported by the finding that higher P3 amplitudes during successful Stop trials were not correlated with the N2, therefore, ruling out simple high within-subject covariance of ERP components. Furthermore, the authors could show that the two N2 components both exhibit the same centro-parietal scalp distribution, which seems to support imaging studies concerning the TNT (Anderson et al 2004; Depue et al 2007) and the Stop Signal task (Garavan, Ross, Murphy, Roche & Stein 2002) showing that successful stopping of pre-potent responses is mediated by medial frontal and temporo-parietal brain regions. In line with Bergström et al. (2009a), the authors claim that the N2 reflects early mechanisms of control citing a simultaneous fMRI/EEG study by Garavan et al. (2002), showing that the dlPFC and other medial frontal regions are recruited differentially depending on Stop Signal task speed and difficulty, the dlPFC being more engaged in more difficult task situations. This corresponds with findings of a later no-think modulated frontally distributed positivity by all aforementioned studies (Bergström et al 2009a; Bergström et al 2009b; Bergström et al 2007; Mecklinger et al 2009). Complementing their work on the benefits of anticipatory mechanisms on the suppression of thoughts (see previous paragraph), Hanslmayr, Leipold, Pastötter and Bäuml (2009) could identify a positive component related to the onset of the anticipatory no-think cue after 300 ms and a second later positive component related to the onset of the memory cue being most pronounced 1.6 seconds post stimulus presentation. Both showed a significant reduction in amplitude in response to the no-think condition and both were positively correlated, indicating that the later positive component could be predicted from the early component reflecting anticipatory processes. Interestingly, amplitude reductions were stronger in the late component, indicating preparatory mechanisms signaling the need for suppression elicited by the no-think cue, which then elicit a stronger response when the actual memory cue is presented (Hanslmayr et al 2009). In line with the aforementioned studies, both components showed a fronto-parietal topography. The timing of the positivity, however, and the fact that the late component in the Hanslmayr et al. study (2009) predicted forgetting in the behavioral recall test, indicates that “while a reduction in the late positive component may well reflect the avoidance of automatic recollection, the later

sustained reduction of the positivity seems to reflect item suppression, and to underlie the subsequent forgetting" (p. 2747; Hanslmayr et al 2009).

1.3. The Genetics of Memory

In the recent years several molecules, among others G protein-activated inwardly rectifying potassium (K^+) channels (GIRK) and the cyclic AMP (cAMP)-response element binding protein CREB (e.g. Chung, Ge, Qian, Wiser, Jan & Jan 2009; Koppel & Goldberg 2009), have been associated with memory processes, suggesting them as interesting candidates in the investigation of the underlying processes mediating cognitive control of memories and thoughts.

1.3.1. Cyclic AMP-Response Element Binding Protein 1: CREB1

CREB1 belongs to the leucine zipper family of DNA-binding proteins (Sands & Palmer 2008) and is an activator form of CREB which is expressed ubiquitously throughout the brain (Alberini 2009; Josselyn & Nguyen 2005; Zhou, Won, Karlsson, Zhou, Rogerson, Balaji et al 2009). Activation of the cAMP signal transduction pathway is achieved by ligand binding to G-protein coupled receptors terminating in the phosphorylation of the CREB protein and thereby potentiating its transcriptional activity (Mamdani, Alda, Grof, Young, Rouleau & Turecki 2008; Sands & Palmer 2008). CREB1 has been shown to be crucially involved in processes of long-term memory and synaptic plasticity regulated by long-term potentiation, e.g. in hippocampal neurons. It has for example been shown that CREB knockout mice display significant deficits in a wide range of memory tasks probing for spatial, contextual and cued memories. For a detailed review on CREB functioning and its implications in the formation of memories see e.g. Alberini (2009) or Josselyn and Nguyen (2005). Recently it has been shown that a G-to-A transition alters activity of the CREB promoter (Zubenko, Hughes, Maher, Stiffler, Zubenko & Marazita 2002), providing evidence for a functional single nucleotide polymorphism (SNP). It has been shown that the A allele augments the amplitude of variations in CREB1 promoter activity, thereby enhancing the risk of developing a mood disorder, which are known to encompass deficient executive control and memory functioning (e.g. Fossati, Amar, Raoux, Ergis & Allilaire 1999; Paelecke-Habermann, Pohl & Leplow 2005; Watkins & Brown 2002). The CREB1 SNP (rs2253206) thus provides an interesting molecular target in the investigation of variables influencing thought suppression.

1.3.2. Potassium Channel, Inwardly Rectifying, Subfamily J, Member 6: KCNJ6

The KCNJ6 gene located on chromosome 21q22, first identified by Tsaur, Menzel, Lai, Espinosa, Concannon, Spielman et al. (1995), encodes a putative G protein-coupled inwardly rectifying potassium (K^+) channel (GIRK), that shows strong homology with GIRK2, a previously identified potassium channel gene in mice isolated by Lesage, Duprat, Fink, Guillemare, Coppola, Lazdunski et al. (1994). Inherent to their regulative role in K^+ transmission, GIRK channels play a role in synaptic transmission. Closure of K^+ channels, as a result of an intracellular increase in adenosine triphosphate (ATP) concentration, causes membrane depolarization, which in turn triggers the activation of voltage-sensitive Ca^{2+} channels and the subsequent influx of Ca^{2+}. This, in turn, results in other synaptic processes, such as the mediation of G protein-coupled receptors for neurotransmitters, such as $GABA_B$, NMDA, serotonin, DRD2 etc. (Siegelbaum, Schwartz & Kandel 2000). Blockage of GIRK channels or GIRK null mutations have been demonstrated to abolish membrane depolarization in the process of long-term potentiation in cultured hippocampal neurons implying that GIRK channels are crucial for excitatory synaptic plasticity which is assumed to be the physiological correlate of learning and memory (Chung et al 2009). In a recent linkage study in two independent samples performed by Schuur (2010), KCNJ6 was significantly associated with tests measuring executive functions as well as with memory. Furthermore, Lazary, Juhasz, Anderson, Jacob, Nguyen, Lesch et al. (2011) recently have shown KCNJ6 to be implicated in an increased risk for ruminative response styles, which is regarded a relative stable trait mediating the tendency to retrieve memories as either categories or as specific events (Nolen-Hoeksema 2000; Nolen-Hoeksema & Davis 1999). The group could show that a G-to-A transition resulted in significantly higher ruminative tendencies (Lazary et al 2011), suggesting this transition as a functional SNP implicated in the development of specific personality traits previously associated with altered memory processing as well as with disorders encompassing deficits in executive functions such as mood disorders (e.g. Watkins & Brown 2002). The KCNJ6 SNP (rs2070995), as the CREB1 SNP, is thus considered a potential molecular mediator of thought suppression processes investigated in the current work.

1.4. Introduction to the Methods

1.4.1. Functional Near-Infrared Spectroscopy (fNIRS)

1.4.1.1. Fundamentals of fNIRS

Since its introduction in the late 70's (Jobsis 1977) and the development of multichannel apparatuses in the late 80's and early 90's, functional near-infrared spectroscopy (fNIRS) has been increasingly used to study human brain function in adults (Hoshi & Tamura 1993; Kato, Kamei, Takashima & Ozaki 1993; Villringer, Planck, Hock, Schleinkofer & Dirnagl 1993) and infants (Chance, Leigh, Miyake, Smith, Nioka, Greenfeld et al 1988).

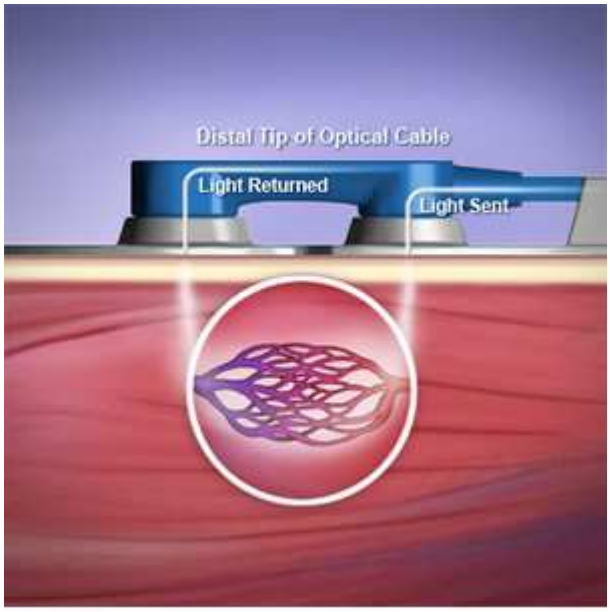

***Figure 2**: Graphical display of fNIRS. Source: http://www.medgadget.com/archives/img/NIRS_FINAL.jpg (retrieved 18-03-2011)*

FNIRS employs near-infrared light to non-invasively measure changes in the concentration of oxygenated (O_2Hb), deoxygenated (HHb) and total (tHb) hemoglobin in the brain, readily penetrating the skull and reaching cortical tissue (Figure 2; for a more detailed description see for example Chance et al 1988; Firbank, Okada & Delpy 1998; Hirth, Villringer, Thiel, Bernarding, Muhlnickl, Obrig et al 1997; Hock, Villringer, Muller-Spahn, Wenzel, Heekeren, Schuh-Hofer et al 1997; Minagawa-Kawai, Mori, Hebden & Dupoux 2008; Wolf & Greisen 2009). Increase of O_2Hb and decrease of HHb (see Figure 3) as a consequence of neuronal activity in certain brain regions is described as neurovascular coupling and is the underlying principle in fMRI measurements investigating the blood oxygenation level dependent (BOLD) signal, which will be described in more detail in section 1.4.2. (Logothetis & Wandell 2004).

Correlations between measurements acquired with fNIRS and other functional imaging methods (Huppert, Hoge, Diamond, Franceschini & Boas 2006; Kennan, Kim, Maki, Koizumi & Constable 2002; Ohmae, Ouchi, Oda, Suzuki, Nobesawa, Kanno et al 2006; Strangman, Boas & Sutton 2002), moderate to high reliability indices (Plichta, Herrmann, Baehne, Ehlis, Richter, Pauli et al 2006a, 2007; Plichta, Herrmann, Ehlis, Baehne, Richter &

Fallgatter 2006b), in addition to its fast, save and easy use (Fallgatter, Ehlis, Wagener, Michel & Herrmann 2004; Obrig, Wenzel, Kohl, Horst, Wobst, Steinbrink et al 2000; Strangman et al 2002) justify the application of this methodology in various areas of research including motor activity (Holper, Biallas & Wolf 2009; Morihiro, Tsubone & Wada 2009), mental tasks (Ehlis, Herrmann, Wagener & Fallgatter 2005; Hoshi, Huang, Kohri, Iguchi, Naya, Okamoto et al 2011; Kubo, Shoshi, Kitawaki, Takemoto, Kinugasa, Yoshida et al 2008), auditory stimulation (Ehlis, Ringel, Plichta, Richter, Herrmann & Fallgatter 2009; Kotilahti, Nissila, Nasi, Lipiainen, Noponen, Merilainen et al 2009; Sakatani, Chen, Lichty, Zuo & Wang 1999) and language (Dieler, Tupak & Fallgatter 2011) in healthy as well as in patient populations.

Different fNIRS systems have evolved over the years. The most widely used method measures the intensity of the reflected near-infrared light via continuously emitting sources (i.e. continuous wave systems, CW systems). By measuring light scattering between a light emitter and a detector, which are sufficiently separated, the proportion of reflected light can be traced back to cortical tissue surrounding the emitter-detector pair (Minagawa-Kawai et al 2008; Okada, Okamoto, Morinobu, Yamawaki & Yokota 2003). Intensity changes in two or even more wavelengths are then converted into concentration changes of O_2Hb and HHb by use of the modified Lambert-Beer law (for a more thorough description see Minagawa-Kawai et al 2008; Obrig & Villringer 2003).

Because NIR light does not travel through tissue unscattered and therefore the exact volume of tissue pervaded by detected light is not known CW systems are unable to derive absolute values of O_2Hb and HHb concentrations (Minagawa-Kawai et al 2008). Systems solving this problem are time-domain and frequency-domain systems, which can determine the average path length of the reflected light (for a review see Minagawa-Kawai et al 2008; Wolf, Ferrari & Quaresima 2007).

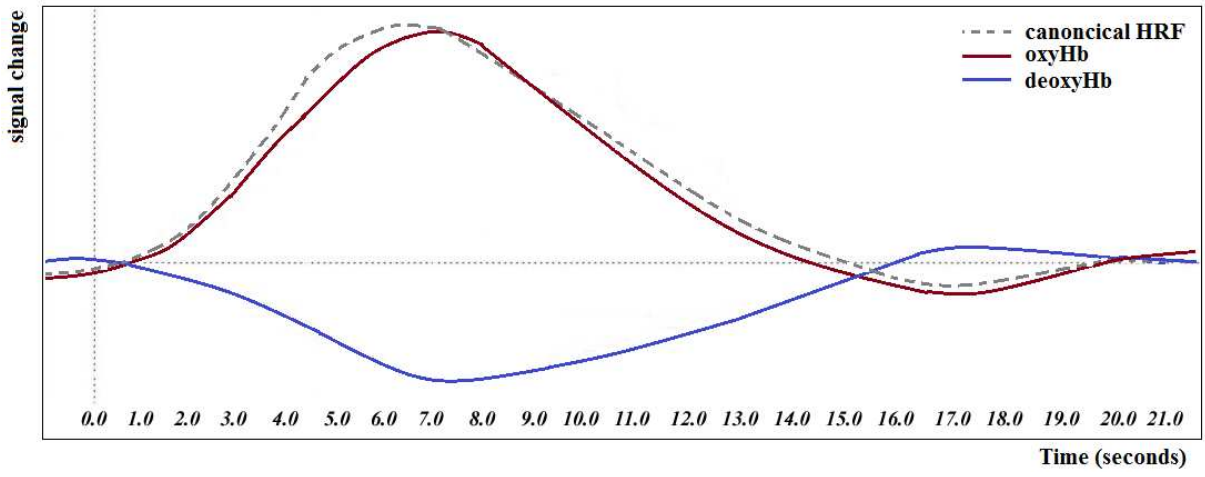

***Figure 3**: Schematic display of the hemodynamic response function. The development of the typical canonical HRF measured in BOLD fMRI imaging and the time course of the HRF of oxygenated and deoxygenated hemoglobin measured in fNIRS are shown separately*

1.4.1.2. Advantages of fNIRS

Several advantages as compared to other imaging methods make fNIRS an attractive tool for researching human brain function in various domains from basic sensorimotor mapping (e.g. Xu, Takata, Ge, Hayami, Yamasaki, Tobimatsu et al 2007) to the study of higher cognitive functions, such as executive functions (e.g. Fallgatter, Muller & Strik 1998). It has been shown to be a reliable tool for studies of higher cognitive functions due to its spatial resolution which is sufficient to map cortical processes (e.g. Schecklmann, Ehlis, Plichta & Fallgatter 2008). In addition it is easily combinable with other neurophysiological methods such as EEG and ERP, which can provide more adequate source localization and temporal resolution (Kennan et al 2002). Furthermore it is a cheap, quick and portable solution relatively insensitive to body or head movements, providing the researcher with freedom in task design and the possibility to study populations such as patients, children or elderly, known to be problematic in settings such as fMRI studies requiring the subject to lie still in a very narrow and noisy environment.

1.4.1.3. Limitations of fNIRS

There are some limitations of fNIRS that have to be mentioned. (1) Although quite well, the spatial resolution is lower than for fMRI and is limited by its penetration depth of only a few centimeters (Chance et al 1988; Lloyd-Fox, Blasi & Elwell 2010; Minagawa-Kawai et al 2008), as well as by light absorption and scattering depending on the measured tissue composition (cerebrospinal fluid, white or gray matter, for a review see Okada, Firbank, Schweiger, Arridge, Cope & Delpy 1997). Furthermore, no anatomical images can be acquired. There are, however, tools in development allowing for a coregistration between an anatomical image acquired by MRI and the fNIRS-derived hemodynamic response (e.g. see Aslin & Mehler 2005; Whalen, Maclin, Fabiani & Gratton 2008) (2) Temporal resolution, with an acquisition rate of up to hundreds of hertz (Huppert et al 2006) is better than for fMRI but is lower than for EEG (Minagawa-Kawai et al 2008), which has a sampling rate of up to a thousand hertz (Mauguière 1999). (3) A definite attribution of the fNIRS signal as originating from cerebral tissue is sometimes difficult. Hemodynamic responses measured in the probes include systemic vascular changes stemming from various sources (e.g. heart rate, skin circulation or blood pressure, Minagawa-Kawai et al 2008). (4) Continuous wave fNIRS systems cannot measure the exact optical path length and have to rely on mathematical models, such as the modified Lambert-Beer law (Delpy, Cope, van der Zee, Arridge, Wray & Wyatt 1988) or simulated light propagation in sophisticated models of the brain (Okada et al

1997). (5) So far no general standard has been introduced regarding fNIRS instrumentations, signal processing, data analysis, as well as first- or second level statistics. (6) Some minor concerns are the establishment of a stable contact between skin and optic fiber and potential disturbance of the light by dark hair.

1.4.2. Functional Magnetic Resonance Imaging (fMRI)

Measurements with fMRI are based on changes in blood oxygenation, which is taken as a physiological marker and interpreted as indirectly reflecting changes in neuronal activity. The most common technique to measure these changes with fMRI is the blood oxygenation level-dependent (BOLD) contrast, which has first been described by Ogawa and colleagues in the late 80's (Ogawa, Lee, Kay & Tank 1990; Ogawa, Lee, Nayak & Glynn 1990) BOLD fMRI takes advantage of the fact that changes in neural activation causes regional changes in the concentration of O_2Hb and HHb through neurovascular coupling: changes in neural firing are followed by regional decreases in O_2Hb and relative increases in the concentration of HHb in the blood. This initial, often very subtle effect is followed by a much larger increase in levels of O_2Hb due to a massive oversupply of oxygen-rich blood. O_2Hb concentration levels reach their maximum after about six seconds (Fox, Raichle, Mintun & Dence 1988; Heeger & Ress 2002). Finally HHb concentration returns to its baseline level after an initial undershoot after approximately 24 seconds (Heeger & Ress 2002). See Figure 3 for a schematic depiction of a typical hemodynamic response.

Signal changes in BOLD fMRI are determined by the paramagnetic properties of HHb and diamagnetic properties of O_2Hb (Kim & Ugurbil 1997) By means of fNIRS, mechanisms of BOLD-related signal changes have been elucidated in more detail (Grinvald, Frostig, Siegel & Bartfeld 1991). They described an increase in HHb content peaking approximately 2.5 seconds after stimulus onset. This has been interpreted as reflecting the local increase in oxygen demand by altered neural firing which is not yet compensated by an increase in regional cerebral blood flow (rCBF). Subsequently a compensatory increase in rCBF and oxygen supply was observed that led to a net decrease in HHb, which has been shown to spread out in a much larger area than the initially observed increase in HHB, and which is equivalent to the signal increase observed in BOLD fMRI (Bandettini, Wong, Hinks, Tikofsky & Hyde 1992; Di Salle, Formisano, Linden, Goebel, Bonavita, Pepino et al 1999; Grinvald et al 1991; Kwong, Belliveau, Chesler, Goldberg, Weisskoff, Poncelet et al 1992; Ogawa, Tank, Menon, Ellermann, Kim, Merkle et al 1992). For a detailed description of MRI and BOLD fMRI physics see e.g. Huettel, Song and McCarthy (2004).

It has to be noted that assessing the concentration changes of O_2Hb and HHb in the brain is an indirect measure of neural activity, as outlined above. This entails that any event leading to a vascular response in the brain leads to signal changes in the fMRI BOLD raw data. Furthermore, irregularities in neurovascular coupling, which have been described in certain disorders influence neurovascular processes (Iadecola 2004) and might also hamper interpretation of BOLD signal changes. Through event-locked extraction and modelling procedures, however, signal changes specific to the components of a functional task can be derived.

1.4.3. Electroencephalography and Event-Related Potentials (EEG and ERP)

ERPs are electrical changes in neuronal activity that can be seen in the routine EEG before, during or after sensory, motor, or cognitive events. In other words, ERPs represent the discharge distribution of measurable responses of the brain to environmental (exogenous) or internally (endogenous) generated stimuli. While exogenous ERPs, occur very early (<100ms) and mainly depend on the physical properties of a stimulus, internal ERPs display longer latencies (>100ms) and largely depend on psychological variables, such as the relevance of the stimulus or the current emotional status of the person (Altenmüller & Gerloff 1999). Exogenous ERPs are mainly used as a diagnostic tool, testing, for example the integrity of sensory afferences and efferences (Picton, Bentin, Berg, Donchin, Hillyard, Johnson et al 2000). Endogenous ERPs, seen as neuronal correlates of cognitive and emotional processes are used for psychological and neuroscientific research, since they provide insight into early aspects of information processing, not possible with other measurement techniques such as fNIRS or fMRI (Karmiloff-Smith 2010) or classical neuropsychological methods (Rösler 1982).

ERP amplitudes, in relation to ongoing background EEG, show very small amplitudes ranging from 2-20μVs (Altenmüller & Gerloff 1999). Therefore, signal averaging to improve the signal-to-noise ratio is inevitable in visualizing these responses in contrast to the ongoing EEG activity not related to the stimulus (Dawson 1951; Lopes Da Silva 1999). Two basic assumptions are stated, which have to be taken into account before ERP analysis: (1) the electrical response evoked by the brain is delayed invariably relative to the stimulus and (2) the ongoing activity is corrupted by background noise, which can be correlated with the ERP components of interest. In other words, ERPs represent a signal corrupted by additive noise in which the signal can only be detected by improving the signal-to-noise ratio (Lopes Da Silva 1999). For the model behind time averaging the reader is referred to Lopes Da Silva (1999).

Another possible method is analysis of the frequency domain, which is used to isolate ERPs that (1) occur without a fixed phase or time relation to the stimulus, and are therefore difficult to detect in the time domain and (2) are caused by continuous stimulation (see Lopes Da Silva 1999).

Different endogenous components are classified according to their polarity (i.e. "N"=negative and "P"=positive) and their latency (e.g. the N100 is a negative deflection occurring approximately 100ms after stimulus presentation).

Two inherent difficulties in the interpretation of ERP data are: (1) The neuronal correlates or structures generating the observed components are not precisely defined and (2) the separation of components according to the above mentioned classification is artificial and an overlap of components originating in different brain areas can occur (McCallum 1988). Newer tools, such as sLORETA (Pascual-Marqui 2002), however, provide the possibility to localize the source of electrical activity by multi-channel surface EEG recording. Additionally, the combination of EEG with imaging methods such as fMRI or fNIRS provides the possibility to couple electrical discharges with the underlying brain structures.

1.4.4. Transcranial Magnetic Stimulation (TMS) including Theta-Burst Stimulation (TBS)

1.4.4.1. TMS

Since its introduction by Barker, Jalinous and Freeston (1985) in the mid 80's, Transcranial Magnetic Stimulation (TMS) has developed as an important tool in investigating the brain by providing the possibility to modulate neuronal activity in the cortex. It is a non-invasive means of stimulating nerve cells and is regarded as a promising investigational and therapeutical tool in psychiatric or neurological settings (Fitzgerald, Brown & Daskalakis 2002; Wagner, Valero-Cabré & Pascual-Leone 2007).

Through rapidly changing magnetic fields electric currents are induced perpendicular in the brain (see Figure 4), which in turn will cause electrical currents flowing parallel to the plane of the coil (Bonato, Miniussi & Rossini 2006; Hallett 2000). In case of round coils, which are very powerful, the strongest current is induced near the circumference of the coil without any current in the centre (see Figure 4A). Figure-of-eight coils induce the electrical current more focally, producing its maximum at the intersection of the two round parts (see Figure 4B).

TMS can be applied as a single pulse, pairing two pulses (ppTMS) or repetitively, resulting in various pulses per second (rTMS). While stimulation of the visual cortex, inducing phosphenes or a temporary scotoma (Amassian, Cracco, Maccabee, Cracco, Rudell & Eberle 1989), or the motor cortex, inducing motor evoked potentials (MEPs) or temporary disruption of motion perception by stimulating area V5 (Beckers & Zeki 1995) are usually achieved by single pulse TMS, application of ppTMS and rTMS has been shown to be able to manipulate the initiation threshold of these reactions. Response to ppTMS and rTMS may increase or decrease depending on the interstimulus interval (ISI) and the relative strength of the first pulse compared to the following (Kujirai, Caramia, Rothwell, Day, Thompson, Ferbert et al 1993). Usually ppTMS involves the pairing of a supra-threshold stimulus followed by a sub-threshold stimulus. Inhibition is achieved with brief ISIs of 1-6 ms or long ISIs of 50-200 ms (Kujirai et al 1993), while facilitation follows an intermediate ISI of 8-20ms (Fitzgerald et al 2002). PpTMS has been applied to the research of deficits in cortical inhibition in disorders such as schizophrenia (e.g. Fitzgerald, Brown, Marston, Oxley, De Castella, Daskalakis et al 2004), Tourette's syndrome (Ziemann, Paulus & Rothenberger 1997), obsessive-compulsive disorder (Greenberg, Ziemann, Cora-Locatelli, Harmon, Murphy, Keel et al 2000), and epilepsy (Klimpe, Behrang-Nia, Bott & Werhahn 2009; Werhahn, Lieber, Classen & Noachtar 2000), as well as the effect of drugs on inhibitory parameters (e.g. Fitzgerald et al 2004; Pascual-Leone, Manoach, Birnbaum & Goff 2002; Ziemann, Lonnecker, Steinhoff & Paulus 1996). RTMS paradigms are used to study higher cognitive functions (e.g. by increasing or disrupting performance on cognitive tasks, such as object naming (Wassermann, Grafman, Berry, Hollnagel, Wild, Clark et al 1996) and memory (Grafman, Pascual-Leone, Alway, Nichelli, Gomez-Tortosa & Hallett 1994)) or the

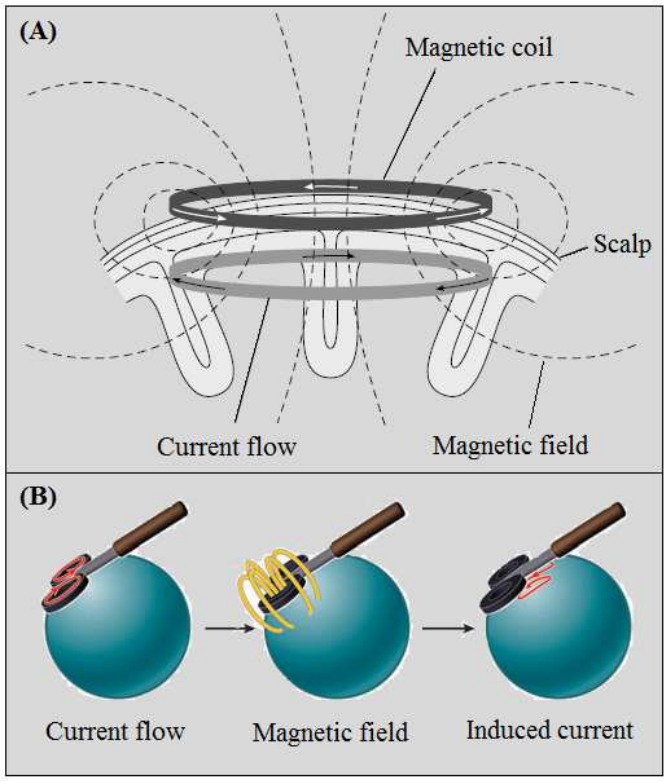

***Figure 4**: Basic principle of Transcranial Magnetic Stimulation. (A) Principles of current induction in a round coil (adapted from Hallett 2000) and (B) principles of current induction in a figure-of-eight coil (adapted from Wagner et al., 2007)*

therapeutical effectivity of TMS for example in the field of depression (Martin, Barbanoj, Schlaepfer, Thompson, Perez & Kulisevsky 2003; Pogarell, Koch, Pöpperl, Tatsch, Jakob, Zwanzger et al 2006), addiction (e.g. cocaine: Camprodon, Martínez-Raga, Alonso-Alonso, Shih & Pascual-Leone 2007; nicotine: Eichhammer, Johann, Kharraz, Binder, Pittrow, Wodarz et al 2003; alcohol: Mishra, Nizamie, Das & Praharaj 2010), or even as a potential alternative to the WADA test in the determination of language dominance presurgically (Epstein, Meador, Loring, Wright, Weissman, Sheppard et al 1999; Jennum, Friberg, Fuglsang-Frederiksen & Dam 1994). For an extended description of the applications of TMS in psychiatry and neuroscience the reader is referred to Fitzgerald et al. (2002).

The above mentioned inhibitory and excitatory effects of rTMS have been compared to the concept of long-term depression (LTD) and long-term potentiation (LTP), which are used to describe neuromodulatory effects of repeated in vivo or in vitro stimulation of neuronal populations, disturbing or improving cell-to-cell communication and are the basics of neural plasticity and learning (George, Nahas, Kozol, Li, Yamanaka, Mishory et al 2003; Huang, Edwards, Rounis, Bhatia & Rothwell 2005)

1.4.4.2. TBS

A newer rTMS protocol is the theta-burst paradigm (TBS) in which 3-5 pulses are administered at 50Hz, repetitively at a frequency of 5Hz (George et al 2003; Huang et al 2005). Two protocols, based on the original TBS protocol have been developed within the last five years, and have been shown to effectively induce LTP and LTD in in vitro brain slices respectively: continuous TBS (cTBS) and intermittent TBS (iTBS). See Figure 5 for an outline of the two protocols.

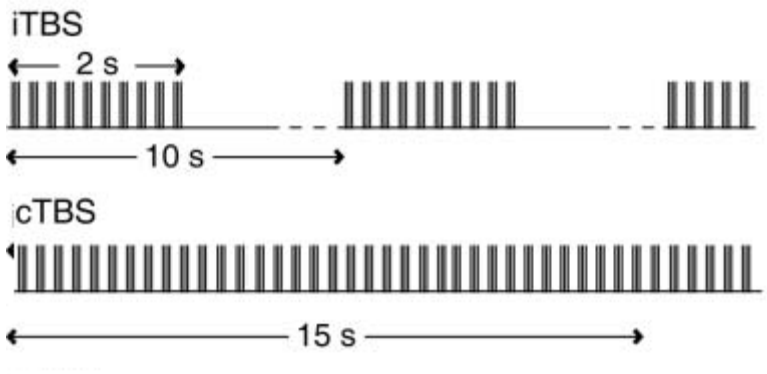

***Figure 5**: Outline of the iTBS and cTBS protocol first introduced by Huang et al. (2005).*

Huang et al. (2005) applied cTBS and iTBS protocols to the human primary motor cortex and observed a suppression of EMG responses and facilitated EMG responses, respectively. Depending on the number of pulses in the protocol the group succeeded in prolonging the effects up to one hour post-stimulation, which outweighs all effects following

other rTMS protocols. Similar results have been published by Franca, Koch, Mochizuki and Huang (2006), who reported an increase in phosphene-threshold by 10% following cTBS.

1.4.4.3. Limitations of TMS and TBS

Limitations of TMS are that the exact mechanisms of neural activation through TMS are not yet well understood (Wagner et al 2007), but the observation that stimulation produces a corticospinal volley with indirect waves rather than with an early direct wave indicates that activation changes are induced at the synaptic level (Di Lazzaro, Oliviero, Profice, Saturno, Pilato, Insola et al 1998). Furthermore, the biological effects of TMS on network activity are not clearly defined yet. Only one network model for TMS exists, accounting for over 33.000 neurons with approximately five million modelled synapses and reproducing experimental TMS results (Esser, Hill & Tononi 2005). Autoradiographic measures with 2-DG tracers have demonstrated that network effects are not physiologically restricted to the stimulated brain site, but spread to neighboring or even distant regions (Valero-Cabré, Payne, Rushmore, Lomber & Pascual-Leone 2005).

Furthermore, one major issue is safety, since incidents of induced epileptic seizures have been reported (Paulus 2005). Following established safety protocols, however, the risk of adverse effects is minimal (Wassermann 1998) and especially TBS protocols have been described to minimize seizure risk and other side-effects due to their proportionally weaker stimulation strengths as compared to classical rTMS protocols (Grossheinrich, Rau, Pogarell, Hennig-Fast, Reinl, Karch et al 2009; Huang et al 2005; Paulus 2005).

1.5. Thesis Outline and Research Questions

As becomes apparent from the number of studies using the TNT described in section 1.2., the topic of cognitive inhibition has gained increasing attention in the research community. Various potentially influencing variables, ranging from the emotional content of the to-be-inhibited thoughts to personality traits such as for e.g. anxiety, depressed mood states, rumination or working memory capacity have been investigated. Although progress has been made unravelling the processes underlying thought suppression at a behavioral or neural level a number of open questions still exist. Not all studies have been able to replicate Anderson and Green's (2001) original finding of successful disruption of memory traces of previously suppressed thoughts to a rate below baseline, which is deemed one of the major criteria for proving the existence of an active cognitive mechanism working at the level of executive functions (Anderson & Green 2001; Anderson et al 2004).

As shown in paragraph 1.2.2. special focus has been set on the influence of stimulus valence on the suppression of thoughts. Results of these studies, however, are inconsistent. Some have shown better suppression of negative stimuli (Depue et al 2006; Joormann et al 2005) while others have shown better suppression of positive stimuli (Hertel & Gerstle 2003; Marx et al 2008). Two hypotheses have emerged regarding the outcomes of cognitive control over negatively valenced thoughts: First, Depue et al. (2006) and Lambert et al. (2010) have claimed better suppression of negative memories due to their heightened salience and better accessibility to cognitive control. Second, Marx and colleagues (2008) showed better suppression of positive words, supporting the view that negative information is more elaborately processed during encoding and therefore less prone to cognitive inhibition. In addition to the inconsistency regarding the facilitating or impairing effect of stimulus valence on thought inhibition, no study has been found directly comparing neutral, positive and negative stimuli in the same group of subjects. The first aim of the present study was thus to investigate how the emotional content of the to-be-suppressed stimulus material influences cognitive inhibition using a between-subject design.

Research Question 1: How does the valence of the stimulus material influence thought inhibition in the Think/No-Think paradigm?

As just mentioned, studies investigating differences in TNT performance regarding the valence of the used stimuli have, although inconsistent, found evidence of differential inhibition of neutral, positive and negative thoughts. All these studies, however, have been performed on a behavioral basis, and thus lack the ability to disentangle whether the differences found between the suppression of neutral, positive and negative stimulus material are due to a single cognitive control mechanism acting on emotional and neutral information to a different degree, or distinct processes inhibiting the intrusion of emotional and neutral stimuli. Evidence, however, exists that manipulation of emotional vs. neutral information is associated with greater activity of prefrontal cortices (Gray, Braver & Raichle 2002; Hamann 2001), as well as increased recruitment of subcortical regions (Canli, Zhao, Brewer, Gabrieli & Cahill 2000; Maratos & Rugg 2001), hinting at a similarly distributed neural network acting differently on emotional and neutral information.

Research Question 2: Does inhibition of neutral or emotional thoughts engage the same or distinct neural networks?

The role of the dlPFC as top-down control region in thought inhibition has been supported by three fMRI studies (Anderson et al 2004; Depue et al 2010; Depue et al 2007). Furthermore, it has repeatedly been shown that the amount of signal change observed in the right dlPFC is predictive of the eventual suppression effect observed in the behavioral recall test. The third aim of the current work was thus the investigation of the influence of external manipulation of dlPFC activation on the performance in the TNT to strengthen the proof of the role of dlPFC activation in cognitive control exerted over unwanted thoughts

Research Question 3: Can performance in the Think/No-Think paradigm be improved by increasing activation in the right dlPFC by means of intermittent TBS?

Various fMRI and ERP studies have been conducted in the last few years, investigating the neural systems underlying thought inhibition and several attempts have been made to link findings from these two methods. These attempts, however, have been only speculative since they were based on different studies or based on results obtained in other domains of executive control (e.g. the Go/Nogo paradigm). Taking advantage of fNIRS to be easily combinable with EEG (see section 1.4.1. and 1.4.3.), another aim was the direct correlation of functional activation in the dlPFC as measured by fNIRS and the corresponding ERPs as well as their interaction in modulating the subsequently measured behavioral suppression effect.

Research Question 4: How do ERPs found to be related to the intentional suppression of thoughts in the TNT correlate with activation in the dlPFC and how does this correlation relate to the behaviorally measurable suppression effect?

In addition to the most basic investigation of the neural network implemented in the suppression of thoughts, personality traits such as anxiety (Waldhauser et al 2010) or depressive symptoms, including ruminative response styles (Hertel & Gerstle 2003; Hertel & Mahan 2008; Joormann et al 2005; Wessel et al 2005) have been a topic of interest since it was assumed that performance in the TNT is critically influenced by these factors. As described in section 1.2.2., results regarding the modulation of suppression performance have been inconsistent, ranging from an enhancing effect of anxious and depressive symptoms on the ability to successfully inhibit thought intrusions (Joormann et al 2005) to an impairing

(Hertel & Gerstle 2003) or no effect (Wessel et al 2005) of these factors. Sample sizes in these studies have been quite small and therefore may not be able to detect subtle differences in the suppression effect, which has been discussed as presenting with only small to moderate effect sizes (Bulevich et al 2006). Furthermore, comparisons have been, at least in some studies, performed between patient cohorts and healthy control subjects. Confounding factors, implicated in patient studies, such as medication, co-morbidities etc. might thus have led to the inconsistent findings. A further aim of this work was thus to investigate the influence of these personality traits in a large sample of healthy control subjects.

Research Questions 5: How do personality traits such as anxiety or depressive symptoms modulate the ability to exert cognitive control over unwanted thoughts?

Finally, the contribution of variations in two genetic SNPs, which have recently been linked with memory performance and ruminative response styles (CREB1 and KCNJ6), were of interest in disentangling the factors contributing to the ability of preventing thought intrusions at a behavioral and neurophysiological level.

Research Question 6: Are there genetic factors influencing cognitive control processes in the TNT?

2. Materials and Methods

2.1. General Remarks

All analyses were performed with SPSS Version 18 (SPSS Inc.). In cases of a violation of the assumption of sphericity when performing calculations with the general linear model (GLM), indicated by a significant chi^2 value in the Mauchly-Test ($p < .05$), the degrees of freedom were adjusted, following Quintana and Maxwell (1994): in case of a Huynh-Feldt $\varepsilon \geq 0.75$ according to the Huynh-Feldt correction, and in case of a Huynh-Feldt $\varepsilon < 0.75$ according to the Greenhouse-Geisser correction. To correct for the accumulation of the alpha error during multiple testing, the conventional significance cutoff of $p < .05$, was adjusted by means of Bonferroni correction when performing post-hoc t-tests.

For all studies participants were screened for the absence of past and present psychiatric axis I disorders with a short questionnaire including items from the SKID-I interview (German version of the Structured Clinical Interview for DSM IV, Wittchen, Zaudig & Fydich 1997).

Each study was reviewed and approved by the Ethics Committee of the University of Wuerzburg, and all procedures involved were in accordance with the 2008 version of the Declaration of Helsinki. All participants gave written informed consent after comprehensive explanation of the experimental procedures.

2.2. Pilot Study

2.2.1. Sample

15 right-handed healthy subjects, recruited from the staff of the University Clinic Wuerzburg (4 men, age: 28.2 ± 6.28 years) participated in this study.

2.2.2. The TNT

The version of the Think/No-Think paradigm used in this study was adapted from Anderson's original design (Anderson & Green 2001, see Figure 1). During the study phase, subjects were presented with 45 pairs of unrelated German nouns twice. Afterwards they viewed the first word of the pair (cue word) together with two alternative words, from which they had to select the previously learned partner word (i.e. target). The second word was also taken from the previously learned wordlist to prevent recognition effects. This phase was repeated until subjects responded correctly to more than 80% of the words each on two consecutive cycles.

In the subsequent Think/No-Think part of the paradigm, brain activation was measured with fNIRS. Subjects were presented with blocks of six cue words, each preceded by the instruction (5 seconds) either to suppress the previously learned partner word and to prevent thinking about it at all (i.e. no-think), or to recall the partner word and think about it (i.e. think) during the following block. Subjects were instructed to focus on each word in the block for the entire time it was presented (4 seconds, i.e. each block lasted 24 seconds) to prevent perceptual avoidance and to generate a constant threat that the associated memory might intrude into consciousness. Each block was presented 5 times, preceded by the instruction and separated by the presentation of a fixation cross (24 seconds), resulting in 15 no-think and 15 think blocks in total.

In the final recall test, participants were given a list with all cue words and asked to fill in all of the partner words they remembered. This served as behavioral control whether suppression had really and effectively occurred. Hypothetically, recall should be worse for the no-think words than for the think words, since the memory trace should be disturbed when suppression of the associated word was successful (e.g. Anderson & Green 2001; Anderson et al 2004; Depue et al 2007). The baseline condition (3 words per valence condition), in which word pairs are learned during training, but not actively manipulated (i.e. neither appear in the think or no-think condition), served as control condition, and has in previous studies been

shown to be recalled worse than the think-items, but better than the no-think items (Anderson & Green 2001; Depue et al 2006).

Words were taken from the Berlin Affective Word List (Vo, Conrad, Kuchinke, Urton, Hofmann & Jacobs 2009; Vo, Jacobs & Conrad 2006), selecting the 15 most positively and 15 most negatively, as well as the 60 most neutrally rated words. For characteristics of the partner words see Table A - 1. Word pairs were formed coupling a neutral word (e.g. Geruch, Visum, Skat; engl: smell, visa, skat) with a positive (e.g. Liebe; love), negative (e.g. Folter; torture) or neutral word (e.g. Reihe; row), so that all cue words were neutral. An overview of the paradigm is given in Figure 6.

	Study / Training	**Think/No-Think**	**Recall**
Think	GERUCH - REIHE	GERUCH	GERUCH
No-Think	VISUM - LIEBE	VISUM	VISUM
Baseline	SKAT - FOLTER		SKAT
		Functional Near-Infrared-Spectroscopy	

Figure 6*: Schema of the Think/No-Think paradigm as used in the pilot study ('Geruch – Reihe' = Smell –Row; 'Visum – Liebe' = Visa – Love; 'Skat –Folter' = Skat – Torture)*

2.2.3. FNIRS

The theory behind fNIRS has been described in section 1.4.1. in detail. The system used in this study was a CW system (ETG-4000 Optical Topography System; Hitachi Medical Co., Japan), operating with two different wavelengths (695 ± 20 and 830 ± 20 nm) and a time resolution of 10 Hz to measure relative changes of absorbed near-infrared light. These changes are transformed into concentration changes of O_2Hb, HHb, and tHb as indicators of brain activity by means of a modified Lambert–Beer law (Obrig & Villringer 2003). The unit is mmol×mm, i.e. changes of O_2Hb, HHb, and tHb concentration depend on the path length of the near-infrared light, which is unknown in our examination. A 52-channel array of optodes was used that covered an area of 30×6 cm at the frontal region of the head (interoptode distance = 3 cm). This array consisted of 17 light emitters (semiconductor lasers) and 16 photo-detectors (Avalanche photodiodes) each of which detected the reflected near-infrared light of its surrounding emitters. A measuring point of activation (i.e. channel) was defined as the region between one emitter and one detector. The array was fastened to the head by elastic straps with regard to the standard positions of Fpz and T3/T4 according to the international

10–20 system for EEG electrode placement (Jasper 1958; Okamoto, Dan, Sakamoto, Takeo, Shimizu, Kohno et al 2004). See Figure 7 for a depiction of probe set placement.

2.2.4. Data Analysis and Statistics

2.2.4.1. Behavioral Data

Two subjects had to be excluded due to problems with data acquisition, resulting in a sample of 13 subjects (3 men). Percentages of recalled words were calculated for no-think trials, think trials and baseline trials. Performance was calculated for the three valence conditions separately. A 3 x 3 repeated-measures ANOVA with the within-subject factors valence (neutral, positive, negative) and condition (baseline, think, no-think) was performed.

For the description of psycholinguistic characteristics and possible differences due to valence between the selected words, univariate (i.e. valence) ANOVAs were calculated for emotional mean, arousal, imageability, letters, phonemes, syllables, and word frequency using the rating material provided by Vo et al. (2009).

To investigate differences in brain activation measured with fNIRS between subjects being successful in the suppression of words versus those subjects who did not succeed or comply with the instruction, a behavioral suppression index (BSI) was calculated according to Depue et al. (2007). This index was acquired by subtracting the mean percentage of recalled no-think words from the mean percentage of recalled baseline words summed over the three valence condition. The greater this index is the better the subject is at suppressing the stimulus material during the no-think trials.

2.2.4.2. FNIRS Data

Prior to statistical analysis of the functional imaging data using the general linear model (GLM), the high frequency portion of the signal was removed by applying the system build-in moving average (MA) filter with a time window of 5 seconds which has an approximate cut-off frequency of 0.08 Hz. This MA filter removes frequency components such as pulse waves (approximately 0.6–1.2 Hz) and respiration oscillations (approximately 0.1–0.5 Hz). A 7-element discrete cosine transform basis set was used to account for slow drifts in the measurement. Consecutively, the GLM was applied using the hemodynamic response function (HRF) provided by the SPM 5 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). The HRF was convolved with a boxcar function and used for the derivation of O_2Hb and HHb parameters, by means of regression analysis (so-called beta weights). A time course for each condition was calculated by

averaging all blocks of one condition, resulting in 6 by 52 beta values. Significant positive beta weights indicate an increase in the concentration of the O_2Hb data and negative beta weights indicate a decrease in the HHb concentrations. For a more detailed description of fNIRS analysis the reader is referred to Plichta et al. (2006a; 2006b).

Regions of interest were defined a-priori according to the coregistration of fNIRS channels to MNI space by Dan (2010). Channels forming the right dlPFC were #3, #4, #14, and #25 and those forming the left dlPFC were #7, #8, #18, and #28. See Figure 7 for the positioning of the probeset and the location of the channels used for the ROI analyses.

The ROIs were entered in a 3 x 2 x 2 ANOVA with the factors valence, condition and side. Additionally a 3 x 2 ANOVA with the factors valence and condition were calculated separately for the right and left dlPFC. To investigate signal changes in the ROIs during think and no-think trials relative to baseline (i.e. activation during presentation of the fixation cross) paired samples t-tests contrasting activation during the task period (i.e. think or no-think) against baseline-activation, were performed consecutively. This additional analysis is performed because it is argued that the classical no-think/think contrast does not allow for the isolation of effects solely associated with either condition (Depue et al 2007). Lastly, directed/one-sided correlation analyses with the BSI summed over the three valences were performed for the difference in activation during no-think and think trials in ROIs showing a significant or marginally significant condition effect.

All analyses were performed for O_2Hb and HHb.

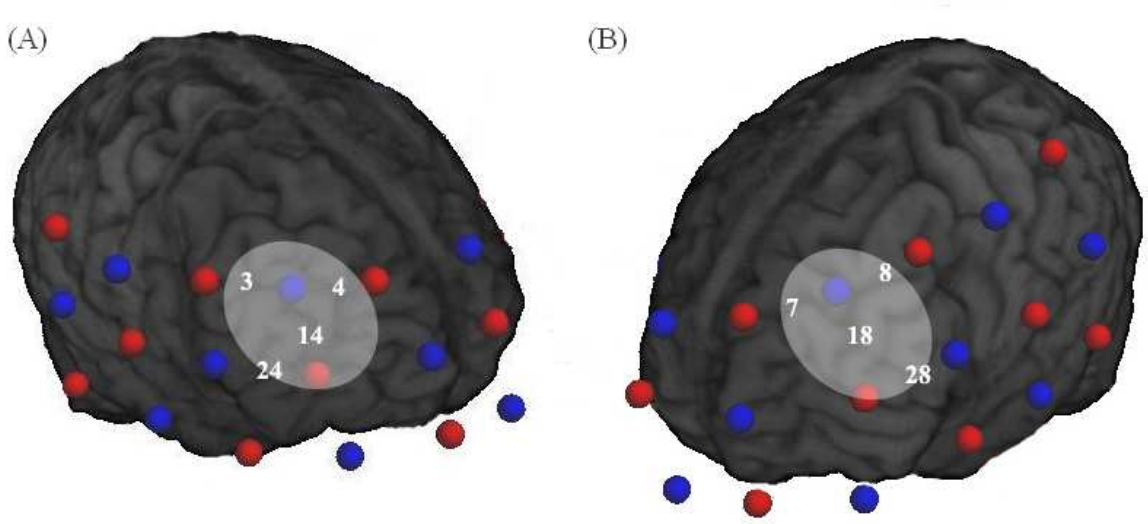

***Figure** 7: Outline of the fNIRS probeset and the ROIs (shaded area) used for the subsequent statistical analyses plotted on the MR scan of a single subject. (A) Right hemisphere and (B) left hemisphere*

2.3. Emotion Study

2.3.1. Sample

A total of 20 subjects, recruited via advertisement in the local media, participated in the experiment (age 29.50 ± 10.68; 7 men).

2.3.2. The TNT

The measurement took place on two separate days, allowing for the within-subject investigation of valence effects (i.e. neutral, positive and negative) and increasing the number of TNT repetitions without creating an uncomfortable and unendurably long experimental setting. On the first day subjects were trained on 26 face-picture pairs (see Table A - 2 for stimulus material) of one of the valence condition, including 8 neutral filler pairs used for practice of the TNT instruction prior to the measurement. Each pair was shown twice for 5 seconds each (i.e. study phase) before subjects were presented with the face cue and 4 of the pictures, including three non-target pictures (taken from the studied pictures to prevent recognition effects) and the target picture, from which they had to choose the correct one. Feedback was provided whether the answer was right or wrong, and the correct face-picture pair was presented again for 3 seconds. The training phase was repeated until subjects responded correctly to 90% of the trials. Before the actual measurement started, subjects were given the TNT instructions (see paragraph 2.2.2.) and completed 5 practice runs on the 8 filler pairs. The think condition was indicated by two green bars framing the face stimulus, while the no-think condition was indicated by two red bars. On the second day the whole procedure was performed for the remaining two valence conditions. The second day differed only in the number of face-picture pairs (i.e. 36 in total, thus 18 pairs per missing valence condition) and the cancellation of the practice trials. Order of valence was randomized between the participants.

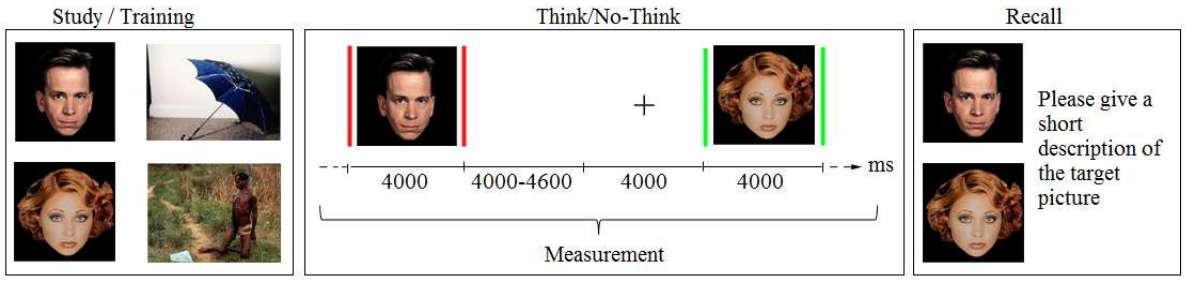

***Figure 8**: Depiction of the TNT paradigm used in the three subsequent studies*

FNIRS was measured using a rapid event-related design following guidelines by Wager and Nichols (2003) for fMRI design optimization. Faces were presented randomly for 4 seconds, separated by a variable interstimulus interval of 4 to 4.6 seconds, and randomly interleaved with a fixation cross presented for 4 seconds serving as a null event (33% of total trial number). Each face was presented 12 times, resulting in a total of 72 think and 72 no-think trials per valence condition.

Finally, subjects were given a list with all face cues and were asked to give a short description of the associated picture cue. Figure 8 gives an outline of the TNT procedure.

2.3.3. FNIRS

For a description of the fNIRS system used in this study, as well as probeset positioning see paragraph 2.2.3. and Figure 7.

2.3.4. Data Analysis and Statistics

2.3.4.1. Behavioral Data

To control for significant differences in the valence ratings between the neutral, positive and negative IAPS pictures, as well as non-significant differences in arousal between the positive and negative pictures, two univariate ANOVAs with the factors valence and arousal were calculated respectively using the rating material provided by Lang, Bradley and Cuthbert (2005).

Suppression performance was investigated by means of a repeated-measures ANOVA with the factors condition (i.e. think, baseline, and no-think) and valence (i.e. neutral, positive, and negative).

The BSI was calculated as described earlier (see paragraph 2.2.4.1.).

2.3.4.2. FNIRS Data

Preprocessing of the data was performed in accordance with the procedures described in 2.2.4.2. Since an event-related design was used in this study, the HRF, however, was convolved with a stick function.

Additionally to analysis of the whole time series, the experiment was divided in halves and the time series of each half was analysed separately. The rationale behind this was the observation of previous studies that a solid suppression effect (i.e. below-baseline recall of no-think items) occurred only after several suppression attempts (e.g. Anderson & Green

2001; Depue et al 2006). Furthermore, Depue et al. (2007) reported increased prefrontal activation in the first half and a significant drop in percentage signal change in the second half of the experimental time series. So the question of interest was whether we could replicate the finding of differential activation in the dlPFC with regard to the amount of attempts to control unwanted thoughts.

Regarding the whole time series, the ROIs were entered in a 3 x 2 x 2 ANOVA with the factors valence, condition and side.

Comparing performance throughout the time series of the experiment, a 2 x 3 x 2 x 2 repeated-measures ANOVA with the factors condition, valence, half and side was calculated. Factors showing a significant interaction were entered in follow-up repeated measures ANOVAs, with the factors condition, valence and side as well as valence, condition and half.

Lastly, directed/one-sided correlation analyses were performed for activation-differences between no-think and think trials with the BSI summed over the three valences separately for the first and second half of the experimental time series.

All analyses were performed for using the same ROIs defined in 2.2.4.2 separately for O_2Hb and HHb.

2.4. FMRI Study

2.4.1. Sample

66 healthy individuals (age: 25.26 ± 5.19; 27 men) were recruited via advertisement in the local press.

2.4.2. The TNT

The procedure was the same as described in 2.3.2., except for using only neutral and negative IAPS pictures (Lang et al 2005; see Table A - 2), in order to limit scanning time to a reasonable duration. Additionally, the measurement was completed within one session per subject. Subjects learned the association between 44 face-picture pairs (i.e. faces serving as cues and pictures serving as target in the later TNT phase), including 8 filler pairs used for practice of the TNT instruction, to a criterion of 90%.

Event-related settings were chosen according to those already described in 2.3.2.

2.4.3. FMRI

Imaging was performed using a 1.5 T Siemens Magnetom Avanto TIM-system MRI scanner (Siemens, Erlangen, Germany) equipped with a standard 12 channel head coil. In a single session, 24 4-mm-thick, interleaved axial slices (in-plane resolution: 3.28 x 3.28 mm) oriented at the AC-PC transverse plane were acquired with 1 mm interslice gap, using a T2*-sensitive single-shot echo planar imaging (EPI) sequence with following parameters: repetition time (TR; 2000 ms), echo time (TE; 40 ms), flip angle (90°), matrix (64 x 64), and field of view (FOV; 210 x 210 mm^2). The first 6 volumes were discarded to account for magnetization saturation effects.

2.4.4. Data Analysis and Statistics

2.4.4.1. Behavioral Data

Differences in the recall of the three conditions (i.e. think, baseline, and no-think) and the potential modulation by valence (i.e. neutral, negative) were investigated in a 3 x 2 ANOVA.

The BSI was calculated as described earlier (see paragraph 2.2.4.1.).

2.4.4.2. FMRI Data

Data preprocessing was performed using statistical parametric mapping software (SPM8, Wellcome Department of Cognitive Neurology, UK), implemented in Matlab 7.6

(The MathWorks Inc., Natick, MA). Slice-time correction was applied and images were realigned. The computed mean image of the scans was used as the source image for spatial normalization of the data. In the next step, data were spatially smoothed, using a 10-mm FWHM Gaussian isotropic kernel. Each voxels' time series was filtered with a high-pass filter to 1/128 Hz in order to remove low-frequency noise. Finally, an autoregressive model with a lag of 1 was applied to correct for temporal autocorrelation.

Due to problems with data acquisition (e.g. inclomplete acquisition due to technical problems) and data quality (movement artefacts,) only 46 subjects were included in the statistical analyses.

ROIs were chosen based on previous findings by (Anderson et al 2004; Depue et al 2007) and defined using the WFU PickAtlas Tool (Maldjian, Laurienti & Burdette 2004; Maldjian, Laurienti, Kraft & Burdette 2003). ROIs encompassed bilateral hippocampus, amygdala and dlPFC (BA9/46). Correction for multiple comparisons within these regions was realized by utilizing a Monte Carlo simulation approach running in AlphaSim (Ward 2000; provided with the AFNI software) with a single voxel p-value of 0.05. The spatial intercorrelations between the voxels, as modeled by the FWHM of a Gaussian kernel, were obtained from SPM8. With this procedure ROI specific cluster-sizes corresponding to a corrected threshold of $p < .05$ or $p < .1$ were determined respectively (see Table 2). These cluster-sizes were applied in all further image-analyses ensuring a corrected α-level of 5% (respective F- or T-statistics of the peak voxel are given in parentheses).

A 2 x 2 ANOVA with the factors condition (think, no-think) and valence (neutral, negative) was calculated separately for each ROI. To further investigate signal change during the two experimental conditions relative to baseline (i.e activation during presentation of the fixation cross) paired-samples t-tests were performed.

For further statistical analyses data of each ROI was extracted using REX (http://www.nitrc.org/projects/rex/), a standalone MATLAB-based tool.

***Table 2**: Region-specific cluster sizes ensuring a corrected α-level of $p < .05$ or $p < .1$*

Region of Interest	**Cluster Size**	
	p < .05	**p < .1**
Right dlPFC	565	422
Left dlPFC	553	431
Right Hippocampus	181	123
Left Hippocampus	159	110
Right Amygdala	75	37
Left Amygdala	61	40

To investigate effective control over memory, think and no-think trials were divided into successfully inhibited, thus forgotten, no-think (NT_f), remembered no-think (NT_r), successfully remembered think (T_r) and forgotten think trials (T_f). A 2 x 2 x 2 ANOVA with the factors condition, success and valence was calculated for bilateral amygdala and hippocampus. For signal changes in the dlPFC, a linear trend analysis was performed investigating a linear increase from $T_f < NT_r < T_r < NT_f$.

To investigate the development of signal change in the separate ROIs throughout the experiment, the time series was divided into quartiles (i.e. 3 trials per condition and item). Paired samples t –tests were performed investigating activation changes during no-think trials relative to baseline (i.e. activation during presentation of the fixation cross) within each quartile separately for the ROIs.

Finally, correlation analyses were performed investigating correlations in signal change between the three ROIs and correlations between the difference during no-think and think trials with the BSI.

2.5. TBS Study

2.5.1. Sample

35 healthy subjects were tested for this study. Two subjects only completed the baseline measurement. The remaining 33 were randomly assigned to either the verum iTBS (N = 17; age = 24.06 ± 2.70; 5 men) or sham iTBS group (N = 16; age = 24.69 ± 3.59; 8 men).

Differences between the two groups (i.e. verum and sham) in gender, handedness, smoking status and graduation were compared by means of chi-square tests. Differences between the groups in age, motor threshold, stimulation status and the psychometric evaluations were investigated by means of independent samples t-tests.

In a brief telephone interview participants were screened for a previous treatment with TMS, and exclusion criteria for a treatment with TMS following the Wassermann protocol (1998).

The baseline and post-iTBS measurement took place on two separated days (mean distance: 1.36 ± 3.24 days).

2.5.2. The TNT

In this study only negative IAPS pictures (Lang et al 2005: for IAPS codes see Table A - 2) were paired with neutral faces from the database used by Depue et al. (2007).

For the baseline measurement, subjects were trained on 26 face-picture pairs, including 8 practice pairs. Following training, the TNT procedure was performed as described earlier (see paragraph 2.3.2.).

For the post iTBS measurement, subjects were trained on 18 face-picture pairs. Following training and fixation of the fNIRS optodes and ERP electrodes, the individual resting motor threshold (RMT) was determined over the right primary motor cortex, followed by the iTBS stimulation (i.e. verum or sham) over the right dlPFC (for a more thorough description of the TMS and iTBS protocols see below). The measurement was started right after iTBS (mean onset delay in seconds: 2.39 ± 0.83).

Data was acquired according to the parameters described previously (see paragraph 2.3.2.) and following guidelines by Wager and Nichols (2003).

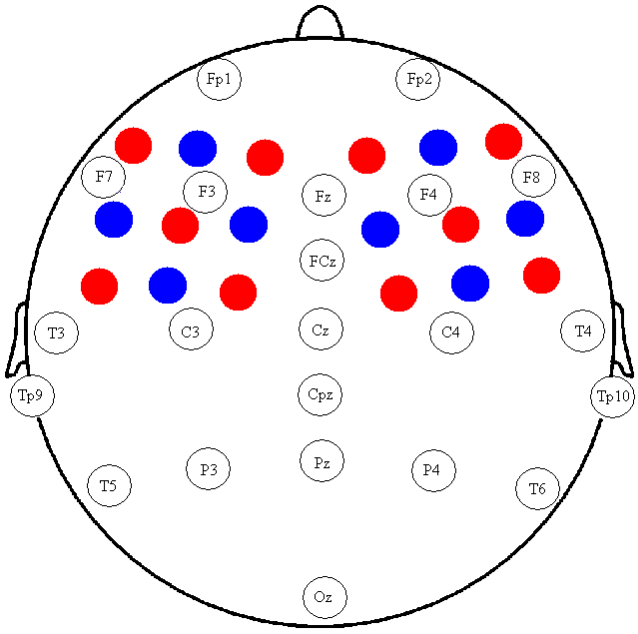

***Figure 9**: Schematic display of electrode and fNIRS probeset position. Open circles = electrode positions, red circles = light emitters, blue circles = light detectors*

2.5.3. FNIRS

The system used in this study was the same continuous wave system (ETG-4000 Optical Topography System; Hitachi Medical Co., Japan) described in paragraph 2.2.3. However, two 3-by-3 probe sets were integrated in a Neuroscan EasyCap (EasyCap GmbH, Inning am Ammersee, Germany) covering the right and left prefrontal cortex with 24 measurement channels (see Figure 9 and 10).

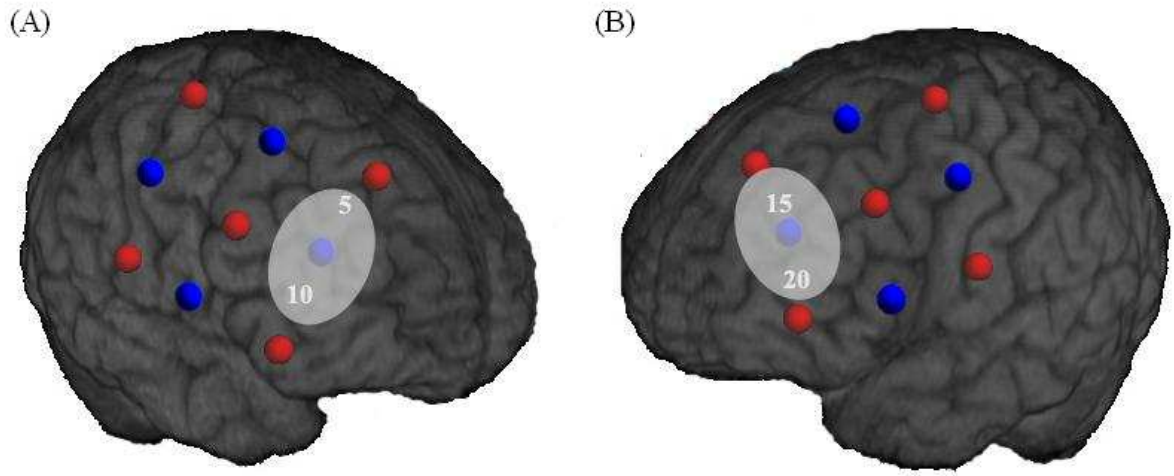

***Figure 10**: Outline of the fNIRS probeset and the ROIs (shaded area) used for the subsequent statistical analyses plotted on the MR scan of a single subject. (A) right hemisphere, (B) left hemisphere*

2.5.4. ERPs

ERPs were recorded from 22 Ag/AgCl scalp electrodes embedded in a Neuroscan Easycap (see Figure 9) with three additional linked electrodes measuring the electro-oculogram (EOG) with a 64-channel QuickAmp amplifier (Brain Products, Munich, Germany) and the Vision Recorder data acquisition software (version 2.0, Brain Products, Munich, Germany). Data were referenced online to an avergage reference. The vertical EOG was measured from an electrode placed below the right eye referenced to Fp2, and the horizontal EOG was recorded from an electrode placed right to the right eye (referenced to an electrode left to the left eye). Midline electrodes were Fz, FCz, Cz, Cpz, Pz, and Oz. Left and right hemisphere sites were Fp1/2, F3/4, F7/8, C3/4, T3/4, T5/6, P3/4, and the mastoids.

Sampling rate was set to 1000Hz with a sampling interval of 1000µs. All channels were amplified with a band-pass from DC to 200Hz. The inter-electrode impedances were kept below 5kΩ.

Data was filtered online with a low-cutoff filter of 1.59 seconds and a high-pass filter of 100Hz. Additionally, a 50Hz notch filter was applied.

2.5.5. TBS

The iTBS was administered according to the stimulation protocols described by Huang and colleagues (2005; see Figure 5 paragraph 1.4.4.2.). Prior to stimulation of the right dlPFC, the individual RMT was determined over the right primary motor cortex. RMT is defined as the stimulation intensity required to produce a motor response by applying a single TMS pulse to primary motor cortex that can be observed visually in 80% of the trials (Fitzgerald et al 2002). The verum group was stimulated with a figure-of-eight coil (MC-B70, 80 mm diameter, Medtronic MagPro, Duesseldorf, Germany) and the sham group was stimulated with a shielded figure-of-eight coil (MC-P70, 80 mm diameter, Medtronic MagPro, Duesseldorf, Germany) at 80% of the individual RMT. Stimulation was performed over electrode position F4, which, according to the international 10/20 system for electrode adjustment (Jasper 1958), is located over the right dlPFC (Herwig, Satrapi & Schonfeldt-Lecuona 2003).

Mean RMT and stimulation strength for the verum group were 46.82 ± 6.34 and 37.47 ± 5.05 and 46.63 ± 7.53 and 37.00 ± 6.06 for the sham group.

2.5.6. Data Analysis and Statistics

2.5.6.1. Behavioral Data

Percentages of recalled pictures were calculated for no-think, think and baseline trials for the two measurements. These percentages were entered into a 3 x 2 x 2 ANOVA with the within-subject factors condition (i.e. baseline, think, no-think) and time (i.e. pre and post iTBS) and the between-subject factor group (i.e. verum and sham).

An additional 3 x 2 x 2 ANOVA with the same factors, however, including only successfully learned face-picture pairs was calculated.

The BSI was calculated as mentioned above and by means of a median-split the sample was divided in a group of good suppressors (> median) and bad suppressors (< median) separately per measurement day. Chi-square tests were calculated additionally, comparing suppressor type on day 1 and day 2 between the groups.

Paired samples t-tests were performed comparing the valence and arousal ratings between the two picture sets selected for the two measurements (i.e. baseline and post iTBS) to assure non-significant differences between the two sets.

2.5.6.2. FNIRS Data

Preprocessing of the data was performed in accordance with the procedures described in 2.2.4.2. The HRF, however, was convolved with a stick function to model the single events.

ROIs were formed a priori encompassing channel #5 and #10 for the right dlPFC and #15 and #20 for the left dlPFC (Figure 10).

A repeated-measures ANOVA with the factors condition (i.e. fixation, think, no-think), time (i.e. baseline, post iTBS measurement), group (i.e. verum, sham), and side (i.e. right, left dlPFC) was performed. Again, signal change relative to baseline (i.e. activation during presentation of the fixation cross) was investigated by means of paired samples t-tests.

Correlation analyses were performed for the difference between think and no-think trials and the BSI for the baseline measurement.

To test the hypothesis of a linear increase in O_2Hb (no-think forgotten > think remembered > no-think remembered/think forgotten > baseline) and linear decrease in HHb (no-think forgotten < think remembered < no-think remembered/think forgotten < baseline), depending on condition and success in the right dlPFC linear trend tests were calculated.

Analyses are performed for O_2Hb and HHb.

2.5.6.3. ERP Data

Analyses were performed using the Vision Analyzer software (version 2.0, Brain Products, Munich, Germany). Epoch duration for analyses was 2000 ms, plus a 200 ms pre-stimulus period used for baseline correction. Eye blinks were filtered out prior to averaging by means of the implemented ocular correction algorithm by Gratton and Coles (1989).

Grand average ERPs were formed for the two conditions (think and no-think) in the first step of the analysis. For the second step of the analysis average ERPs were calculated for successful and unsuccessful recall or suppression (as investigated through the final recall test) for the two conditions separately, resulting in four average curves (i.e. recalled think, forgotten think, recalled no-think, and forgotten no-think) after controlling for initial learning status of the face-picture association. Mean number of remaining trials were: 45.45 ± 11.88 (recalled think), 11.16 ± 13.09 (forgotten think), 46.42 ± 19.37 (recalled no-think), and 4.32 ± 18.56 (forgotten no-think). Automatic peak detection was performed for five components elicited by think and no-think trials after visual inspection of the grand average ERPs. Statistical analyses were based on the following scalp electrodes: frontal (F3/4 and Fz), central (C3/4 and Cz) and parietal (P3/4 and Pz). For topographical analyses data (mean activation derived from the baseline and post iTBS measurement) from 14 electrodes was pooled according to 7 regions (frontopolar: Fp1/2; frontal: Fz, F3/4; frontocentral: FCz; central: Cz, C3/4; parietocentral: Cpz; parietal: Pz, P3/4; occipital: Oz), and normalized according to the vector scaling method described by McCarthy and Wood (1985) in order to eliminate confounding effects of amplitude differences.

Repeated-measures ANOVAs, with the within-subject factors condition (i.e. think and no-think), time (baseline and post iTBS), laterality (i.e. left, central, and right) and the between-subject factor group (i.e. verum and sham) were calculated per region and ERP component.

Separate analysis of successful think and no-think trials as measured by suppression and retrieval success in the recall test was not performed due to the small number of trials left in each condition after artefact correction.

Topographical analysis was performed for two components showing enhanced amplitudes for think trials with the same central distribution. The vector-scaled difference values between the two conditions were entered in a time window-by-region ANOVA separately for the two components showing enhanced amplitudes for think trials.

Scalp potential maps were generated using the build-in two-dimensional spherical spline interpolation and a radial projection from Cz, which respects the length of the median arcs.

For the regression analyses the difference wave between the conditions was calculated and analyses were performed for each component and region separately. Afterwards, a regression analysis with the BSI as dependent variable was performed separately for each component.

Finally, one-sided correlations between activation during no-think trials in the right and left dlPFC in the fNIRS measurement and the difference value of ERP components reflecting the no-think < think contrast (i.e. N2, N4, and late negativity) were calculated.

2.6. Correlations Between and Interaction of BSI, Psychometric Evaluations and Functional Imaging Data

2.6.1. Sample

Behavioral data from the emotion study, the fMRI study and the modulation study were merged, resulting in a total sample size of 145. Concerning the different valences, 108 cases were obtained for neutral pictures, 32 cases existed for positive pictures and 143 for negative picture.

2.6.2. Psychometric Evaluations

Questionnaires were filled out in their German version by subjects participating in the emotion study (2.3.), the fMRI study (2.4.) and the modulation study (2.5.).

Multiple Choice Vocabulary Test (Mehrfachwahl-Wortschatz-Test, MWT-B)

The MWT-B (Lehrl 2005) measures general intelligence and has been shown to correlate well (i.e. $r > .72$) with other intelligence tests measuring global IQ, such as the Hamburg Wechsler Intelligence Scale for adults (HAWIE, Wechsler 1956), the Leistungsprüfsystem (LPS, Horn 1961), or the Analytical Intelligence Test (AIT, Meili 1971). Subjects have to mark in row of five strings the one actually existing word.

Beck Depression Inventory – Revision (BDI-II)

The BDI-II (Hautzinger, Keller & Kühner 2006) is an instrument validating the severity of depression in adults, and has been developed in accordance with the DSM-IV (American Psychiatric Association 1994). It encompasses not only cognitive and affective, but also somatic and vegetative symptoms. 21 items are answered item-specific on 4 levels (0 - 3).

Various publications have proven its reliability and validity in patients and healthy subjects and are listed in the manual (Hautzinger et al 2006). Cutoff-values are given in the manual as follows: 0-8 no depression, 9-13 light depression, 14-19 mild depression, 20-28 medium depression, 29-63 severe depression. Hautzinger et al. (2006) emphasize, however, that it is important to investigate the specific items regarding their content, since the BDI only gives a global indication of depressive symptomatology (e.g. special attention is to be given to item 9, asking for suicidal ideation).

Hospital Anxiety and Depression Scale (HADS)

The HADS (Herrmann, Buss & Snaith 1995) is a questionnaire used to screen for anxious and depressive symptoms, present in the past week, on two subscales. It is comprised of 14 items (i.e. 7 for each subscale, with item-specific response possibilities on 4 levels (0–3)), adding up to 0-21 points on each subscale. Symptoms screened for in the anxiety subscale follow the guidelines of the DSM-III-R (American Psychiatric Association 1987) and ICD-10 (World Health Organization 2007), regarding generalized anxiety disorder. Items on the depression subscale include questions focussing on anhedonic symptoms of depression, encompassing the most crucial aspects of the disorder according to the DSM-III-R (American Psychiatric Association 1987) and ICD-10 (World Health Organization 2007). Scores below 7 are interpreted as unobtrusive, values between 7 and 10 reflect the presence of some pathology, and scores above 11 are regarded as noticeably pathological. The manual of the HADS provides detailed information on the interpretation of these cutoff-scores, ensuring high interrater and test-retest reliability (Herrmann et al 1995). The fast application of the HADS makes it easily combinable with other screening tools.

Generalized Depression Scale (Allgemeine Depressions Skala; ADS)

The ADS (Hautzinger & Bailer 1993) is a 20-item screening tool focussing on emotional, motivational, cognitive, somatic, and motor symptoms observed in depression. The relevant time range encompasses the last 7 days including the day of administration. Answers are given on 4 levels rated from 0 – 3 (0 = rarely/less than 1 day, 1 = sometimes/1 to 2 days, 2 = frequently/3 to 4 days, 3 = mostly/5 to 7 days). Before addition of the item scores, four items have to be reversed (i.e. item 4, 8, 12, and 16), resulting in a maximum score of 60 with a critical score of > 23 found in 94% of acutely depressed patients as diagnosed by the DSM-III-R (American Psychiatric Association 1987). The ADS has been shown to highly correlate with other depression questionnaires such as the BDI (Hautzinger et al 2006) or the ‘Befindlichkeits-Skala’ (Bf-S: Zerssen 1986).

Interpretation of the ADS scores is provided threefold: (1) as a screening tool in the general population, higher ADS scores indicating an increased possibility to identify subjects fulfilling the diagnostic criteria of depression according to the DSM-III-R (American Psychiatric Association 1987) or ICD-10 (World Health Organization 2007). (2) Indicating the severity of depressive symptoms and their changes over the course of the treatment in clinically diagnosed subjects. And (3) screening for depressive symptoms accompanying other disorders or diseases and predicting treatment response and coping. This profound

description of the interpretation in the manual (Hautzinger & Bailer 1993) provides good interrater and test-retest reliability.

Ruminative Response Scale of the Response Style Questionnaire (RSS)

The RSS of the Response Style Questionnaire (Kühner et al 2007) measures coping with depressive moods through 21 items, describing specific reactions (e.g. "If I feel sad or depressed, I think about how lonely I feel", "..., I think how weak I am and that I cannot motivate myself to do anything") on a 4-point Likert-scale (1 = almost never, 2 = sometimes, 3 = frequently, 4 = almost always).

Test-retest reliability is reported around r_{tt} = .60 in healthy control subjects (Bürger & Kühner 2007) and patients with Major Depressive Disorder (MDD; Bagby, Rector, Bacchiochi & McBride 2004).

State-Trait Anxiety Inventory (STAI)

The STAI (Laux, Glanzmann, Schaffner & Spielberger 1981) has been developed on the grounds of Spielberger's Trait-State Anxiety Model (Spielberger 1997). Two concepts are measured by the STAI: (1) State anxiety, which is defined as "an emotional state, defined by tension, solicitude, nervousness, agitation, fear of future events, as well as increased autonomic nervous system activity" (p. 7: Laux et al 1981). And (2) trait anxiety, which is defined as "relative stable inter-individual differences in viewing situations as dangerous, followed by an increase in state anxiety" (p. 7: Laux et al 1981). Two subscales have been developed to measure the two concepts. The State scale encompasses 20 items measuring the current status concerning anxiety (e.g. "I am tense", "I am worried") and stability (e.g. "I feel calm", "I feel content"). Answers indicate how well the statement applies on 4 levels (i.e. 1 = not at all, 2 = somewhat, 3 = moderately, 4 = very much). The Trait scale tests general proneness to anxiety (e.g. "I lack self-esteem") or stability (e.g. "I am happy"). Answers, again, indicate on what level the statement applies (i.e. 1: almost never, 2: sometimes, 3: often, 4: almost always).

Interpreted are the sum scores (after reversal of scores on item 1, 2, 5, 8, 10, 11, 15, 16, 19, and 20 on the State scale and item 21, 26, 27, 30, 33, 36, and 39 on the Trait scale). The minimum of 20 points reflects the absence of any current (i.e. state) or general (i.e. trait), while 80 reflects the maximal intensity of current or general anxiety. Test-retest reliability for the Trait scale was found satisfactory at about r_{tt} = .80. Low test-retest reliability inherent to the State scale (around r_{tt} = .30) is compensated for by satisfactory internal consistency of r_c =

.90. A more detailed description of reliability issues can be found in the manual (Laux et al 1981).

Positive and Negative Affect Schedule (PANAS)

The PANAS (Krohne, Egloff, Kohlmann & Tausch 1996) comprises 20 items measuring current positive (PA) and negative affect (NA) on two subscales. Each item is rated on a 5-point Likert scale, ranging from 1 = very slightly or not at all to 5 = extremely.

PA has been defined as the extent to which a person feels enthusiastic, active and alert. In other words high scores on the PA subscale characterize a state of concentration, energy and interest, while low PA reflects sadness and lethargy (Watson, Clark & Tellegen 1988). NA, on the other hand is described as encompassing a state of distress and disengagement. High NA is manifesting itself in aversive mood states, such as anger, fear or guilt. Low NA is describing a state of calmness and serenity (Watson et al 1988).

The two subscales of the English version of the PANAS (Watson et al 1988) have been shown to correlate to a certain extent with the BDI (Beck, Ward, Mendelson, Mock & Erbaugh 1961) and the STAI State Scale (Spielberger et al 1970).

For a description of the validation of the German version, the reader is referred to (Krohne et al 1996)

2.6.3. Data Analysis and Statistics

2.6.3.1. BSI and Psychometric Data

Means were calculated for the PANAS and STAI-State scores when two scores (due to two measurement days) existed after controlling for non-significant differences between the two measurements ($p > .2$). Furthermore, the two values from the think, baseline and no-think condition derived from the baseline and post-measurement in the TBS study were merged, resulting in one score by calculating the mean. Calculations were performed with the BSI for negative pictures due to the larges sample size in this valence condition.

To test for the facilitating effects of depressive and anxious symptoms, and intelligence on thought suppression two different analyses were performed. First, directed/one-sided bivariate correlations were calculated between the BSI and the continuous scores obtained from administering the MWT-B. Second, psychometric measures were clustered according to their objective sensitivity to depression (i.e. rumination, BDI, HADS-Depression and ADS) or anxiety (i.e. HADS-Anxiety, PANAS and STAI-Trait) and entered into separate multiple regressions with the BSI.

Exploratively, univariate ANOVAs were applied to compare differences in the BSI due to gender and education.

2.6.3.2. Correlations with Functional Imaging Data

Concerning fNIRS data, as for the correlations and regression analyses, analyses are performed only on the imaging data derived from processing of the negative no-think items (i.e. no-think > fixation) in the right and left dlPFC.

One-sided bivariate correlations were calculated between activation levels during negative no-think trials in the right and left dlPFC and the above described psychometric evaluations. Furthermore, bivariate correlations between the BSI and activation in the right and left dlPFC during no-think trials were calculated for the fNIRS data. Analyses are performed for O_2Hb and HHb.

Additionally correlations with the psychometric evaluations were calculated for fMRI data considering the neutral[1] no-think > fixation contrast in the right dlPFC and the neutral no-think < fixation contrast in the amygdala and hippocampus.

2.6.3.3. Interaction of BSI and fNIRS data with Psychometric Data

To investigate the interplay between the BSI and activation in the dlPFC during no-think trials a z-transformed interaction term was calculated for the two variables and correlated with the z-transformed scores of the single questionnaires. This interaction term is thought to reflect only that amount of dlPFC activation explained by actual inhibitory processes; in other words, the higher the interaction between the two factors, the more the observed dlPFC activation contributes to the end results of lower recall of no-think items.

[1] Only neutral trials were taken into account, since it was shown that suppression of negative pictures was unsuccessful in the fMRI study (see paragraph 3.31.)

2.7. Genetical Analyses

DNA was extracted from EDTA blood using a desalting method.

For statistical analyses regarding effects of the two genotypes of interest (i.e. KCNJ6 and CREB1), data from negative trials (largest sample) was investigated in case of the behavioral data and fNIRS data. Both SNPs were in Hardy-Weinberg Equilibrium ($p > .1$).

2.7.1. Behavioral Data

Separate condition-by-genotype ANOVAs were calculated for KCNJ6 and CREB1, using data from the behavioral recall test for negative pictures from the emotion, the fMRI and the TBS study (KCNJ6: N = 114, CREB1: N = 113).

2.7.2. FNIRS Data

Based on the interaction yielded in the 3 x 2 ANOVA for KCNJ6 on the behavioral level, a 2 x 2 ANOVA, with the factors condition and genotype was calculated for the right and left dlPFC separately.

2.7.3. FMRI Data

A 2 x ANOVA, with the factors condition (i.e. think and no-think) and genotype (i.e. KCNJ6) was calculated for the right dlPFC, bilateral amygdala, and bilateral hippocampus.

3. Results

3.1. Pilot Study

3.1.1. Behavioral Data

Table 3 contains information on the sample.

***Table 3**: Sample characteristics pilot study*

Total Sample Size	15
Age	28.20 ± 6.28
Gender: men	4
Handedness (right)	15
Smoking status (yes)	0
Graduation	
Abitur	15
Training Cycles	2.00 ± 0.00

The ANOVA showed only a trend towards a significant main effect of condition ($F_{(2,24)} = 2.62$; $p < .1$). Directed/one-sided post-hoc Bonferroni corrected t-tests showed this effect as resulting from significantly higher recall of think than no-think ($p < .05$) and marginally significant higher recall of think than baseline-words ($p < .1$). There was no main effect for valence ($F_{(2,24)} = 2.05$, $p > .1$) or an interaction between the two factors ($F_{(4,48)} = 1.09$, $p > .1$). Figure 11 is displaying the mean percentages of recalled think, baseline and no-think words.

The one-factorial ANOVA considering psycholinguistic aspects of the selected words resulted in a significant effect for emotional mean ($F_{(2,42)} = 3818.25$; $p < .001$) and arousal ($F_{(2,42)} = 71.99$; $p < .001$), as well as imageability ($F_{(2,42)} = 4.28$; $p < .05$). Bonferroni corrected post-hoc t-tests revealed a significant difference between the emotional means between all three valence conditions ($p < .001$) and significant differences in the arousal ratings between neutral and negative words and positive and negative words ($p < .001$), negative words having the highest arousal ratings. Imageability ratings differed significantly between neutral and negative words ($p < .05$), negative words showing higher imageability ratings. Concerning letter count, phonemes, syllables and word frequency no differences between the three valence conditions were found. See Table A -1 for the stimulus material and its characteristics

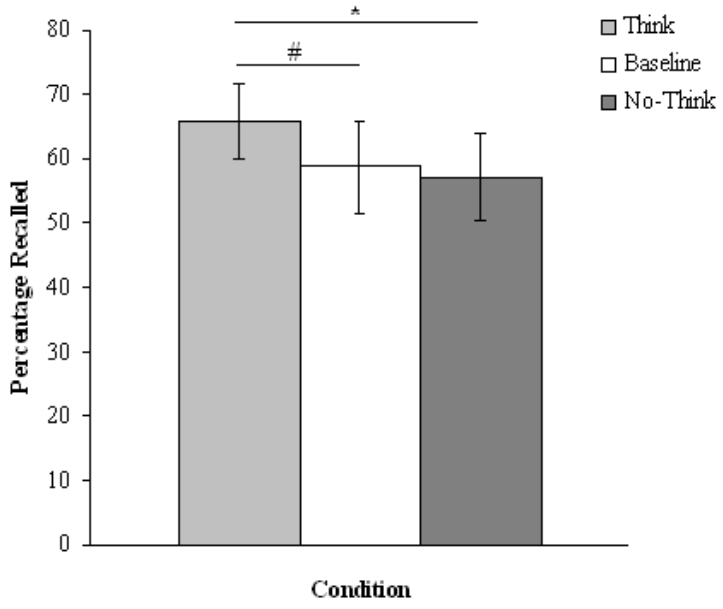

***Figure 11**: Effect of condition in the behavioral recall test. # p < .1, * p < .05 (one-sided)*

3.1.2. FNIRS Data

3.1.2.1. Oxygenated Hemoglobin

The 2 x 3 x 2 (condition-by-valence-by-side) ANOVA revealed a trend towards a significant main effect of condition ($F_{(1,14)} = 2.99$, $p = .1$), reflecting higher activation during no-think than during think trials. Post hoc paired t-tests showed the condition effect as reflecting increased activation during no-think trials as compared to baseline ($T_{(14)} = 2.17$, $p < .05$), rather than reduced activation of think trials relative to baseline (see Figure 12A).

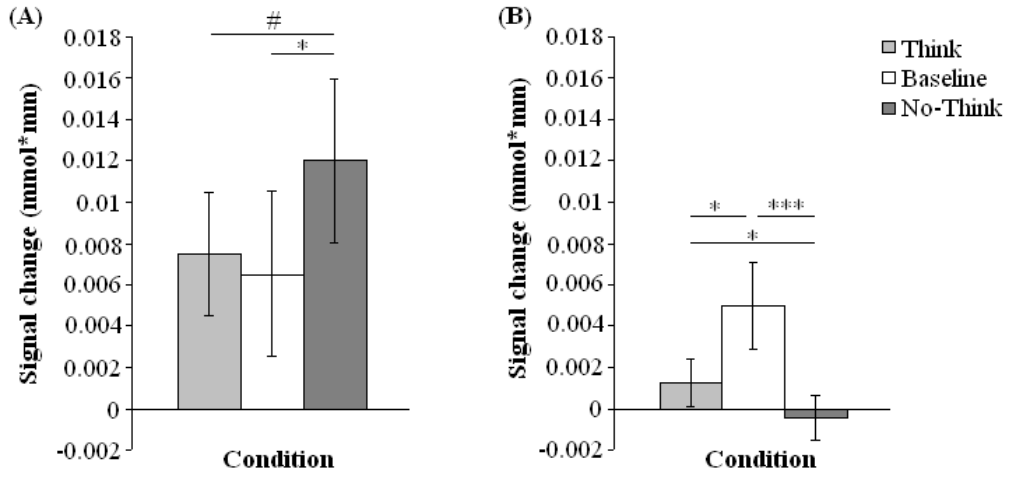

***Figure 12**: Signal change of (A) O_2Hb in bilateral dlPFC and (B) HHb in right dlPFC during think and no-think trials relative to baseline. # p =.1, * p < .05, *** p < .001*

Directed/one-sided correlation analyses showed a marginally significant correlation between the BSI and dlPFC activation during no-think trials ($r = .43$, $p < .1$; see Figure 13).

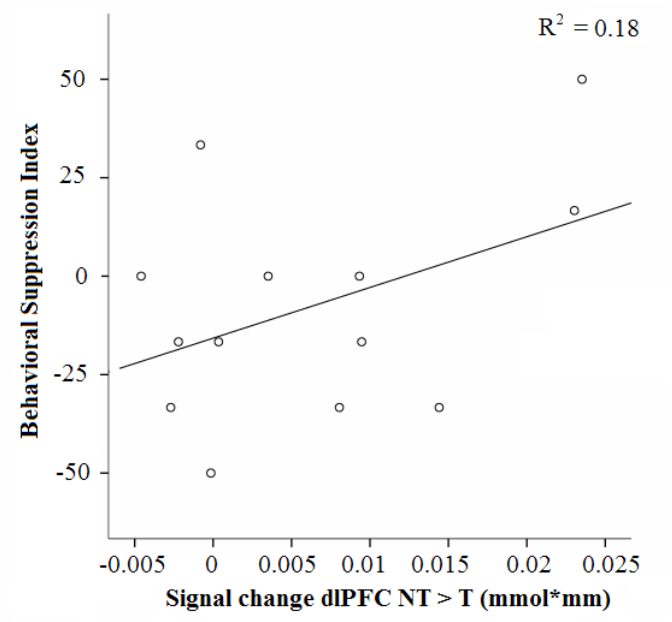

***Figure 13**: Correlation between activation in the dlPFC during no-think trials and the BSI found in O_2Hb*

Right dlPFC

No effects were found in the ANOVA just considering the right hemisphere.

Left dlPFC

No effects were found in the ANOVA just considering the left hemisphere.

3.1.2.2. Deoxygenated Hemoglobin

No significant effects were found in the 3 x 2 x 2 ANOVA.

Right dlPFC

The 3 x 2 ANOVA for the right dlPFC showed a significant main effect of condition ($F_{(1,14)} = 4.95$, $p < .05$), which was caused by the expected higher decreases in HHb during no-think trials. Post-hoc paired t-tests showed significantly decreased HHb during think than during baseline ($T_{(14)} = -2.81$, $p < .05$), but even more decreased HHb during no-think than during baseline ($T_{(14)} = 4.001$, $p < .001$). See Figure 12B.

No significant correlation between activation in the right dlPFC during no-think trials and the BSI was found.

Left dlPFC

No effects were found in the left dlPFC.

3.2. Emotion Study

3.2.1. Behavioral Data

A description of the sample characteristics can be found in Table 4.

The GLM calculated for the valence ratings of the selected IAPS pictures revealed a significant main effect of valence ($F_{(2,34)} = 740.13$, $p < .001$), reflecting significant differences between all three valences (all $p < .001$). The GLM calculated for the arousal ratings revealed a significant main effect of arousal ($F_{(2,34)} = 14.61$, $p < .001$), reflecting a significant difference in arousal ratings between the neutral and positive ($p < .01$) and the neutral and negative pictures ($p < .001$).

***Table 4**: Sample description Emotion Study*

Total Sample Size	20
Age	29.50 ± 10.68
Gender: men	7
Handedness (right)	20
Smoking status (yes)	5
Graduation	
Abitur	16
Mittlere Reife	4
MWT (raw score)	30.70 ± 3.84
Training Cycles	1.45 ± 0.58

The 3 x 3 (condition-by-valence) ANOVA showed a significant main effect of condition ($F_{(2,38)} = 16.46$, $p < .001$), owing to significantly higher recall of think- than no-think pictures ($p < .01$) and baseline picture ($p < .001$). See Figure 14 (left). No significant difference between baseline and no-think pictures was found ($p > .1$).

Considering only the previously learned pictures, the 3 x 2 ANOVA did not yield any different results. A main effect of condition was observed ($F_{(2,38)} = 16.97$, $p < .05$), owing to significantly higher recall of think than baseline ($p < .001$) or no-think pictures ($p < .01$). Again, no significant difference was found between the recall of no-think and baseline pictures (Figure 14 (right)).

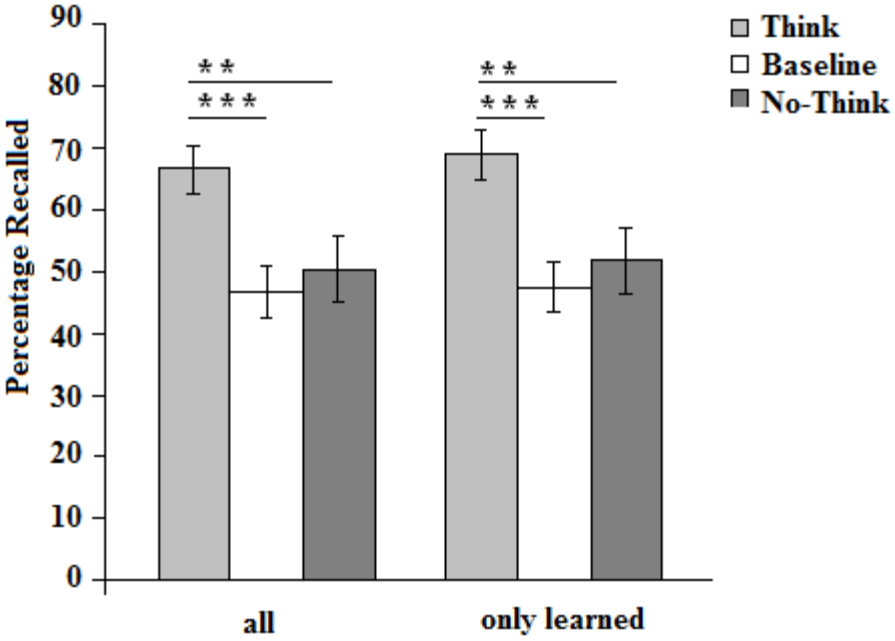

***Figure 14**: (A) Main effect of condition for all pictures, irrespective of initial learning status (left) and only for the learned pictures (right); * p < .05, ** p < .01, ** p < .001*

3.2.2. FNIRS Data

Oxygenated Hemoglobin

Whole Time Series

The 2 x 3 x 2 (condition by valence by side) ANOVA yielded a significant main effect of condition ($F_{(1,19)}$ = 16.00, p < .01), no-think trials activating the dlPFC more than think-trials, as well as a trend towards a condition-by-side interaction ($F_{(1,19)}$ = 3.86, p < .1). Figure 15 shows the interaction, which results from a stronger condition effect in the right (p < .001) than in the left hemisphere (p < .01).

Post-hoc paired t-tests were performed to investigate signal changes during no-think and think trials relative to baseline. A significant increase in O_2Hb during no-think but not think trials relative to baseline was shown in the right ($T_{(19)}$ = -2.49, p < .05) and left dlPFC ($T_{(19)}$ = -2.18, p < .05). See Figure 15.

No significant correlation between signal changes in right or left dlPFC with the BSI was found.

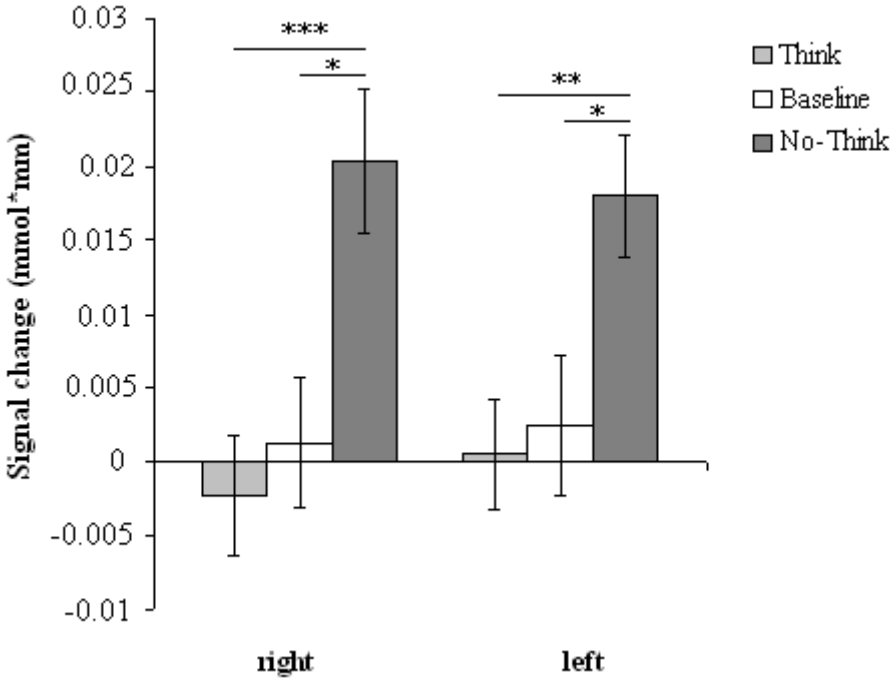

***Figure 15**: Condition-by-side interaction throughout the whole time series resulting from a stronger condition effect in the right dlPFC. Furthermore, it is shown that the condition effect most likely results from an increase in activation during no-think trials relative to baseline. * p < .05, ** p < .01, *** p < .001*

Split in Halves

The 2 x 3 x 2 x 2 (condition x valence x side x half) ANOVA yielded a significant main effect of condition ($F_{(1,19)} = 13.70$, $p < .01$), reflecting higher activation during no-think than during think trials. Furthermore, a marginally significant interaction between condition and side ($F_{(1,19)} = 3.38$, $p < .1$) was found, resulting from a stronger NT > T effect in the right than in the left dlPFC, as described above. Finally, a significant three-way interaction between condition, side, and half ($F_{(1,19)} = 6.24$, $p < .05$) was observed.

The follow-up 2 x 2 ANOVA with the factors condition and side calculated per half, resulted in a significant main effect of condition ($F_{(1,19)} = 21.88$, $p < .001$) and a significant interaction between condition and side ($F_{(1,19)} = 6.16$, $p < .05$) in the first half and a trend towards a condition-effect ($F_{(1,19)} = 3.81$, $p < .1$) in the second half. To further investigate the origin of the decreased condition effect, post-hoc paired t-tests comparing signal change between the first and the second half were calculated separately for the right and left dlPFC. As depicted in Figure 16, a significant drop in signal change was observed in the second half for the no-think trials, right ($T_{(19)} = 3.29$, $p < .01$) stronger than left ($T_{(19)} = 2.77$, $p < .05$). No difference in activation during think trials over the time series of the experiment was found.

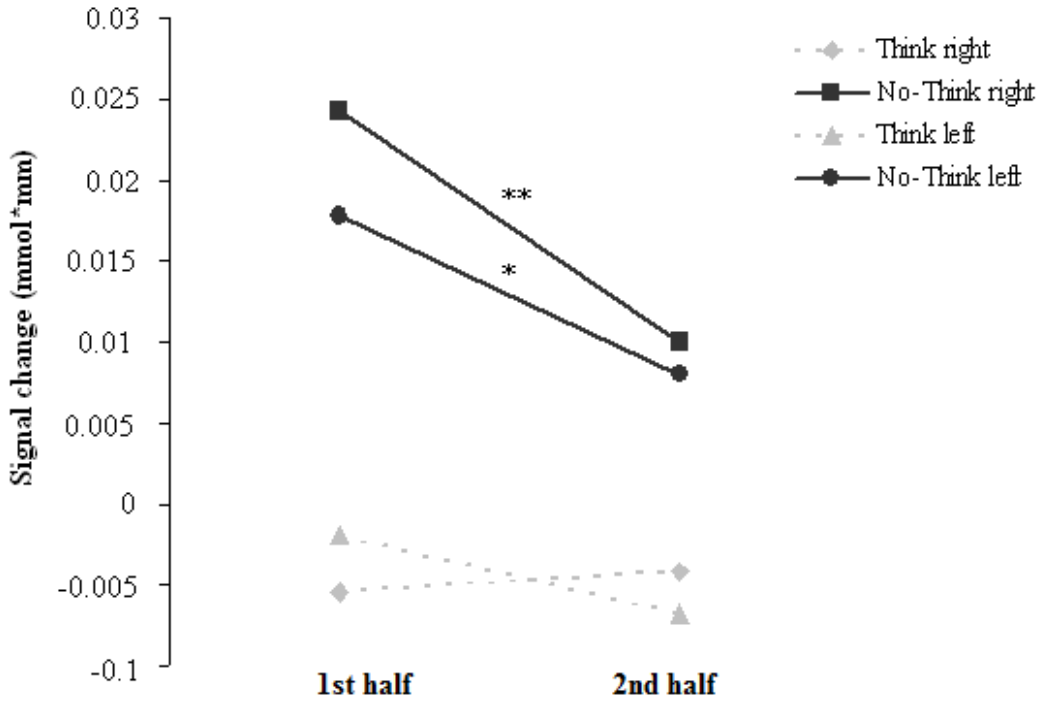

***Figure 16**: Signal change for think and no-think trials in the first and second half of the time series in O_2Hb in the right and left dlPFC. * p < .05, ** p < .01*

Significant positive correlations were found between the signal changes in the first half of the experiment in the right (r = .41, p < .05; Figure 17A) and the left dlPFC (r = .39, p < .05; Figure 17B) and the BSI were found.

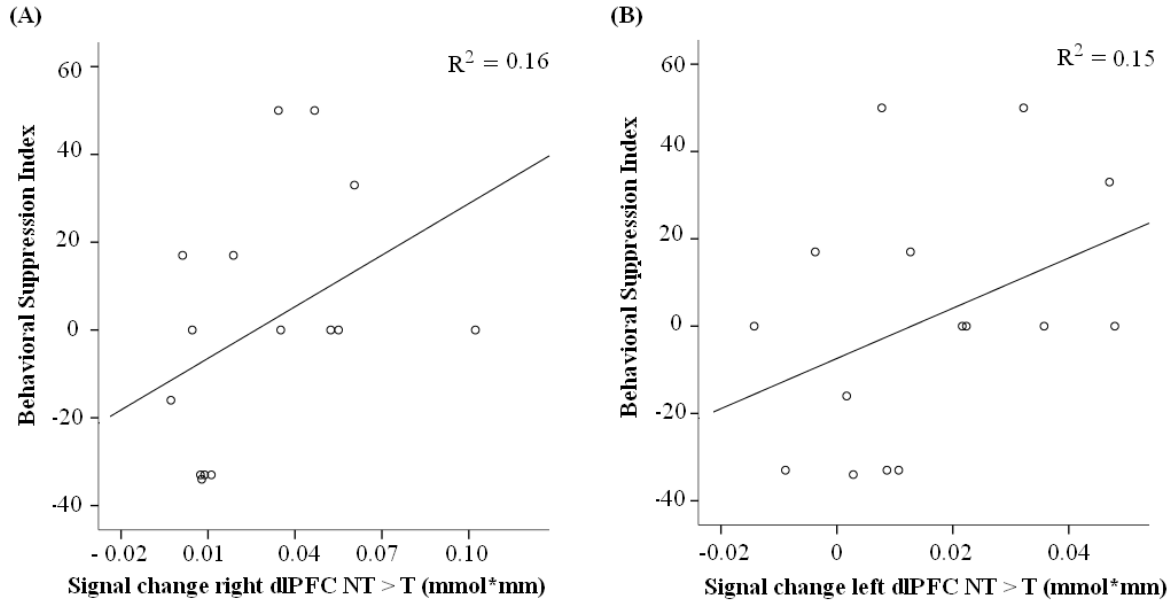

***Figure 17**: Correlation between signal changes and the BSI in the first half during suppression trials in the right (A) and left dlPFC (B)*

Deoxygenated Hemoglobin

Whole Time Series

No significant results were found in the 3 x 2 x 2 ANOVA.

Split in Halves

The 2 x 3 x 2 x 2 (condition x valence x side x half) ANOVA showed no significant results.

3.3. FMRI Study

3.3.1. Behavioral Data

See Table 5 for the sample characteristics.

***Table 5**: Sample description of fMRI study*

Total Sample Size	65
Age	25.28 ± 5.23
Gender: men	27
Handedness (right)	59
Smoking status (yes)	18
Graduation	
Abitur	60
Mittlere Reife	4
Qualifizierter Hauptschulabschluss	1
MWT (raw score)	31.13 ± 3.33
Training Cycles	1.92 ± 1.01

For calculations regarding picture characteristics see paragraph 3.2.1[1].

A significant main effect of valence was found, reflecting higher overall recall of neutral than negative pictures ($F_{(1,64)} = 11.27$, $p < .01$). Furthermore, a significant valence-by-condition interaction was observed ($F_{(2,128)} = 3.83$, $p < .05$). One-sided post-hoc paired t-tests were performed to investigate this interaction. A trend towards significantly lower recall of neutral no-think than think pictures ($T_{(64)} = 1.8$, $p < .05$) as well as marginally significantly lower recall of no-think than baseline pictures ($T_{(64)} = 1.83$, $p < .05$) was observed. Unsuccessful suppression in the negative condition was reflected by marginally significant higher recall of no-think than baseline pictures ($T_{(64)} = -1.50$, $p < .1$). Significantly higher recall of think than baseline pictures, however, could be shown ($T_{(64)} = 2.18$, $p < .05$). See Figure 18 for the graphical depiction of the results.

3.3.2. FMRI Data

A marginally significant main effect of condition, owing to higher activation during no-think trials was found in the right dlPFC ($T_{(180)} = 4.43$, $p < .1$). Additional paired-samples t-tests showed that this effect reflected higher activation during no-think and think than during baseline trials (no-think: $T_{(45)} = 4.86$, $p < .001$, think: $T_{(45)} = 3.44$, $p < .01$), activation during

[1] The same neutral and negative IAPS pictures were chosen as in the Emotion Study (see Table A – 2)

no-think trials and think trials differing significantly ($T_{(45)} = 2.87$, $p < .01$). A significant main effect owing to higher activation during think than during no-think trials was found in the right ($T_{(180)} = 3.18$, $p < .05$) and left amygdala ($T_{(180)} = 3.51$, $p < .05$), as well as in the right ($T_{(180)} = 4.80$, $p < .001$) and left hippocampus ($T_{(180)} = 4.39$, $p < .001$). A marginally significant condition-by-valence interaction, owing to higher activation during negative than neutral think trials was found in the left amygdala ($F_{(1,180)} = 7.14$, $p < .1$).

Results from the post-hoc t-tests investigating signal changes during the task conditions relative to baseline and each other are summarized in Table 6. See Figure 19 for the outcome of the 2 x 2 ANOVA.

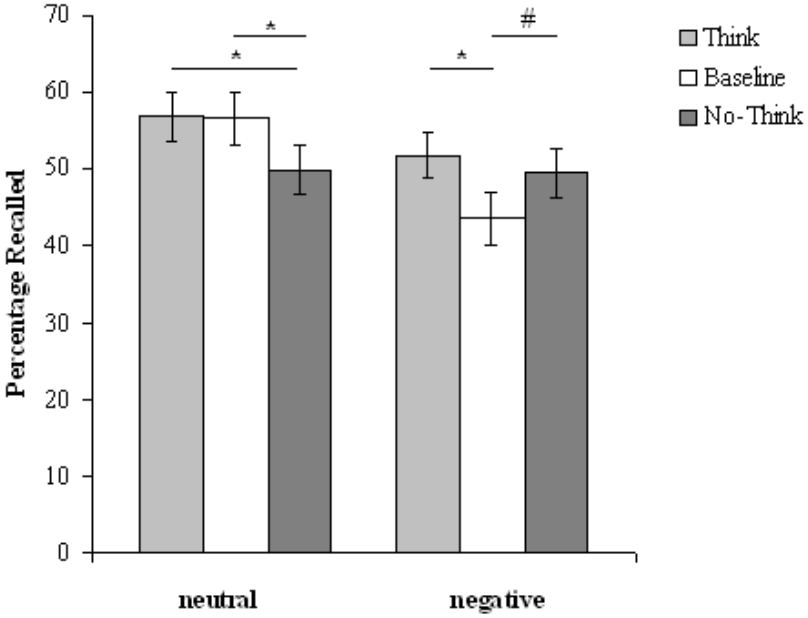

***Figure 18**: Behavioral data of fMRI study. One-sided: # p < .1, * p < .05*

Behavioral Suppression/Recall Status

The 2 x 2 x 2 ANOVA with the factors condition, success and valence showed significant condition-by-success interactions in the right amygdala ($F_{(1,31)} = 5.631$, $p < .05$) and the right hippocampus ($F_{(1,31)} = 4.86$, $p < .05$). Post-hoc paired t-tests were performed to investigate this interaction. Signal change in the right amygdala seems to be modulated stronger by successful think trials as compared to successful no-think trials ($T_{(31)} = 3.23$, $p < .01$) than by unsuccessful think than unsuccessful no-think trials ($T_{(31)} = 2.62$, $p < .05$; Figure 20A). Right hippocampal activation showed the same pattern (successful: $T_{(31)} = 3.4$, $p < 01$, unsuccessful: $T_{(31)} = 2.93$, $p < .01$). In addition, a marginally significant different response pattern for successful and unsuccessful no-think trials was found ($T_{(31)} = -1.73$, $p < .1$; Figure 20B). Neither the left amygdala nor the left hippocampus did show any modulation of the above described condition effect by success.

***Table 6**: Summary of the post-hoc t-tests investigating signal change during no-think and think relative to baseline and each other in each ROI showing a think-no-think difference*

Region of Interest	Effect	T-value	p-value	df
right dlPFC	no-think > baseline	4.86	< .001	45
	think > baseline	3.44	< .01	45
	no-think > think	2.87	< .01	45
right amygdala	no-think < baseline	1.82	< .1	45
	think > baseline	0.27	n.s.	45
	think > no-think	3.52	< .001	45
left amygdala	no-think < baseline	1.53	n.s.	45
	think > baseline	0.64	n.s.	45
	think > no-think	3.09	< .01	45
right hippocampus	no-think < baseline	2.68	< .01	45
	think > baseline	0.64	n.s.	45
	think > no-think	4.10	< .001	45
left hippocampus	no-think < baseline	2.08	< .05	45
	think > baseline	1.26	< n.s.	45
	think > no-think	4.90	< .001	45

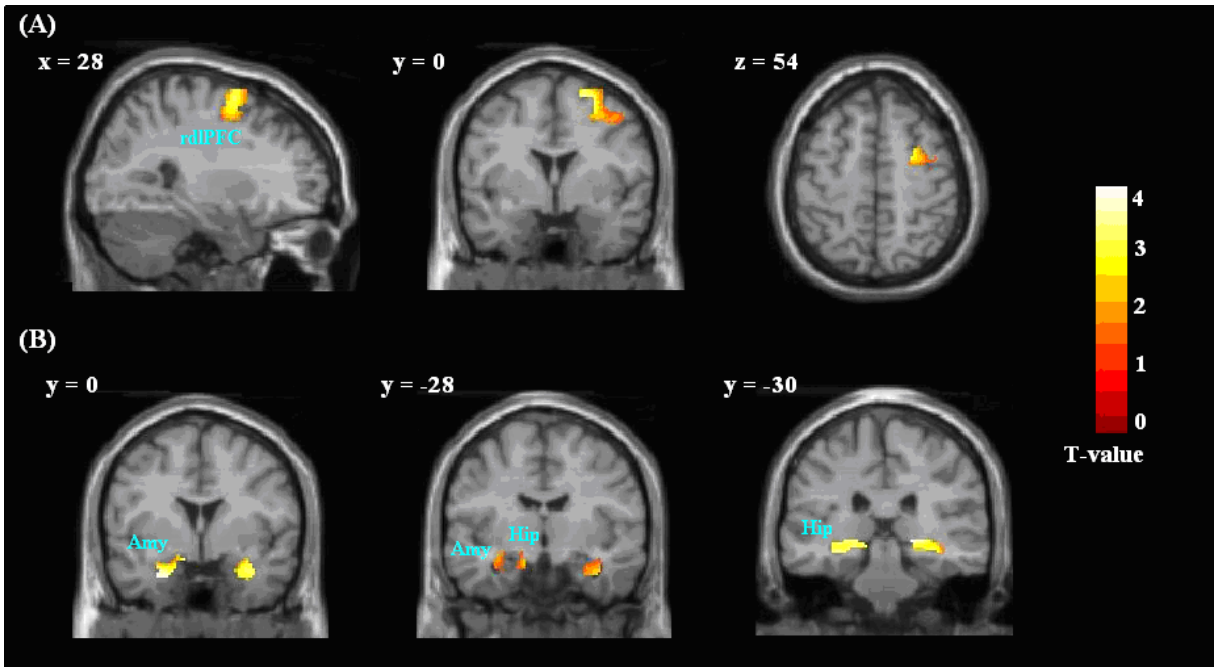

***Figure 19**: Statistical parametric maps (SPMs) were thresholded at p < .05 with the ROI-specific cluster size for p < .1 as determined by AlphaSim (Ward 2000; provided with the AFNI software. See Table 2). (A) Depiction of the cognitive control processes reflected by the no-think > think contrast and (B) depiction of the memory-related processes apparent in the think > no-think contrast.*

Linear trend analysis performed on the right dlPFC revealed a marginally significant linear increase in the BOLD signal from unsuccessful think and no-think to successful think and finally successful no-think trials ($F_{(1,31)} = 4.08$, $p < .1$).

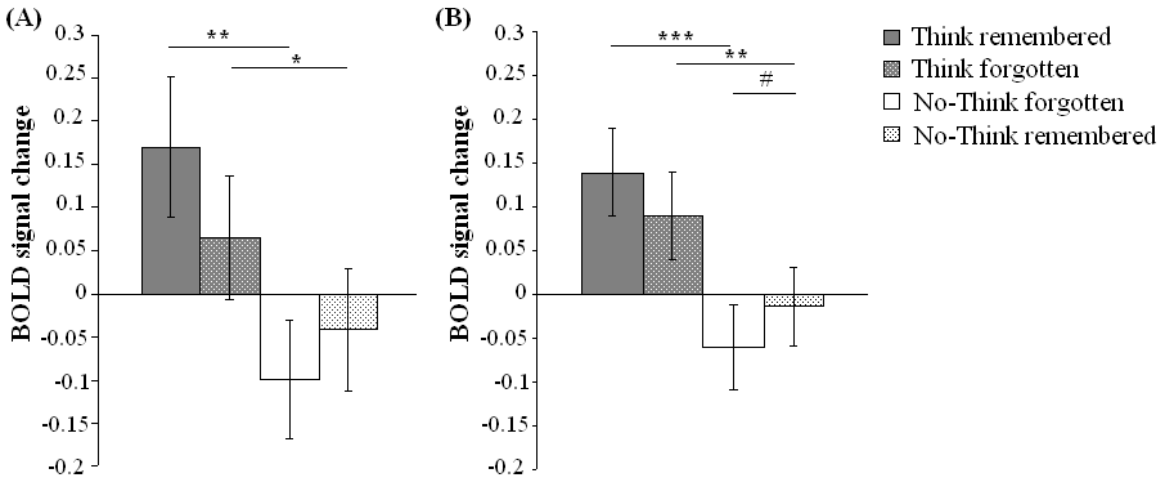

***Figure 20**: Signal change in the right amygdala (A) and right hippocampus (B) in response to successful think or no-think trials and unsuccessful think or no-think trials, respectively. # $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$*

Time Course Analysis

BOLD signal change of the no-think trials over the time course of the experiment was investigated by comparing activation during no-think trials in the three ROIs against the baseline period by means paired samples t-tests (Figure 21). Activation in the right dlPFC was increased relative to baseline in the first three quartiles (1^{st}: $T_{(45)} = 5.28$, $p < .001$, 2^{nd}: $T_{(45)} = 2.70$, $p < .05$, 3^{rd}: $T_{(45)} = 2.53$, $p < .05$), however, decreased during the final quartile ($T_{(45)} = -5.99$, $p < .001$). Activation in the bilateral amygdala was decreased relative to baseline in the second half of the experiment (3^{rd}: $T_{(45)} = -1.68$, $p < .1$ 0.1, 4^{th}: $T_{(45)} = -2.33$, $p < .05$). The hippocampus followed the exact same pattern (3^{rd}: $T_{(45)} = -2.53$, $p < .05$, 4^{th}: $T_{(45)} = -2.77$, $p < .01$).

Correlation between the ROIs

One-sided bivariate correlations were calculated between signal changes in the ROIs, considering the quartile with the maximal think/no-think difference.

A significant negative correlation emerged for the difference between no-think and baseline trials in the first quartile in the right dlPFC and the right hippocampus in the last quartile ($r = -.271$, $p < .05$, one-sided).

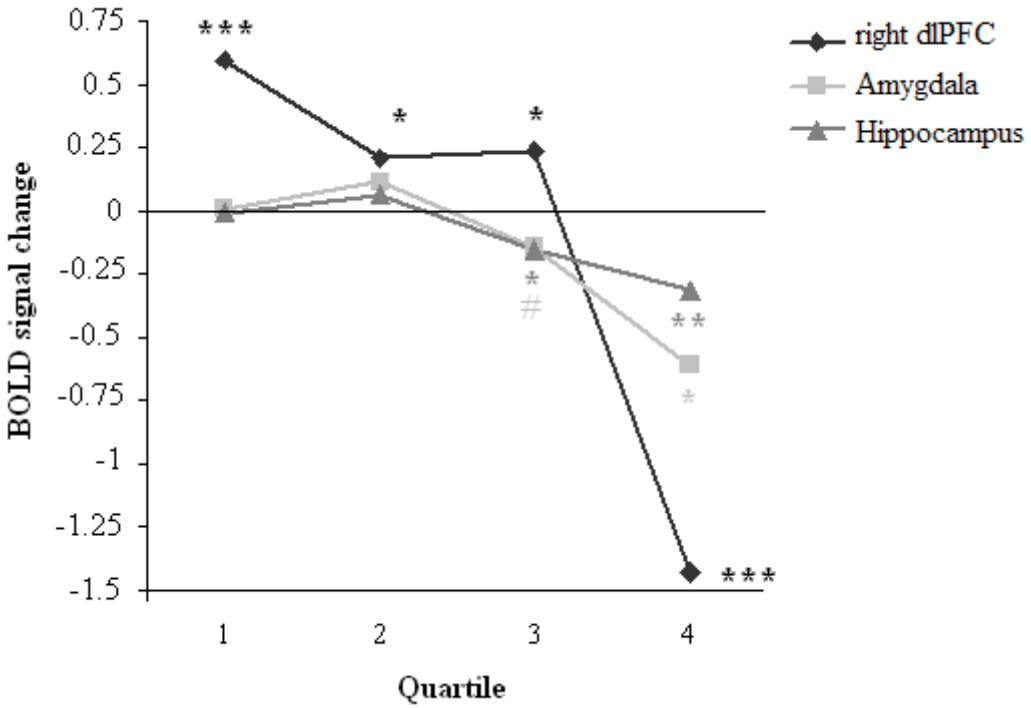

***Figure 21**: BOLD signal change in the three ROIs outlined over the time course of the experiment. Significant differences from baseline for each ROI are shown and indicated by color. # $p < .1$, ** $p < .05$, **, $p < .01$, *** $p < .001$*

Correlation with BSI

Bivariate correlations were calculated between the think/no-think difference for the quartile with the strongest think/no-think difference in each ROI separately for the two valence conditions. Only correlations with the BSI for neutral pictures were found, probably owing to the above described insufficient suppression of negative pictures. Table 7 summarizes the results of the correlation analyses.

***Table 7**: Summary of the correlation analyses calculated between the signal change in each ROI and the BSI for neutral pictures.*

Region of Interest	Pearson's correlation coefficient	p-value
right dlPFC	.292	< .05
right amygdala	-.386	< .01
left amygdala	-.281	< .1
right hippocampus	-.322	< .05
left hippocampus	-.299	< .05

3.4. TBS Study

3.4.1. Behavioral Data

Group comparisons of the sample characteristics and psychometric evaluations showed no significant differences between the verum and the sham group (see Table 8).

Paired-samples t-tests performed for the valence and arousal ratings of IAPS pictures selected for the baseline and the post-iTBS measurement did not reveal significant differences.

***Table 8**: Sample description and statistical comparison of psychometric data between the two groups*

	Verum	**Sham**	**Statistical value**	**p-value**	**df**
Total sample size	17	16	//		
Age	24.06 ± 2.70	24.69 ± 3.59	T = -0.57	.573	31
Gender (men)	5	8	χ^2 = 1.46	.226	1
Handedness (right)	16	14	χ^2 = 0.44	.509	1
Smoking status (yes)	6	5	χ^2 = 0.06	.805	1
Graduation			χ^2 = 0.44	.509	1
Abitur	16	14			
Mittlere Reife	1	2			
Motor Threshold	46.82 ± 6.38	46.63 ± 7.54	T = .08	.935	31
Stimulation Strength	37.47 ± 5.05	37.00 ± 6.05	T = .24	.810	31
Training Cycles	01.38 ± 0.60	01.13 ± 0.22	T = 1.61	.117	31
Questionnaires					
MWT (raw score)	30.08 ± 2.15	31.19 ± 2.29	T = -.39	.695	31
BDI	06.94 ± 7.39	06.94 ± 6.79	T = .001	.999	31
PANAS positive mean	29.79 ± 5.10	30.97 ± 6.72	T = -.57	.574	31
PANAS negative mean	12.18 ± 1.89	12.19 ± 1.99	T = -0.6	.987	31
ADS	10.24 ± 7.22	12.25 ± 7.04	T = .81	.423	31
HADS-D-Depression	02.88 ± 2.91	03.62 ± 2.92	T = -.73	.470	31
HADS-D-Anxiety	05.00 ± 3.64	04.69 ± 3.23	T = .27	.791	31
Rumination	00.79 ± 0.39	00.81 ± 0.46	T = -.14	.890	31
Life Events Count	08.59 ± 3.98	08.25 ± 3.82	T = .25	.805	31
Life Events Impact	02.56 ± 0.82	02.66 ± 0.69	T = -.37	.711	31
STAI-Trait	35.03 ± 4.67	33.31 ± 5.48	T = -.06	.949	31
STAI-State mean	39.82 ± 9.19	40.06 ± 12.05	T = .97	.339	31
Suppressor Type (good)					
pre iTBS	10	13	χ^2 = 1.96	.161	1
post iTBS	14	7	χ^2 = 5.31	**.021***	1
Suppressor Type with learning status (good)					
pre iTBS	10	13	χ^2 = 0.03	.853	1
post iTBS	14	7	χ^2 = 5.04	**.025***	1

3.4.1.1. Regardless of Learning Status

The 3 x 2 x 2 ANOVA for recalled pictures, regardless of learning status yielded a significant main effect of condition ($F_{(1.83,56.65)} = 10.94$, $p < .001$) and time ($F_{(1,30)} = 11.34$, $p < .01$), as well as a trend towards a significant interaction between time and group ($F_{(1,31)} = 6.68$, $p < .1$). Post-hoc Bonferroni corrected t-tests of the main effect for condition showed significantly more recalled think-pictures than baseline-picture ($p < .01$,) and significantly less recalled no-think-pictures than think-pictures ($p < .001$). The main effect of time resulted from overall more recalled pictures on day 2. Post-hoc t-tests were performed separately for the two groups and showed a significant difference in the overall percentage of recalled pictures only in the verum stimulated group ($T_{(16)} = -4.75$, $p < .001$). See Figure 22A for a depiction of the interaction.

The chi-square test comparing suppressor type by group revealed a significantly higher number of good suppressors in the verum group post iTBS ($\chi^2 = 5.31$, $p < .05$; see Table 8).

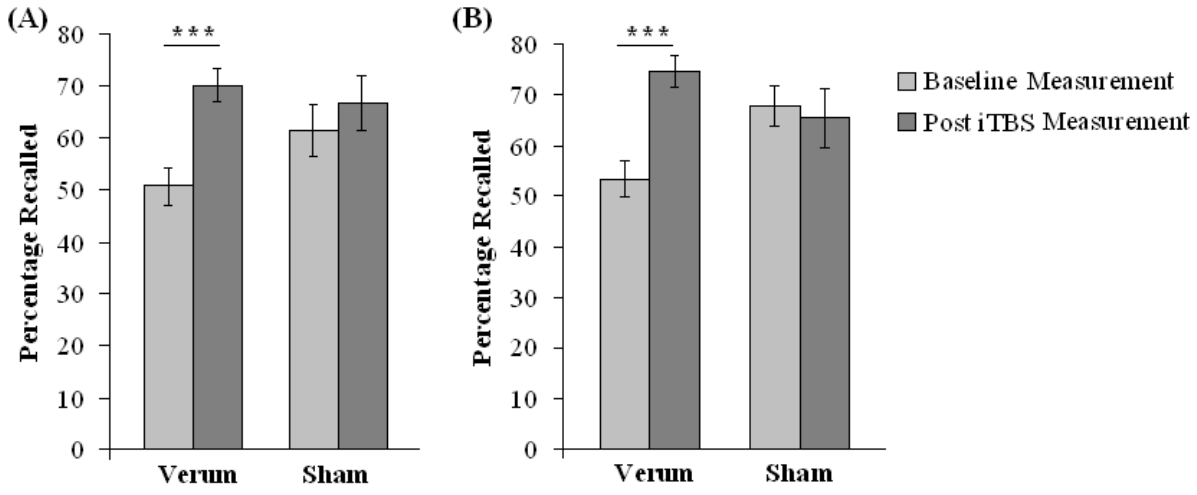

***Figure 22**: Time-by-group interaction (A) regardless of learning status, and (B) taking learning and status into consideration. *** p < .001*

3.4.1.2. Taking Learning Status into Consideration

The 3 x 2 x 2 ANOVA for recalled pictures taking the initial learning status of the face-picture pairs into consideration showed a significant main effect of condition ($F_{(2,62)} = 8.164$, $p < .01$) and time ($F_{(1,31)} = 6.390$, $p < .05$), as well as a significant interaction between group and time ($F_{(1,31)} = 10.449$, $p < .05$; Figure 22B). Post-hoc t-tests were performed

separately for the two groups and showed a significant difference in the overall percentage of recalled pictures only in the verum stimulated group ($T_{(16)} = -6.67$, $p < .001$)

The chi-square test comparing suppressor type by group revealed a significantly higher number of good suppressors in the verum group post iTBS ($\chi^2 = 5.038$, $p < .05$; see Table 8).

3.4.2. FNIRS Data

Oxygenated Hemoglobin

The 3 x 2 x 2 x 2 (condition-by-time-side-group) ANOVA yielded a significant main effect of condition ($F_{(1.68,46.97)} = 4.24$, $p < .05$), resulting from higher activation during no-think than during baseline trials (one-sided post-hoc Bonferroni $p < .01$) and marginally significant higher activation during think trials ($p < .1$). A significant main effect of time ($F_{(1,28)} = 6.82$, $p < .05$), stemming from overall higher signal changes during the post iTBS measurement was also obtained. Furthermore, a significant interaction between side and group ($F_{(1,28)} = 4.37$, $p < .05$), reflecting higher overall O_2Hb changes in the right dlPFC in the verum group only, and a marginally significant condition-by-side interaction ($F_{(2,56)} = 2.57$, $p < .1$) were found.

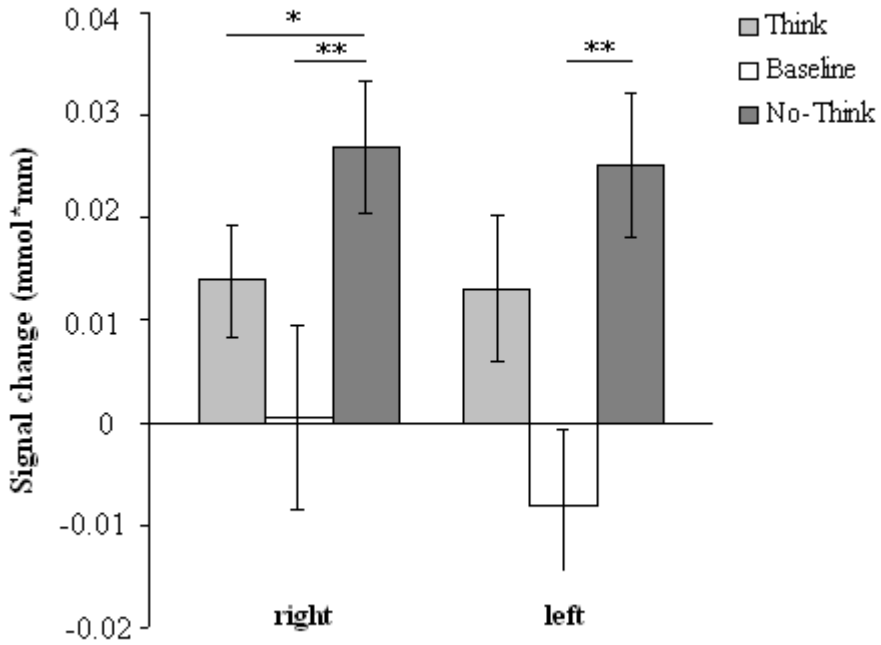

***Figure 23**: Signal changes (O_2Hb) during think and no-think trials relative to baseline. * $p < .05$, ** $p < .01$, one-sided*

One-sided post hoc Bonferroni corrected t-tests, performed to investigate the interactions between condition and side showed significantly higher activation during no-

think than during think ($p < .05$) and during baseline trials ($p < .01$) in the right dlPFC and higher activation during no-think than during baseline trials in the left dlPFC ($p < .01$). See Figure 23.

No significant correlations between signal change in the right or left dlPFC and the BSI were found.

Deoxygenated Hemoglobin

The 3 x 2 x 2 x 2 (condition-by-time-by-side-by-group) ANOVA yielded only a marginally significant condition-by-group interaction ($F_{(2,56)} = 2.98$, $p < .1$). One-sided post-hoc paired t-tests were performed separately for the two groups and showed a significant decrease in HHb during no-think relative to think trials only in the verum group ($T_{(15)} = 1.87$, $p < .05$). The sham group showed higher HHb signal changes relative to baseline irrespective of the condition (think: $T_{(15)} = -1.89$, $p < .05$, no-think: $T_{(15)} = - 2.10$, $p < .05$). The group specific activation patterns are shown in Figure 24.

No significant correlations between signal change in the right or left dlPFC and the BSI were found.

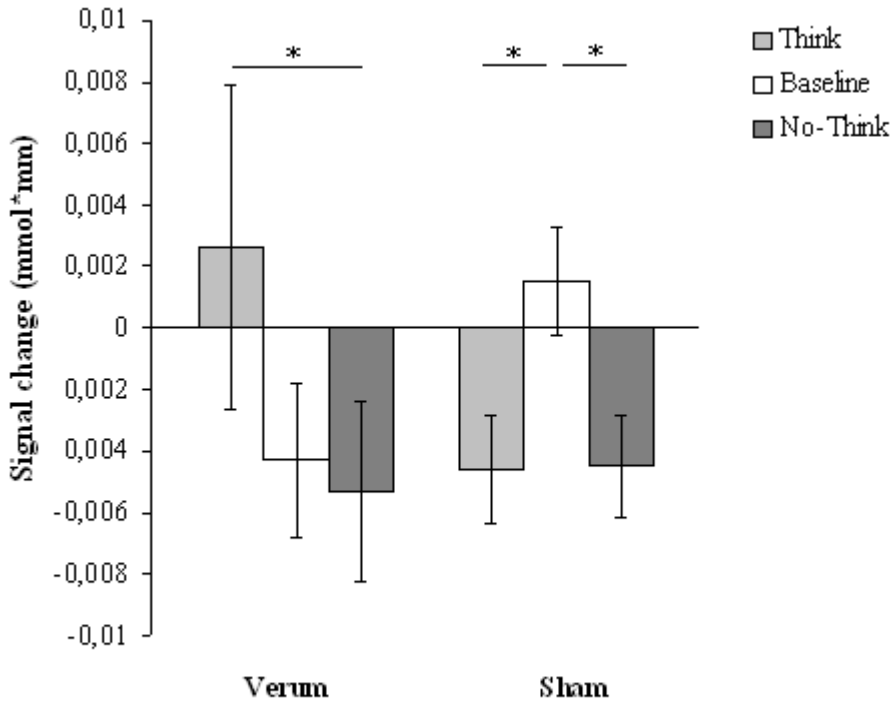

***Figure 24**: Pattern of HHb signal changes of think and no-think relative to baseline trials depicted for the verum and sham group separately. * p < .05 (one-sided)*

3.4.2.1. Linear Trend Analysis

Oxygenated Hemoglobin

Linear trend analysis performed on the measurement data from the baseline measurement yielded a significant result only for the right dlPFC ($F_{(1,22)} = 4.14$, $p = .05$), showing a linear increase in signal change from unsuccessful think and no-think to successful think and finally successful no-think trials (Figure 25).

No significant correlations between signal change during successful no-think trials and the BSI were found.

Deoxygenated Hemoglobin

A marginally significant linear trend was obtained in right dlPFC concerning signal changes in HHb ($F_{(1,22)} = 4.23$, $p < .1$; Figure 25).

No significant correlations between signal change during successful no-think trials and the BSI were found.

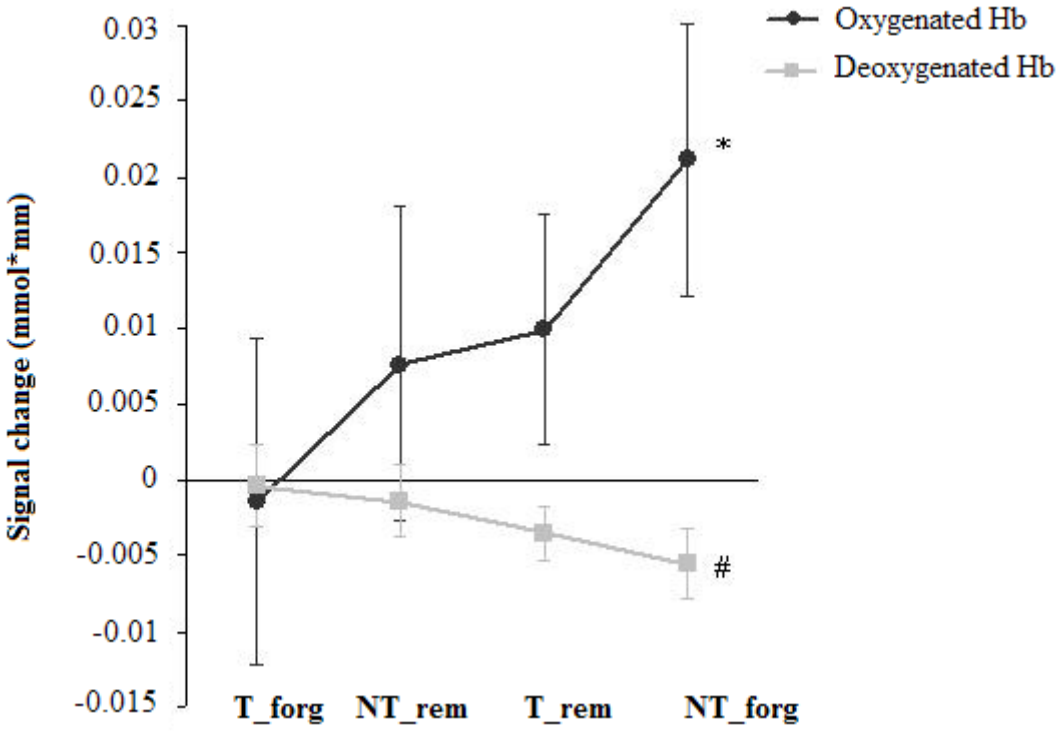

***Figure 25**: Linear trend lines for O_2Hb and HHb. # $p < .1$, * $p < .05$*

3.4.3. ERP Data

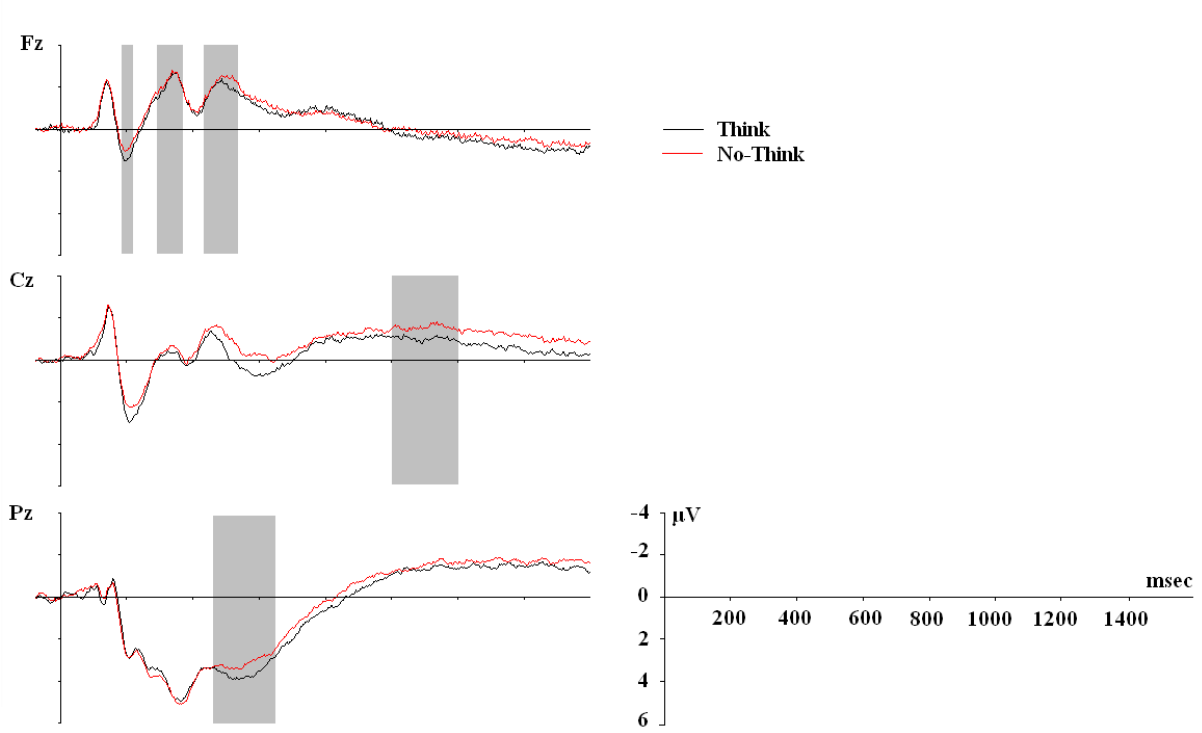

***Figure 26**: Grand Average ERPs of the think and no-think trials for all face-picture pairs (regardless of initial learning status and later successful recall or suppression) at the three midline electrodes Fz, Cz, and Pz. Shaded areas delineate the time windows used for the detection of the peaks, which were used for the statistical analyses*

3.4.3.1. Regardless of Learning and Suppression Status

Grand average ERPs for the Think and No-Think condition derived from all face-picture pairs, regardless of learning status and successful recall or suppression, respectively, are depicted in Figure 26 at the three midline electrodes. Five components were isolated, which were elicited by think and no-think trials: (a) a P2 component, peaking around 208ms (b) an N2, peaking around 312ms, (c) an N4, peaking around 476ms, (d) a parietal positivity partly overlapping with the N4, peaking at 560ms, and (e) a central negativity, peaking around 1100ms. Peak time did not differ significantly between the baseline and post iTBS measurements in any of the components ($p > .1$).

Analyses are performed separately for each component.

P2 (180-230ms)

Frontal

A significant main effect of condition ($F_{(1,31)} = 13.65$, $p < .01$), reflecting an enhanced P2 during think-trials was found. Furthermore, a marginally significant main effect of laterality ($F_{(2,62)} = 2.47$, $p < .1$), reflecting the highest P2 at Fz and a significant time-by-laterality interaction was ($F_{(2,62)} = 3.66$, $p < .05$) were found. The interaction was due to an overall decrease in P2 amplitude from the first to the second measurement in F3 ($F_{(1,31)} = 5.96$, $p < .05$) and Fz ($F_{(1,31)} = 3.12$, $p < .1$) as compared to F4, as investigated by a post-hoc contrast analysis.

Central

Significant main effects of condition ($F_{(1,31)} = 13.10$, $p < .01$) and laterality ($F_{(2,62)} = 24.29$, $p < .001$), reflecting the same pattern as in frontal regions as well as a significant condition-by-laterality interaction ($F_{(2,62)} = 4.73$, $p < .01$), were found. Post-hoc paired t-tests showed this interaction as resulting from a stronger condition effect at Cz ($T_{(34)} = 3.61$, $p < .01$) and C3 ($T_{(34)} = 3.59$, $p < .01$) than at C4 ($T_{(34)} = 2.44$, $p < .05$).

Parietal

A significant main effect of laterality ($F_{(2,62)} = 14.01$, $p < .001$) and a marginally significant main effect of time ($F_{(1,31)} = 3.88$, $p < .1$) were found. The laterality effect was due to higher activation at Pz than at P3 ($p < .001$) and P4 ($p < .05$) and the time effect due to higher positivity during the second measurement.

N2 (280-370ms)

Frontal

A significant main effect of laterality ($F_{(2,60)} = 5.76$, $p < .01$), reflecting generally higher negativity at F3 than at Fz ($p < .01$) and F4 ($p < .05$) was found. Furthermore, a marginally significant interaction between condition and laterality ($F_{(2,60)} = 2.92$, $p < .1$), mirroring an enhanced N2 for no-think trials at at Fz than at F3/F4 (one-sided: $T_{(34)} = 1.37$, $p < .1$) was observed. Lastly, a significant condition-by-laterality-by-group interaction was found ($F_{(2,60)} = 3.46$, $p < .05$), which reflected a significantly enhanced N2 for no-think trials only in the sham group (one-sided: F3: $T_{(15)} = 2.50$, $p < .01$; Fz: $T_{(15)} = 1.44$, $p < .1$; F4: $T_{(15)} = 1.66$, $p < .1$).

Central

Only a marginally significant laterality effect ($F_{(2,60)}$ = 2.60, p < .1) was found, reflecting higher negativity at Fz than at F4 (p < .1).

Parietal

A significant main effect of laterality ($F_{(2,60)}$ = 6.31, p < .01) was found, mirroring decreased negativity at F4 as compared to Fz (p < .05) or F3 (p < .01).

N4 (430-540ms)

Frontal

A marginally significant main effect of condition ($F_{(1,30)}$ = 1.84, p = .1) was observed, reflecting an enhanced N4 for no-think trials.

Central

A significant main effect of laterality ($F_{(2,60)}$ = 12.79, p < .001), stemming from overall more negativity at Cz than at C3 (p < .01) or at C4 (p < .001). Furthermore, a significant laterality-by-time-by-group ($F_{(2,60)}$ = 4.46, p < .05), reflecting higher increased overall negativity in the verum group at C4 than at Cz ($F_{(1,30)}$ = 10.62, p < .01) or at C3 ($F_{(1,30)}$ = 6.52, p < .05) post iTBS as investigated by post-hoc contrast analyses.

Parietal

Only a significant main effect of laterality emerged ($F_{(2,60)}$ = 3.20, p < .05), reflecting significantly reduced negativity at Pz as compared to P3 (p < .05).

Late Positivity (450-640ms)

Frontal

A marginally significant main effect of time was found ($F_{(1,31)}$ = 3.26, p < .1), stemming from higher positivity during the baseline measurement. Furthermore, a significant time-by-laterality interaction was observed ($F_{(2,62)}$ = 3.54, p < .05), which reflected this lower post-iTBS positivity as being present only at Fz ($F_{(1,31)}$ = 3.35, p < .1) and F3 ($F_{(1,31)}$ = 5.88, p < .05), as shown by post-hoc contrast analyses.

Central

A significant main effect of condition was obtained ($F_{(1,31)} = 4.24$, $p < .05$), reflecting higher positivity during think trials. A marginally significant laterality-effect was found ($F_{(2,62)} = 2.56$, $p < .1$), which was caused by marginally higher overall positivity at C4 than at Cz ($p < .1$). Lastly, a significant condition-by-laterality interaction was revealed ($F_{(2,62)} = 3.54$, $p < .05$), which was due to a significantly higher positivity during think trials at Cz ($T_{(34)} = 2.78$, $p < .01$) and marginally significantly higher positivity during think trials at C4 ($T_{(34)} = 1.92$, $p < .1$), as shown by post-hoc paired-samples t-tests performed on the mean think and no-think trials (baseline and post-iTBS).

Parietal

Only a significant main effect of laterality ($F_{(2,62)} = 8.57$, $p < .01$), owing to overall higher positivity at Pz ($p < .01$) and at P4 ($p < .1$) than at P3.

Late Negativity (1000-1200ms)

Frontal

No significant results were obtained for the late negativity at frontal electrodes.

Central

A significant main effect of condition emerged ($F_{(1,31)} = 4.17$, $p = .05$), reflecting more negativity during no-think trials. Furthermore, a significant main effect of laterality was found ($F_{(2,62)} = 36.44$, $p < .001$), resulting from significantly more negativity at Cz than at C3 and C4 (both $p < .001$). Additionally, a significant laterality-by-group interaction was observed ($F_{(2,62)} = 3.93$, $p < .05$), which was due to significantly more negativity in the verum group at Cz than at C3, as shown by post-hoc contrast analysis ($F_{(1,31)} = 7.04$, $p < .05$).

Parietal

A significant main effect of laterality was shown ($F_{(2,62)} = 19.25$, $p < .001$), which was caused by significantly higher condition-independent negativity at C4 and Cz than at C3 (both $p < .001$).

Topographical Analyses

The ANOVA investigating topographical differences in the distribution of the enhanced think trials found in the P2 and late positivity showed no significant component-by-

region interactions, indicating that the effect reflects a single process which is prolonged in time.

Scalp distribution maps of the 5 components are shown in Figure 27.

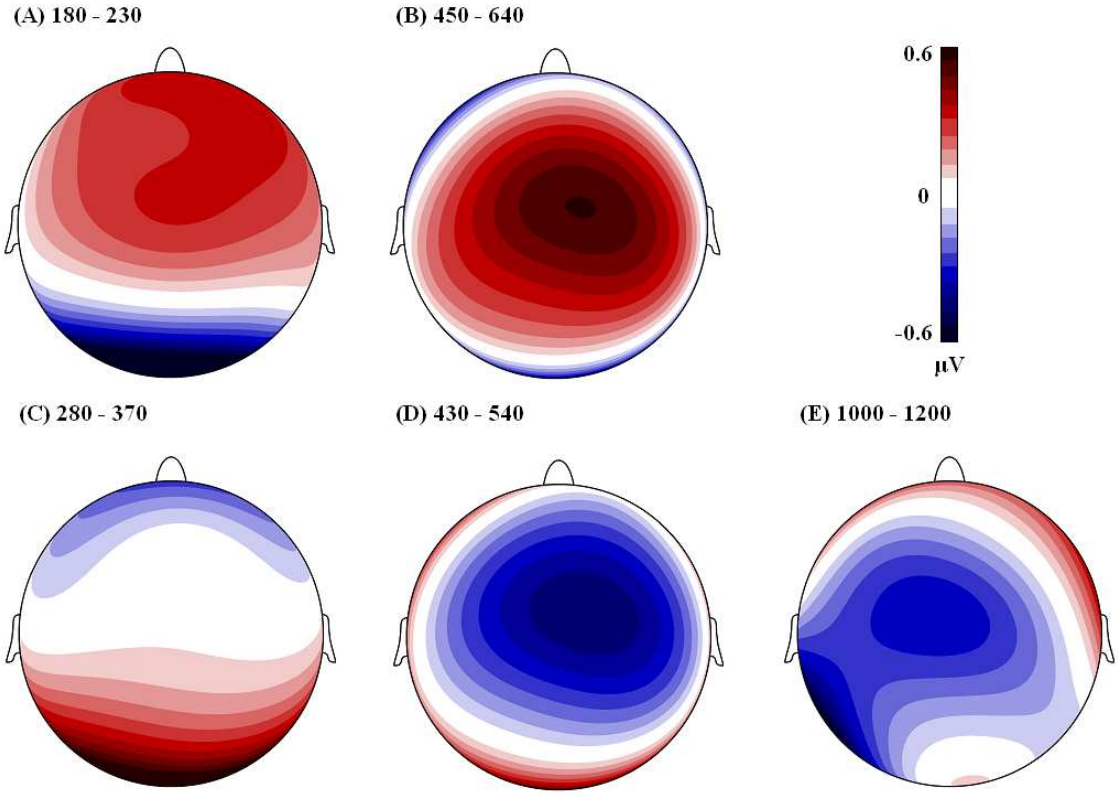

***Figure 27**: Scalp distribution maps derived from the difference wave between the two conditions separately for each component. (A) and (B) show the distribution of the two components reflecting higher activation during think trials and (C) – (E) show the scalp distribution of the three components with higher voltages during no-think trials*

3.4.3.2. Regression between ERP and BSI

The linear regression analysis with the BSI as dependent variable and the difference wave of the late negativity reached significance during the baseline measurement, indicating that the late negativity component validly predicts the later behavioral outcome (adj R^2 = .29, $F_{(2,30)}$ = 3.71,p < .05). Investigating the coefficients more closely, however, only negativity at central electrodes significantly predicted a linear increase in the BSI (B = -13.71, β = -.58, $T_{(31)}$ = -2.66, p < .05), explaining R^2 = .21 of the whole unadjusted R^2 = .29 (see Figure 28). Post iTBS, the difference wave of the late negativity did not predict the BSI.

None of the other components significantly predicted the outcome of the performance in the behavioral recall test of the baseline or the measurement post-iTBS.

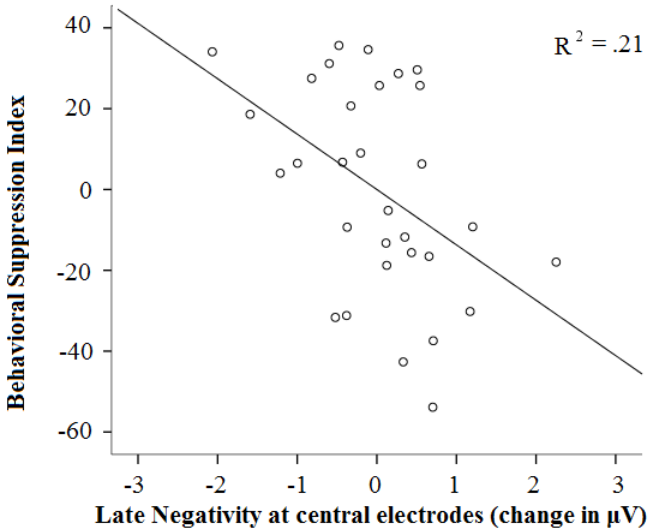

***Figure 28**: Regression line of the late negativity at central electrodes and the BSI of the baseline measurement*

3.4.3.3. Correlations between fNIRS and ERPs

One-sided bivariate correlations were calculated between the no-think > think contrast derived from the fNIRS measurement and the difference wave of the ERP components showing higher peaks during no-think trials (i.e. N2, N4, and the late negativity).

Oxygenated Hemoglobin

No significant correlations emerged.

Deoxygenated Hemoglobin

A positive correlation between the late negativity at frontal electrode sites and signal change in response to no-think trials in the right ($r = .28$, $p < .1$) and left dlPFC ($r = .36$, $p < .05$) was found (Figure 29).

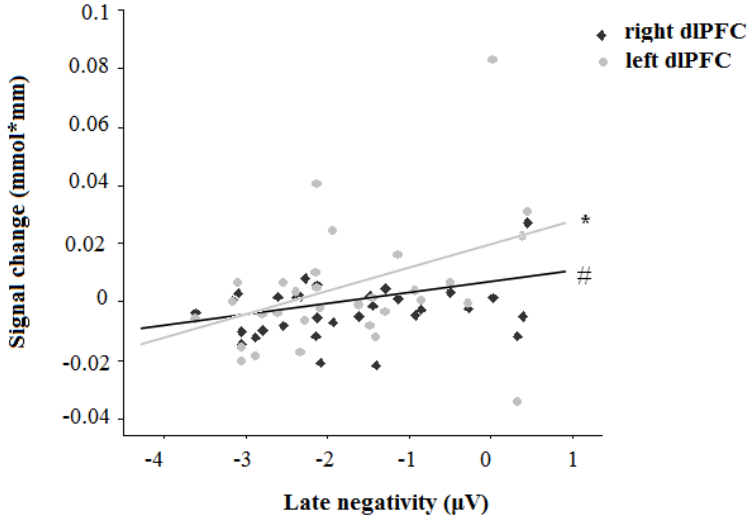

***Figure 29**: Correlation between signal changes in the right and left dlPFC during no-think trials and the difference value of the late negativity. # $p < .1$, * $p < .05$ (one-sided)*

3.5. Regression and Correlation Analyses

3.5.1. BSI and Psychometric Measures

No significant correlations were found between the BSI and the MWT-B.

The regression model including psychometric evaluations of depression (i.e. rumination, BDI, HADS-Depression and ADS) explained a significant proportion of variance in the BSI (adj $R^2 = .04$, $F_{(4,133)} = 2.44$, $p = .05$). However, only rumination scores predicted a linear decrease in the suppression performance ($B = -19.21$, $\beta = -.28$, $T_{(131)} = -2.41$, $p < .05$), explaining $R^2 = .04$ of the whole unadjusted $R^2 = .07$ (see Figure 30A). The regression model including psychometric evaluations of anxiety (i.e. HADS-Anxiety, PANAS and STAI-Trait and -State) did not significantly explain any variance in the BSI (adj $R^2 = .01$, $F_{(5,103)} = 1.28$, $p > .1$), however, the STAI-Trait index seems to explain some of the variance in the BSI ($B = -.78$, $\beta = -.26$, $T_{(99)} = -2.01$, $p < .05$), explaining $R^2 = .04$ of the whole unadjusted $R^2 = .06$ (see Figure 30B).

Neither the univariate ANOVA including gender, nor the univariate ANOVA including graduation yielded significant results ($p > .1$).

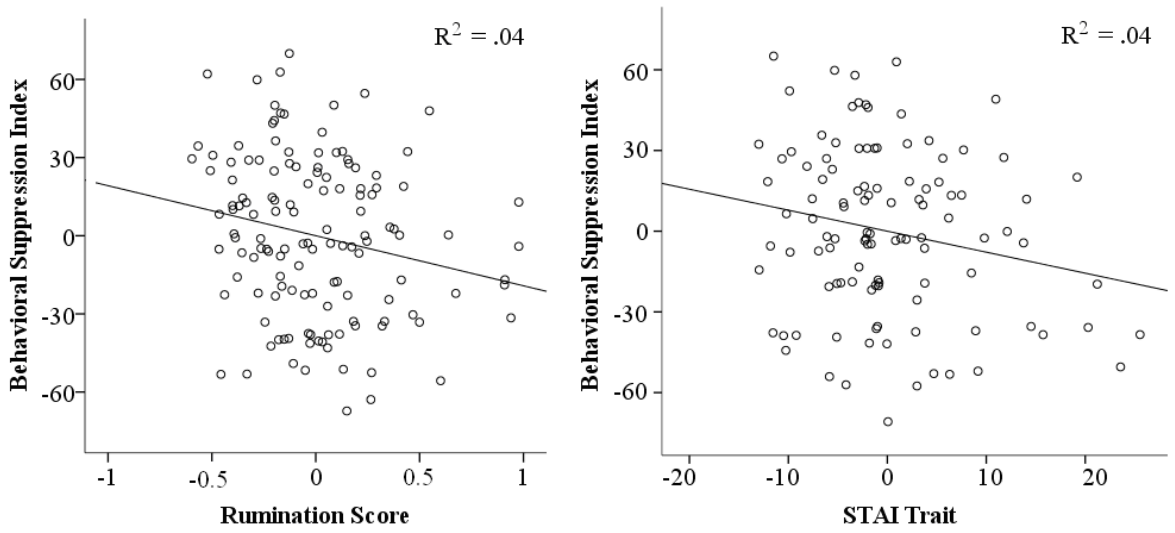

***Figure 30**: Regression coefficients of the Rumination and STAI trait score and the Behavioral Suppression Index (BSI)*

3.5.2. Functional Imaging Data and Psychometric Data

3.5.2.1. FNIRS Data

Oxygenated Hemoglobin

Significant positive correlations between right dlPFC activation during no-think trials were found with the BDI ($r = .25$, $p < .05$; $N = 51$), the ADS ($r = .27$, $p < .05$; $N = 50$), and the depression subscale of the HADS ($r = .26$, $p < .05$; $N = 50$). Marginally significant positive correlations were obtained with the RSS ($r = .19$, $p < .1$; $N = 50$) and the STAI trait scale ($r = .30$, $p < .1$; $N = 30$). BDI ($r = .22$, $p < .1$) and ADS ($r = .18$, $p < .1$) marginally correlated with left dlPFC activation during no-think trials.

No correlations were found with the BSI.

Deoxygenated Hemoglobin

For HHb marginally significant negative correlations between right dlPFC activation and the RSS ($r = -.19$, $p < .1$) as well as the STAI trait-scale ($r = -.30$, $p < .1$) and a positive correlation between signal changes in the left dlPFC and the anxiety subscale of the HADS ($r = .27$, $p < .05$) emerged.

No correlations were found with the BSI.

3.5.2.2. FMRI Data

Only a significant negative correlation between below-baseline activation during no-think trials in the left hippocampus and the RSS was found ($r = -.208$, $p < .1$).

3.5.3. Interaction Term with Psychometric Data

3.5.3.1. FNIRS Data

Oxygenated Hemoglobin

Significant negative correlations between the interaction index of the BSI with activation in the right dlPFC and the ADS, the HADS depression subscale, the STAI state scale, and the negative symptoms subscale of the PANAS were found. Marginally significant negative correlations were obtained with the RSS and the BDI. See Table 9 for the correlation coefficients.

No significant correlations were found in the left dlPFC.

Deoxygenated Hemoglobin

Significant positive correlations were found between the interaction index in the right dlPFC and the ADS, the depression subscale of the HADS, the STAI state and trait scale, the RSS, and the BDI. The correlation with the negative subscale of the PANAS was marginally significant.

In the left dlPFC, significant positive correlations were shown between the ADS, the HADS depression scale, the negative symptom scale of the PANAS, the RSS, the STAI Trait scale and the BDI. Correlations with the STAI State scale approached significance.

See Table 9 for the correlation coefficients.

3.5.3.2. FMRI Data

No significant correlations were found.

***Table 9**: Correlation coefficients resulting from correlation analyses between the interaction index of the BSI with activation in the dlPFC and the single scores of the psychometric evaluations, * $p < .05$, ** $p < .01$, # $p < .1$*

Region of Interest	Correlation	Pearson's correlation coefficient	p-value	N
Right dlPFC – O_2Hb	ADS	-.280	.049 *	50
	HADS- depression	-.303	.033 *	50
	STAI state	-.293	.037 *	51
	STAI trait	-.293	.039 *	50
	PANAS negative	-.375	.007 **	51
	RSS	-.253	.077 #	50
	BDI	-.243	.086 #	51
Left dlPFC - O_2Hb	//			
Right dlPFC - HHb	ADS	.311	.028 *	50
	HADS- depression	.313	.027 *	50
	STAI state	.321	.022 *	51
	STAI trait	.354	.012 *	50
	PANAS negative	.266	.059 #	51
	RSS	.300	.035 *	50
	BDI	.287	.041 *	51
Left dlPFC - HHb	ADS	.412	.003 **	50
	HADS- depression	.392	.005 **	50
	STAI state	.245	.083 #	51
	STAI trait	.297	.036 *	50
	PANAS negative	.308	.028 *	51
	RSS	.311	.028 *	50
	BDI	.337	.016 *	51

3.6. Genetical Analyses

3.6.1. Behavioral Data

The 3 x 2 (condition (only negative items)-by-KCNJ6) ANOVA showed a significant main effect of condition ($F_{(2,224)}$ = 8.87, p < .001) and a significant condition-by-KCNJ6 interaction ($F_{(2,224)}$ = 3.26, p < .05). See Figure 31 for a depiction of the interaction.

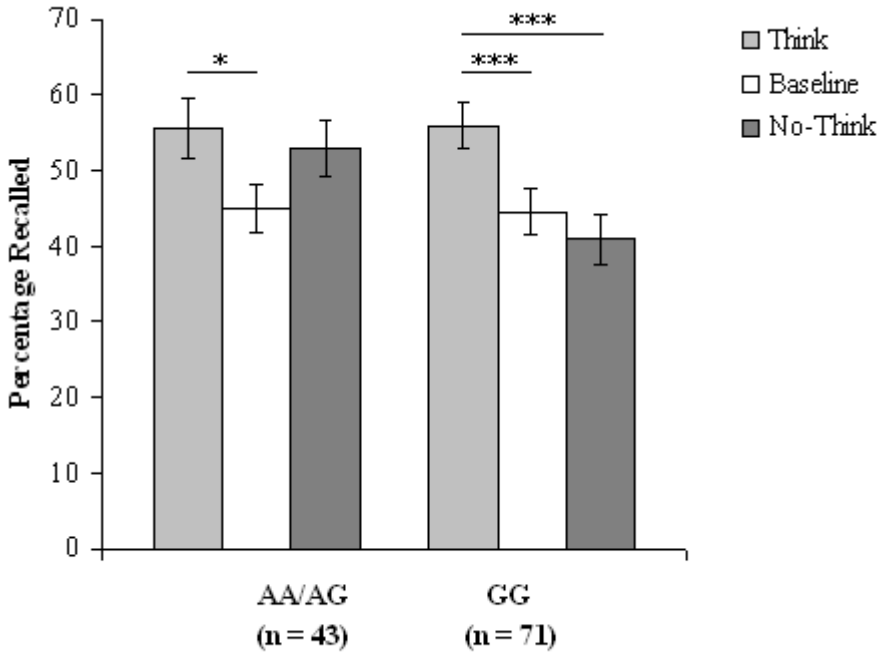

Figure 31**: Condition-by-genotype interaction for the KCNJ6 SNP; * p < .05, p < .001*

The 3 x 2 ANOVA for the CREB1 SNP only revealed an overall main effect of condition ($F_{(2,222)}$ = 11.75, p < .001), resulting from a significant higher recall of think than no-think pictures (p < .001) and baseline pictures (p < .001). No interaction was found.

3.6.2. Functional Imaging Data

Functional Near Infrared Spectroscopy

No significant modulation of dlPFC activation by KCNJ6 was found.

Functional Magnetic Resonance Imaging

A significant condition-by-genotype interaction, owing to higher activation in carriers of at least one A-allele emerged in the right dlPFC for the NT > T contrast ($F_{(1,144)}$ = 12.67, p

< .05; Figure 32), indicating the need to exert higher cognitive effort during the attempted cognitive control. No significant interactions were found in the amygdala or the hippocampus.

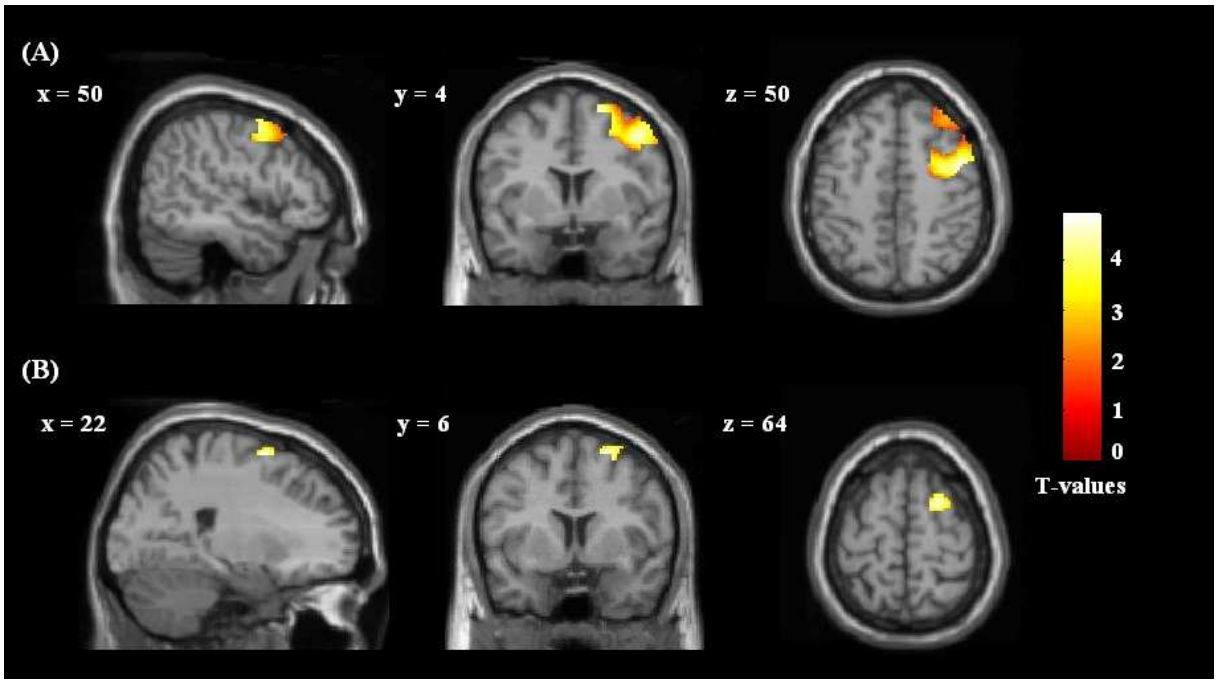

***Figure 32**: More activation in carriers of at least one A-allele of the KCNJ6 SNP (A) than homozygous carriers of the G-allele (B) was observed in the right dlPFC during no-think trials. SPMs are thresholded at p < .05 (uncorr.)*

4. Discussion

The investigation of processes involved in the cognitive inhibition of thoughts and memories has gained considerable attention in the last decade. One of the most commonly used paradigms for researching cognitive inhibition is the TNT (Anderson & Green 2001), which is derived from the widely used Go/Nogo paradigm, applied to the study of inhibition of pre-potent motor responses. The TNT requires the subject to retrieve and activate a previously learned associated thought (i.e. target) in one condition (i.e. think), while to inhibit the memory from entering awareness in the other condition (i.e. no-think) when presented with a cue. Successful inhibition has been shown by Anderson and Green (2001) to result in diminished recall of inhibited (i.e. no-think) versus retrieved (i.e. think) or baseline[1] stimuli, reflecting the disruption of previously established links between two stimuli.

In addition to the attempt to replicate this initial below-baseline suppression of no-think items, which has proven difficult (see Table 1), previous studies on this topic have investigated various aspects interacting with mechanisms recruited during cognitive inhibition. These aspects, among others, included the emotional content of the stimulus material, but results on this topic have been inconclusive. While some researchers found negative stimuli to be suppressed more effectively than neutral (Depue et al 2006) or positive stimuli (Lambert et al 2010), others showed impaired suppression of negative relative to positive thoughts (Marx et al 2008). Two hypotheses have emerged explaining the facilitated or impaired suppression of negative thoughts respectively, based on findings of differential encoding and consolidation of neutral and emotional material at the neural level (Kensinger & Corkin 2004): (1) Facilitated cognitive control, and thus better suppression of negative thoughts has been explained by the idea that highly salient negative information is more accessible due to more elaborated processing already during encoding (Lambert et al 2010). (2) The opposite pattern of impaired inhibitory control over negative thoughts has also been explained in the light of better encoding of emotionally negative material, however, it is claimed that this results in increased demands on processes guiding intentional suppression of negative thoughts relative to less well elaborated neutral or positive thoughts in the TNT (Marx et al 2008). Considering that investigation of the influence of valence on thought inhibition was performed by different studies using different stimulus material, slightly differing experimental setups as well as patient and control samples the generalization of

[1] Cue-target associations that are established in the study phase, but that are neither inhibited nor retrieved during the TNT phase. For a thorough description of the TNT procedure see section 1.2.1.

these findings is difficult. One aim of the present work was therefore to establish the relative modulatory contributions of these factors to cognitive inhibition measured through the TNT paradigm. Meeting the inconsistent findings regarding stimulus valence, two of the presented studies (i.e. pilot and emotion study) have for the first time[1] compared suppression of neutral, positive and negative stimuli directly within one sample.

The other line of past research investigating cognitive inhibition has focused on the neurophysiological and electrophysiological processes underlying the behaviorally observable impaired recall of previously suppressed stimuli. Three fMRI studies have isolated a fronto-hippocampal network being activated during thought inhibition in the TNT (Anderson et al 2004; Depue et al 2010; Depue et al 2007). Increased activation of the dlPFC has been consistently found during no-think attempts. Its implication in thought suppression has further been corroborated by correlation analyses showing that percentage signal change reliably predicted subsequent recall impairment of suppressed items. The hippocampus, which has been established as being essential for memory formation and consolidation (e.g. Bliss & Collingridge 1993; Squire 1992) and which is anatomically connected to the dlPFC through the fornix and the retrosplenial cortex (Morris et al 1999; Petrides & Pandya 2006), has been found to be reduced in activation during no-think trials. Importantly, Depue et al. (2007) could show that the largest decrease in hippocampal activation was found during the suppression of items, which were actually forgotten in the post-experimental recall test[2]. Furthermore, they could show lower activation levels during forgotten no-think than during forgotten think trials, which has been interpreted as evidence for an active suppression mechanism. The interaction of both structures has been suggested by correlation analyses indicating that the degree of hippocampal deactivation can be predicted by dlPFC activation (Depue et al 2007). ERP studies have further provided evidence of active suppression mechanisms in the brain. Several ERP components have been reported, two, however, have been prominent in all ERP studies using the TNT so far. A late positive shift around 500 ms, which was reduced in amplitude during no-think relative to think trials, was consistently shown in all experiments (Bergström et al 2009a; Bergström et al 2009b; Bergström et al 2007; Hanslmayr et al 2009; Mecklinger et al 2009). A second, N2-like component has been shown to be increased during execution of no-think relative to think trials (Bergström et al 2009b; Mecklinger et al 2009). Bergström et al. (2009b) presented convincing evidence for an

[1] To the best knowledge of the author

[2] Hippocampal activation during suppression of subsequently forgotten no-think items was shown to drop below baseline activation levels, while activation of later remembered no-think items showed an increase relative to baseline, although to a lesser extent than during think trials

implication of the N2 in voluntary suppression by showing an even larger increase in amplitude in subjects applying suppression versus subjects applying thought substitution strategies during no-think trials. Topographical analyses have shown a centro-parietal distribution of the N2, which has been interpreted as reflecting the electrophysiological correlates of the fronto-temporal network found in the fMRI studies mentioned earlier. Although it is likely that the late positivity and the N2 reflect activation in the fronto-hippocampal network[1], no study combining functional neuroimaging and electrophysiological methods has been performed so far making direct correlations impossible. Using different neuroimaging (i.e. fNIRS and fMRI) and electrophysiological (i.e. ERP) methods, another intention of the current work was to extend the knowledge of the neural mechanisms underlying the intentional act of suppression in the TNT. Special attention was given to the modulation of these processes by stimulus valence. As described above, at the behavioral level results regarding the beneficial or impairing effect of valence on successful suppression of thoughts have been inconsistent. Regarding, furthermore, the unreliability of the suppression effect at the behavioral level (see Table 1), and taking into account the consistency of findings derived from neuroimaging and electrophysiological studies, more information concerning the modulation of inhibitory processes by valence (even in the absence of a behaviorally observable suppression effect), might be derived from the investigation of suppression at the neural level. In addition, direct evidence for dlPFC activation as a crucial predictor of memory inhibition in the TNT was tested by means of iTBS, altering neural activity through external stimulation. Furthermore, taking advantage of the easy combinability of fNIRS and ERPs, another question aimed at shedding more light on the correlation between certain ERP components and neural processes engaged in thought suppression.

As already mentioned, replication of Anderson's and Green's (2001) initially reported below-baseline drop of recall performance for no-think items, has been proven difficult by various studies (see Table 1). Some attempts have been made to isolate personality traits (e.g. dysphoria, anxiety, ruminative response styles) possibly explaining the interindividual differences in the ability to successfully inhibit thoughts in the TNT, which in turn might result in the inconsistent findings regarding the suppression effect. Therefore, the final rationale of the current work was the investigation of how certain personality traits might contribute to the moderate success in replicating Anderson's and Green's (2001) original findings. In addition, it was investigated whether two genetic polymorphisms (i.e. KCNJ6,

[1] For a description of correlating findings in studies in other areas of research on inhibitory mechanisms, e.g. in the Stop Signal task, see paragraph 1.2.3.

CREB1), which have recently been linked to memory functioning and ruminative response styles (e.g. Lazary et al 2011; Schuur 2010), might additionally explain some of the interindividual differences in suppression performance.

Results obtained at a behavioral level in the post-experimental recall test and those obtained at the neurophysiological and electrophysiological level will be discussed separately at first. Consequently, the correlation between suppression at the neural and at the behavioral level will be considered in an attempt to generate a holistic picture of thought suppression in the TNT. In the remainder, the discussion will focus on the results (1) obtained in the regression analyses performed on certain personality traits previously found to predict suppression performance and (2) on the influence of the two genetic polymorphisms which were exploratively investigated in this work.

4.1. Discussion of Behavioral Results

Except for the neutral condition in the fMRI study none of the current studies revealed a below-baseline suppression effect of no-think items as found by Anderson and Green in their original study in 2001, reflecting the difficulty encountered by other groups (e.g. Bergström et al 2007; Bulevich et al 2006). In all three other studies overall (i.e. independent of valence) significantly lower recall of no-think relative to think items was, however, found. Although no independent probe test was included in the present work, it can be assumed, in the light of previous research, as well as considering the neuroimaging and electrophysiological evidence (which will be discussed later) that this lowered recall is a result of active suppression, at least to some extent, most likely in the form of a weakening of the cue-target association, and not mere forgetting or interference (see introduction section for this claim). Additional analyses including only those cue-target pairs which were successfully learned as indicated by correctly identified associations in the study phase, showed similar results, thereby providing a stronger basis for the interpretation of lowered recall of no-think stimuli as reflecting suppression and not mere forgetting or not being learned at all. In the remainder, this lowered recall of no-think relative to think items will thus be assumed as reflecting effective thought inhibition.

Interestingly, even in the pilot study, in which suppression and retrieval were performed only five times, a suppression effect emerged. Considering, findings by Depue et al. (2007), who showed hippocampal deactivation to be consistently present only after several no-think trials, this is surprising at first sight. Given, however, the experimental setup of the pilot study, the emerging suppression effect might reflect the benefit of anticipatory processes

(Hanslmayr et al 2010; Hanslmayr et al 2009). Instructions to retrieve or to suppress were presented prior to each think or no-think block, thereby enabling the participants to prepare for suppression or retrieval in advance. Hanslmayr et al. (2010) have shown that presentation of the no-think instruction one second prior to the cue significantly lowered recall of no-think items relative to the classical simultaneous presentation of the instruction. The same group has additionally isolated a distinctive positive ERP component reflecting these anticipatory processes at the neural level (Hanslmayr et al 2009). This early fronto-parietally distributed positive deflection was shown to predict the degree of amplitude reductions in a later condition-related component (i.e. modulated by think or no-think trials) in response to no-think trials. Functional MRI studies investigating cognitive control mechanisms by means of a task switching paradigm, have shown activation of structures such as the prefrontal cortex to be related to the anticipatory cue (e.g. Dreisbach et al 2002; Lavric et al 2008). Lower recall of no-think than think words shown in the pilot study, regardless of the relatively small number of suppression attempts, might thus reflect the activation of anticipatory neural processes, which in turn signal the need for subsequent activation of neural mechanisms relevant for exerting inhibitory cognitive control.

Another surprising result in the light of existing evidence for more profound suppression with practice was obtained in the TBS study. No improvement of the suppression effect, regardless of the TBS effect, was found on the second measurement day. Although previous studies have shown that recall impairment for no-think items increases with practice (Anderson & Green 2001; Depue et al 2006), no study has used a within-subject repeated measures design. The lack of improved suppression due to repeated performance of the TNT in the modulation study might therefore reflect non-compliance by the subjects, since they were prepared to be asked to recall all of the targets after the experiment. This explanation seems to be supported by the fact that overall recall performance, regardless of task instruction, was better after the second measurement day.

Overall lowered recall performance of suppressed relative to retrieved stimuli by itself, however, is not a new finding. One main interest was the clarification of the inconsistent evidence of impaired or improved suppression performance regarding the emotional valence of the to-be-suppressed stimuli.

Modulation by Valence

As mentioned above, results regarding the beneficial or disadvantageous effect of negative or positive relative to neutral valence on thought suppression have been inconsistent. Depue et al. (2006) and Joormann et al. (2005) showed more effective suppression of negative

relative to neutral pictures or positive words respectively. Marx et al. (2008) could replicate suppression of negative thoughts using word stimuli, although inhibitory control over positive words was shown to be more pronounced in this study. All these studies argue for enhanced inhibitory cognitive control over emotional material (i.e. positive or negative). Results obtained in all three present studies modulating stimulus valence clearly contradict this claim. No interaction between condition and valence at all was observed in the pilot and emotion study, indicating no difference in the effectivity of suppressing neutral, positive or negative words or pictures respectively. The observed interaction with valence in the fMRI study, which compared suppression of neutral and negative pictures, reflected successful suppression (i.e. even below-baseline suppression) for neutral no-think pictures only, while even better recall of suppressed negative no-think relative to baseline pictures was found.

It has been shown that negative stimuli lead to more effortful processing than neutral stimuli in general, resulting in better recall (Clore, Schwarz & Conway 1994; Dolcos, LaBar & Cabeza 2004; Kensinger 2004; Kensinger & Corkin 2004). Ineffective suppression of negative material found in the fMRI study might thus reflect increased demands posed on inhibitory control over negative pictures, which are well elaborated during memory encoding, that are not sufficiently met to result in effective disruptions of these memory traces. This interpretation is in line with the idea posited by Marx et al. (2008) explaining better inhibitory control over positive than over negative words in their own and in the study by Hertel and Gerstle (2003), but contradicts other studies having shown better inhibition of negative stimuli (see above). A generalization of this claim, however, is difficult in the light of evenly well suppressed neutral, positive and negative words and pictures in the pilot and emotion study as well as effective suppression of negative pictures in the TBS study. This is especially surprising regarding the Emotion and TBS study since the same face-picture pairs as in the fMRI study have been used. Word and picture material was selected carefully and shown to differ significantly in emotional valence according to the ratings provided with the IAPS and BAWL material (IAPS: Lang et al 2005; BAWL: Vo et al 2006). The null finding of differences in suppression of emotional stimuli relative to each other or relative to neutral material due to ineffective manipulation of stimulus valence can thus be excluded.

Given that, at least in the emotion study, the same stimulus material was used, except for the inclusion of the positive picture set, it might be important to consider the effect of this additional valence condition in an attempt to explain the inconsistent outcomes in the three present studies. In literature focussing on the processing of emotions in a more general context, it has been suggested that positive affect is associated with increased flexibility and

creative problem solving, which is assumed to be regulated by increased recruitment of frontal brain regions (Ashby, Isen & Turken 1999; Isen, Niedenthal & Cantor 1992). It might thus be possible that the inclusion of a positive valence condition in the TNT, as in the pilot and Emotion study, generally induces a more positive motivational state, leading to the activation of processes more flexibly engaging re-appraisal strategies during the learning and encoding phase of the TNT and eliminating the deleterious effects of negative valence on cognitive inhibition in healthy control subjects reported in some previous studies (Hertel & Gerstle 2003; Marx et al 2008). On the other hand contrasting only negative against neutral stimuli, as in the fMRI study, might increase the focus on the negative pictures during encoding, leading to the memory enhancement effect described by McGaugh (2000). Including only a negative valence condition (i.e. TBS study) in turn lacks a reference against neutral material resulting in the observed effective suppression in the present TBS study and in Depue et al. (2007), suggesting that subjects might have been focussing less or even disregarded the negative content of the pictures. Although only speculative, the idea of context dependent performance in the TNT could not only account for the discrepancy in the current work, but also explains some of the inconsistent findings obtained in previous TNT studies investigating the effect of valence on thought suppression in healthy subjects. None of these studies included neutral, positive and negative target stimuli, instead comparison of suppression was either varied between positive and negative (Hertel & Gerstle 2003; Marx et al 2008) or neutral and negative stimuli (Depue et al 2006). Given, however, that Depue et al. (2006) found better suppression of negative than neutral stimuli alternative explanations, such as certain sample characteristics, have also to be taken into account. Interindividual differences in personality traits and the contribution of the KCNJ6 SNP, which will be discussed in section 4.3. and 4.4., might as well contribute to discrepant findings between previous studies and within this work.

Modulation by TBS

A significant improvement of suppression performance following iTBS applied to the right dlPFC could be shown as indicated by a higher number of good suppressors (i.e. BSI scores above the median) in the verum group than in the sham group. This effect was, however, only present in the additionally performed chi-square tests, weakening its interpretation in favor of showing the possibility to improve voluntary thought suppression by external stimulation of the dlPFC. Given the small cell distribution of a sample size of 33 in a 3 x 2 x 2 repeated measures ANOVA and the difficulty to detect small effects on cognitive tasks known to be induced by iTBS (Grossheinrich et al 2009), nonetheless warrants this

additional analysis, and its outcome favors the idea that increasing activation in the right dlPFC improves the ability to voluntarily suppress thoughts in the TNT. The findings could thus be viewed as supporting the assumption that activation in the right dlPFC reflects the initiation of executive control processes actively controlling thoughts from entering awareness and further validate the TNT as a suitable paradigm eliciting these voluntary suppression mechanisms.

4.2. Discussion of imaging and electrophysiological results

Overall effects of thought suppression will be discussed first, before the influence of valence on the TNT at the neural level is mentioned. Finally, the results gathered by modulating dlPFC activation by means of TBS will be considered.

4.2.1. FNIRS and fMRI – The Neural Network Underlying Thought Inhibition

Successful application of fNIRS to measure the involvement of the dlPFC in thought suppression was shown in the pilot, the emotion and the TBS study. The pilot study showed a condition-related increase and decrease in O_2Hb and HHb, respectively, which was strongly driven by higher signal changes during no-think relative to think trials. To interpret this signal change as reflecting suppression-related activation, additional analyses were performed ensuring that the effect was due to increased activation during no-think and not decreased activation during think relative to baseline trials (i.e. activation during fixation). It was shown that only activation during no-think trials differed significantly from baseline activation, favoring the idea of the dlPFC as contributing to active voluntary thought suppression. Investigation of HHb parameters in the pilot study showed a stronger involvement of the right dlPFC, which is in line with other imaging studies investigating the neural basis of the TNT (Anderson & Green 2001; Depue et al 2007). Although only represented in O_2Hb parameters, the same pattern was found in the emotion study. The condition effect reflected increased activation during no-think relative to baseline trials as well as greater recruitment of the right dlPFC. Furthermore, it was shown, in line with Depue et al. (2007), that signal changes were largest during the first suppression attempts (i.e. the first six no-think trials), probably indicating that decreasing cognitive effort is needed with increasing suppression practice as reflected by a function of increased forgetting with the number of no-think attempts in the post-experimental recall test (e.g. Anderson & Green 2001). Again this effect was stronger in the right dlPFC, indicating its special contribution to thought suppression. As in the pilot and emotion study, the TBS study showed increased O_2Hb and decreased HHb during no-think relative to baseline trials becoming apparent in the condition effect of higher signal change

during no-think than during think trials. Again contribution of the right dlPFC was shown to be larger, as a significant difference between activation during think and no-think was only present in the right hemisphere whereas a significant difference between no-think and baseline activation could be observed in bilateral dlPFC. Significant linear trends for both O_2Hb and HHb showing highest right dlPFC activation during eventually forgotten no-think items, lower activation during successfully retrieved think items and even lower activation during retrieved no-think and forgotten think items support the idea of right dlPFC recruitment during an active inhibition process in the TNT.

The dlPFC, however, is only one of the key structures involved in thought suppression in the TNT. Previous studies have shown the hippocampus to be a second contributor to the willful disruption of established memory traces (Anderson & Green 2001; Depue et al 2010; Depue et al 2007). To further investigate the existing evidence of a fronto-hippocampal network working in sync during cognitive control over thoughts, an fMRI study was performed. Higher activation during no-think trials was observed in the right dlPFC. Again, this effect was shown to be due to stronger increases during suppression than during retrieval of pictures when presented with the associated face cue. Activation in bilateral hippocampus was shown to be lower during suppression than during retrieval attempts. Additionally, showing the same pattern bilateral no-think related deactivation of the amygdala was observed, which is most likely due to the exertion of control over the negative stimulus material used. This will be discussed in more detail later. Lower hippocampal activation during no-think attempts, however, could not only reflect inhibitory control over memory contents but also simple disengagement due to the lack of automatic recollection. As already posed by Bergström et al. (2009a) the default state in the TNT might be not to retrieve memories when presented with the cue but that increased intentional control processes are rather activated to achieve successful retrieval than to voluntary avoid recollection. As previously discussed, to be able to ascribe this effect as reflecting neural components of active thought suppression, additional analyses comparing activation elicited by each condition to baseline were performed. It could be shown that activation during no-think trials dropped below baseline in the right amygdala and the right and left hippocampus. Even stronger evidence that hippocampal disengagement actually reflects an active process of thought inhibition and not mere forgetting is provided by the observation that activation was lower than for forgotten think items and only dropped below baseline levels for items that were actually not remembered anymore post-experimentally, as well as showing a significant modulation of hippocampal activation against baseline only by think trials that were later

remembered and no-think trials that were later forgotten. Time series analysis showed dlPFC activation to be significantly increased relative to baseline during the first half of the experiment, as found already in the emotion study, again supporting the idea that fewer resources are needed for thought suppression after some practice. Hippocampal activation was observed to increase in activation during the first half of the trials and only to drop significantly below baseline in the second half. This might be interpreted as showing the activation of still existing memory traces in the beginning of the TNT phase, which are declining with suppression practice until they are disrupted eventually in the end. This interpretation again fits well with the observation of decreasing memory performance for repeatedly suppressed thoughts at the behavioral level.

It has been proposed that the dlPFC exerts inhibitory top-down control over hippocampal activation during the voluntary suppression of thoughts (Depue et al 2007). This idea is supported by showing that activation in the right dlPFC early in the experiment predicts the amount of decreased activation in the right hippocampus during later no-think trials, strengthening the claim that a fronto-hippocampal network is interactively responsible for the voluntary suppression of thoughts in the TNT.

Additional evidence supporting the implication of the dlPFC and the hippocampus in thought inhibition is provided by showing a significant correlation between the suppression performance as indicated by the BSI and higher activation in the dlPFC in the pilot and the emotion study as well as the BSI for neutral pictures and higher activation in the right dlPFC along with lower activation in the hippocampus in the fMRI study. The BSI represents suppression success as measured by means of final retrieval of no-think relative to baseline stimuli post-experimentally. The higher the BSI, the more effective the subject was at suppressing the stimulus material during the no-think trials. Especially interesting and further indicating the validity of this correlation is the observation that in those studies in which no valence effect was found at the behavioral level (i.e. pilot and emotion study) the correlation of the summed BSI was significant, while in the fMRI study successful suppression of only neutral pictures and not negative pictures was reflected by significant correlations between heightened PFC activation and lowered hippocampal and amygdaloid activation only regarding the BSI for neutral pictures.

Modulation by Valence

Special interest in this work was attributed to clarifying the contradictory findings concerning the dependence of suppression performance in the recall test on the valence of the to-be-suppressed stimuli. Findings at the behavioral level have been discussed above, but

have been found to be inconsistent regarding the ability to suppress negative stimulus material. While the pilot and the emotion study showed no difference in the suppression of neutral, positive and negative words or pictures, the fMRI study indicated difficulties in suppressing more salient negative pictures while showing successful inhibitory control over neutral pictures. This inconsistency is hypothesized to reflect a modulatory effect of including positive stimuli which generally leaves subjects in a more positive motivational state, leading to the activation of processes more flexibly engaging re-appraisal, thereby blunting the valence effect during encoding and in turn eliminating differences in the ability to suppress the different stimulus material. Surprisingly, no study using the TNT has investigated the neural networks recruited for the suppression of neutral or emotional material, although altered underlying neural processes have been suggested but not specified (e.g. Depue et al 2006; Depue et al 2007).

Based on results by Ochsner (2000) reporting stronger memory traces for emotional than for neutral stimuli and a study by Kensinger and Corkin (2004) showing increased prefrontal activation during retrieval of emotional relative to neutral words, increased activation during the suppression of emotional stimuli would be expected in order to successfully suppress well-encoded emotional material. The amygdala, known to be involved in the re-allocation of cognitive resources in order to deal with threatening situations (Wager, Phan, Liberzon & Taylor 2003) and to project to the prefrontal cortex (Iversen, Kupfermann & Kandel 2000) could be a possible mediator of increased prefrontal activation. It would be expected to show increased down-regulation during negative no-think trials to enable activation of the extra cognitive resources needed to disrupt the stronger memory traces for negative cue-target associations, which in turn then should be reflected by stronger signal decreases during negative no-think trials in the hippocampus.

The current work could show in all three studies modulating stimulus valence that prefrontal activation was not mediated by valence, potentially explaining both the context-dependent encoding idea stated in paragraph 4.1. and the finding of ineffective suppression of negative pictures in the fMRI study. As hypothesized above, to achieve effective suppression of emotional stimuli increased prefrontal activity would be expected, unless valence effects were blunted due to re-appraisal during encoding when including a third valence condition. The lack of differential activation in the dlPFC found in the fMRI study in the light of ineffective suppression of negative pictures might reflect insufficient activation of the prefrontal cortex in order to block well-elaborated negative pictures, which might be due to insufficient down-regulation of amygdaloid responses during no-think trials, and

consequently insufficient down-regulation of hippocampal activation in order to suppress the strong negative cue-target link, a pattern found in the fMRI study.

As already mentioned in the discussion of the behavioral data, the idea of context-dependent modulation of encoding processes, however, is only speculative and although results at the behavioral and imaging level can be integrated plausibly within this idea, future studies would be needed to account for processes activated during the encoding phase. Additionally, it has to be taken into account that fNIRS can only measure brain activity at the cortical level and that subcortical processes can only be speculated about when using this method. Nonetheless, the suggested model provides an interesting framework for future research investigating modulation of thought suppression by valence and supports the idea that processes during encoding might influence thought suppression more than previously assumed. However, as mentioned before an alternative explanation might be found considering the influence of certain personality traits and molecular mechanisms on thought suppression abilities, which have not been controlled for in previous studies and which will be discussed in paragraph 4.3. and 4.4..

Modulation by TBS

In an attempt to establish the link between dlPFC activation and thought suppression from another viewpoint, iTBS was applied to the right dlPFC in order to investigate the beneficial effects of stimulating this region on the inhibitory control of thoughts. No direct evidence was found for improved thought inhibition by means of iTBS. Changes in O_2Hb showed stronger activation of the right dlPFC and HHb changes indicated higher activation during no-think than during think trials only in the verum-stimulated group, both, however, without any evidence of an effect of time. Although this is quite speculative it might be that heightened overall activation of the dlPFC during the second measurement, as found in the pattern of O_2Hb signal change, might have blunted this effect. In favor of this claim is the above described higher incidence of good suppressors in the verum than in the sham group following iTBS. It seems thus that to some extent suppression performance can be influenced through external stimulation of the right dlPFC, thereby delivering more direct evidence of its contribution to thought inhibition.

4.2.2. ERPs – The Electrophysiological Underpinnings of Thought Inhibition

Five ERP components were isolated which were modulated condition-specific by either think or no-think trials. Two fronto-centrally distributed positive components peaking at about 200 ms and 560 ms were found to reflect suppression-related effects, showing

reduced amplitudes during no-think relative to think trials. Topographical analyses were performed to investigate whether the two components showing the same think > no-think effect and similar scalp distribution, differ in their topographical distribution and, by this, reflect qualitatively different processes generated by different neural sources or if they reflect activity from one neural generator prolonged in time (Rugg & Coles 1995). Results suggested the latter. This is further supported by the same effect of repeated measurement, both components showing overall higher amplitudes during the first measurement day. The later positive component has already been found in previous ERP studies investigating the electrophysiological correlates of thought suppression in the TNT (e.g. Bergström et al 2009a; Bergström et al 2009b; Bergström et al 2007). In studies investigating memory recollection with the old/new recognition paradigm, the late positive component has been shown to increase in amplitude during successful identification of an item as old and even more so during correct identification of its source (Wilding 2000; Wilding, Doyle & Rugg 1995). Other studies have shown an increase in the late positivity during recollection of an item relative to simply indicating it as being familiar (Duzel, Yonelinas, Mangun, Heinze & Tulving 1997). A lack of amplitude modulation related to old/new judgments has been found in patients with hippocampal lesions (Duzel, Vargha-Khadem, Heinze & Mishkin 2001), strengthening the assumption that the late positivity reflects item-specific recollection vs. recollection avoidance during intentional thought suppression. Bergström et al. (2009a) addressed the critical claim that lower amplitudes in the late positive component during no-think trials might also reflect increased amplitudes due to the activation of retrieval processes and that the inhibition of recollection is the default state which does not necessitate the active modulation of neural processes. By switching the task instruction halfway through the experiment for some of the target stimuli, they could show manipulation-related amplitude modulations. Targets that were suppressed in the second half of the experiment after being retrieved during the first half showed even more amplitude reductions than items that were suppressed throughout the whole experiment. Considered in total, this suggests that the fronto-centrally distributed positive components found in the present study might be the electrophysiological correlate of the suppression-related hippocampal reductions observed in the present work and previous fMRI studies by Anderson et al. (2001) and Depue et al. (2010; 2007). Higher overall amplitudes during the first execution of the TNT procedure might reflect the need for increased engagement of control mechanisms. This is supported by previous findings showing an increase of suppression ability with practice (Anderson & Green 2001). The lack of a no-think specific effect as well as no improvement of suppression

performance at day 2 might, however, as already hypothesized in paragraph 4.1, might have been caused by the within-subject design. Participants knew they would have to recall all of the targets in the end, regardless of earlier task instructions. Increased overall amplitudes might thus reflect increased effort or compliance to follow the experimental instructions during the first encounter with the paradigm.

In addition to the suppression-related positive components, three negative components peaking around 300 ms, 500 ms and 1100 ms showed higher amplitudes during no-think trials. The first left frontally distributed negative component likely reflects an N2-like deflection which has been linked to response inhibition in Go/Nogo tasks (Kok 1986; Kopp et al 1996; Van Veen & Carter 2002) and has been found in earlier ERP studies using the TNT (Bergström et al 2009b; Mecklinger et al 2009). Mecklinger et al. (2009) could show a significant correlation between the N2 elicited by no-think and the N2 elicited by inhibition of motor responses in a Stop Signal task, supporting the claim that it reflects more general electrophysiological processes recruited during the overall stopping of unwanted responses, whether cognitive or motor.

The negative component around 500 ms most likely reflects an N4, which has been observed in the time range between 400 to 600 ms during semantic and nonsemantic conflict monitoring at fronto-central electrodes (Hofmann, Tamm, Braun, Dambacher, Hahne & Jacobs 2008; Holcomb 1993; Kiehl 2000; Yang & Zhang 2011). Hofmann et al. (2008) for example showed increased N4 amplitudes during states of high conflict in a lexical decision task using non-word strings. Yang and Zhang (2011) performed a gambling game study and could show increased negativity in the N4 during high risk situations, which were assumed to reflect situations inducing higher conflict between subjects' motivationally based tendencies to receive new cards and the task instruction predicting low chances of success, given the value of the already received cards. Increased negative amplitudes during no-think trials observed in the present work around 500 ms, might thus reflect attentional processes required to control for the conflict between the more natural process of trying to retrieve an association when presented with its cue and the instruction to avoid this recollection. Supporting this idea are results from LORETA source analyses performed by Hofmann et al. (Hofmann et al 2008), showing that the most likely source of the N4 is the medial frontal gyrus, which has been further established as part of the neural network controlling the suppression of unwanted thoughts in the present work.

The late centrally distributed negative component peaking around 1100 ms showed no-think related higher amplitudes as well. Furthermore, it could be shown that this amplitude

increase reliably predicted behavioral suppression performance and significantly correlated with increased activation during no-think trials in bilateral dlPFC. This suggests that the late negativity might most truly reflect suppression related activation in the dlPFC, while the N2, as suggested above is related to general executive control and the N4 to the re-allocation of attentional resources.

Modulation by iTBS

The only component affected by iTBS was the N4, which showed higher overall amplitudes in the actively stimulated group post treatment in the right-lateralized electrode positions. Findings by Hofmann et al. (2008) that the medial frontal gyrus is the most likely neural generator of the N4 supports the assumption that this effect stems from application of iTBS to the right dlPFC. The lack, however, of a specific effect on the no-think related amplitude modulation limits an interpretation in terms of reflecting improved cognitive control. The finding of a higher number of good suppressors in the verum stimulated group as well as the above described increased dlPFC activity during no-think trials found in the fNIRS data, however, might indicate some beneficial effect on thought suppression by increasing activation in the right dlPFC by means of iTBS. Given that no other component showed modulation by iTBS and given that the N4 has been shown to be involved in conflict monitoring, a process involving the activation of attentional resources, it might be that stimulation of the dlPFC results not so much in the alteration of executive control processes per se, but more in the increased allocation of attentional resources to the task at hand, thereby resulting in more efficient thought suppression, as measured by the number of good and bad suppressors in each group. The N4 in the context of the TNT thus most likely reflects more general attention-related, instead of task-specific processes. This idea is supported by the finding that only the late negativity significantly correlated with increased activation of the dlPFC in the fNIRS data, suggesting a dissociation of task-related strategic late and earlier task-independent attentional processes in the dlPFC signalling the need for thought control. This highlights the benefits of a combination of the two methods, taking advantage of defining the spatial location of neural activation by fNIRS and the more accurate investigation of the temporal pattern of activation within this source by ERPs.

4.3. The Influence of Certain Personality Traits on Thought Inhibition

To clarify potential inter-individual differences modulating the ability to actively suppress thoughts in the TNT, regression analyses were performed including measurements of depressive (i.e. RSS, BDI, HADS-D and ADS) and anxious symptoms (i.e. HADS-A,

PANAS, and STAI). While the anxiety-scales did not predict suppression performance as measured by the BSI, overall higher scores in the depression-scales significantly accounted for decreasing success in thought suppression. Replicating findings by Hertel and Gerstle (2003), especially ruminative tendencies, indicated by increased scores on the RSS (Kühner et al 2007), seemed to interfere with successful control over unwanted thoughts. Rumination is described as one of the key features expressed by patients with MDD (Donaldson & Lam 2004; Donaldson, Lam & Mathews 2007), which have repeatedly been shown to perform worse on tasks requiring inhibitory processes (Merriam, Thase, Haas, Keshavan & Sweeney 1999; Trichard, Martinot, Alagille, Masure, Hardy, Ginestet et al 1995), including the TNT (Hertel & Gerstle 2003; Hertel & Mahan 2008; however Joormann et al 2005). This inhibitory deficit has been linked to hypofrontal functioning during depressive states (Dolan, Bench, Brown, Scott & Frackowiak 1994; Galynker, Cai, Ongseng, Finestone, Dutta & Serseni 1998), which is supported by studies showing heightened recruitment of prefrontal regions during execution of inhibition in patients with MDD in order to perform at the same level as healthy control subjects (Harvey, Fossati, Pochon, Levy, Lebastard, Lehericy et al 2005). Although the sample in the current work only comprised healthy subjects, it might be that lower prefrontal functioning constitutes an endophenotype not of depression itself but of ruminative response style, which surfaces in impaired performance on inhibitory tasks and depressive symptoms. This hypothesis is supported by higher no-think related right dlPFC recruitment with increasing scores on the RSS and other measures of depression observed in both O_2Hb and HHb.

As mentioned above, the anxiety-scales used in the current work did not predict interindividual differences in TNT performance as a whole. The trait subscale of the STAI (Spielberger et al 1970), however, significantly correlated with the BSI. Higher trait anxiety significantly interfered with successful thought inhibition, which has been shown previously by Waldhauser et al. (2010). As with depression, intense states of anxiety have been found to result in lowered executive functioning. Eysenck et al. (2007) discussed this effect as resulting from decreased processing efficiency and resources during a state requiring the organism to prepare for fight or flight reactions considered from an evolutionary viewpoint. This idea is supported by higher right dlPFC activation during no-think trials in subjects displaying higher trait anxiety found in both O_2Hb and HHb, which might reflect compensatory 'over-activation' of cognitive resources in anxious subjects.

Integrating the results of impaired suppression at a behavioral level and increased right dlPFC activation in healthy subjects displaying ruminative and anxious tendencies is

suggestive of related processes leading to worse thought suppression at different described levels. This link, however, is only indirect. An integration of both levels, to gain more direct insight into the influence of interindividual differences concerning depression- and anxiety-related symptoms has been attempted by calculating an interaction term between thought suppression at the neural level in the dlPFC and the outcome at the behavioral level measured by the BSI. This interaction term is thought to reflect only that amount of dlPFC activation explained by actual inhibitory processes; in other words, the higher the interaction between the two factors, the more the observed dlPFC activation contributes to the end results of lower recall of no-think items. Interestingly, despite simple positive correlations between ruminative tendencies, other measures of depressive symptoms and trait anxiety and right dlPFC activation, negative correlations between the same psychometric measures and the dlPFC-BSI interaction term were found in either O_2Hb, HHb or both in the bilateral dlPFC. This suggests that, in spite of higher dlPFC activation, possibly due to attempts to compensate for lower prefrontal activation, subjects scoring higher on the applied psychometric measures are less effective in exerting voluntary thought inhibition. In line with this, an alternative idea is that deficient thought suppression, despite increased dlPFC activation is mediated by altered hippocampal activation. Studies have shown heightened hippocampal activity during rumination (Denson, Pedersen, Ronquillo & Nandy 2009) and in remitted depressed subjects scoring high on the RSS (Arnonea, Pegga, Mckiea, Downeya, Elliotta, Deakina et al 2009). It might thus be that increased dlPFC activation is not sufficient to compensate for higher hippocampal activation in subjects displaying ruminative tendencies, which in turn results in the observed diminished suppression success. In favor of this idea is the observed correlation between deactivation of the left hippocampus during no-think trials below baseline and RSS scores in the fMRI study, reflecting that an increased tendency to display ruminative traits is accompanied by less effective down-regulation of the hippocampus during thought suppression. The effect of this correlation, however, only approached significance and correlations with the dlPFC found in the fNIRS data were not found in the fMRI data. Nonetheless, given, that the samples were comprised of only healthy subjects, that variations in RSS scores were small and taking into account the above mentioned study linking increased hippocampal activation and rumination, data gathered in the current work support the hypothesis of ruminative tendencies interfering with thought suppression due to altered functioning of structures involved in these inhibitory processes.

4.4. Influence of CREB1 and KCNJ6

CREB1 has been linked to processes of long-term potentiation, which is known to be the neural basis of synaptic plasticity and memory formation (Alberini 2009; Josselyn & Nguyen 2005). CREB is expressed throughout the brain, including the hippocampus and it has been shown in rodents that poor performance in the Morris water maze was directly correlated with decreased levels of hippocampal CREB (Brightwell, Gallagher & Colombo 2004). Therefore, the current work was interested in whether a functional polymorphism (i.e. rs2253206) in the CREB1 gene might be implicated in interindividual differences in suppression performance in the TNT. An A-to-G transition has been shown to diminish activity of the CREB promoter, increasing the risk for disorders associated with impaired executive functioning such as depression (Zubenko et al 2002). Surprisingly, although thought suppression in the TNT is being accomplished by structures known to be involved in executive functions, no evidence was found for worse performance of carriers of at least one G-allele. This might, since analyses were performed at an explorative level and not in a pre-stratified sample, be due to an insufficient sample size, considering the very small effect sizes of genetical analyses. In favor of this, the interaction, which would indicate better suppression performance of homozygous carriers of the A-allele, just did not achieve significance at trend-level. Given the established role of CREB in the formation of long-term memories, it might, however, also be that the lack of an effect found on thought suppression reflects the long-term memory independent processes in the TNT. It has long been discussed to what extent the TNT measures long-term disruption of memory traces and a very recent study by Meier et al. (2011) has shown a rebound effect of no-think items when memory was probed again one week later. Considering, the more short-term and non-lasting disruption of cue-target associations in the TNT, a lack of an effect of diminished CREB1 functioning through an A-to-G transition, might reflect this long-term memory independence of the TNT at a molecular level. It has furthermore been suggested that the essential mechanism of CREB1 might be compensated for by other unknown variables (Alberini 2009; Josselyn & Nguyen 2005).

The other SNP the current work was interested in, is a G-to-A transition in the KCNJ6 gene (i.e. SNP rs2070995), which has recently been linked with an increased risk of displaying ruminative tendencies and developing anxiety-related disorders (Lazary et al 2011). It could be shown that carriers of at least one A-allele performed worse in the TNT, as reflected by similar recall of think and no-think items in the recall test. These findings are very interesting regarding the strong detrimental influence of ruminative and anxious tendencies on thought suppression discussed in paragraph 4.3. Investigation of differences at

the neurophysiological level revealed more extensive activation in the right dlPFC during no-think trials in carriers of at least one A allele. This increased activation in the absence of respective suppression performance by A allele carriers, might reflect the negative correlation found between the interaction term of dlPFC activation and the BSI with RSS and trait anxiety scores, indicating insufficient additional recruitment of prefrontal regions. It has been stated that higher rumination scores are linked to increased hippocampal activation (Denson et al 2009), which is not sufficiently compensated for even by increased activation of top-down control regions. This claim was supported by showing less effective hippocampal down-regulation below baseline during no-think trials in subjects displaying high ruminative and anxious tendencies. Integrating the results obtained at the behavioral, neurophysiological and genetical level, it seems very likely that the KCNJ6 G-allele at least partly reflects the underlying molecular mechanisms of efficient inhibitory control.

5. Summary and Outlook

The present work was dedicated to the investigation of the neural mechanisms underlying cognitive inhibition/thought suppression as well as the different variables influencing these mechanisms at the cognitive, the neurophysiological and electrophysiological as well as the molecular level. Thought suppression was probed by using Anderson's TNT first introduced in Science in 2001 and its underlying neural mechanisms were investigated by means of fNIRS, fMRI, ERP and TBS.

Neurophysiological data collected with fNIRS and fMRI have added up to the existing evidence of a fronto-hippocampal network working in sync during the voluntary inhibition of unwanted thoughts. Some evidence has been presented suggesting that external stimulation of right dlPFC activation by means of iTBS might improve thought suppression, strengthening the evidence for an implication of this region in the TNT. By combining fNIRS with ERP, a fronto-centrally distributed negative component around 1100 ms could be isolated, most likely reflecting suppression-related activation of the dlPFC. Suppression-related amplitudes showed significant correlations with no-think related activation in the dlPFC and predicted the behaviorally measured suppression effect. Suppression-specific increases of amplitudes in the actively stimulated iTBS group were shown in the N4. Given that no suppression-related iTBS effect was observed in the dlPFC, a dissociation of earlier task-independent attentional processes, as measured by ERPs and late task-related strategies in the dlPFC reflected by the two negative components has been suggested. Two positive components around 200 and 550 ms showing no-think related amplitude reductions were hypothesized to most likely reflect prolonged hippocampal down-regulation. An N2-like component was identified and hypothesized to reflect general top-down control mechanisms exerted during paradigms probing executive functions. This dissociation points to the advantage of combining functional imaging methods and electrophysiological measures in disentangling activation patterns in time, which might at first seem to reflect the same neurophysiological process.

Given inconsistencies in the previous literature, it was considered how stimulus valence would influence thought suppression by manipulating the emotional content of the to-be-suppressed target. Inconsistent findings of the current work regarding the ability to suppress negative word or picture stimuli leave this debate unresolved. It has, however, been hypothesized that performance in the TNT might depend on the combination of valence conditions included in the paradigm. During the learning/encoding phase, inclusion of a positive valence condition might lead to more flexible processing strategies, blunting the

valence effect. Just comparing neutral and negative stimuli might, on the contrary, have introduced an increased contrast between both valences, increasing the subjects focus on the negative stimuli resulting in the inability to suppress negative pictures in the fMRI study. The latter has already been shown by Hertel and Gerstle (2003) and Marx et al. (2008) when comparing positive and negative words and which has been ascribed to results showing better encoding and memory for negative material (Kensinger & Corkin 2004; Ochsner 2000).

Neurophysiological evidence in the present work suggested insufficient down-regulation of the amygdala during suppression of negative pictures as leading to the lack of cognitive resources required to suppress the well-encoded link between face cues and negative pictures. This would require additional activation of the dlPFC relative to the suppression of neutral pictures, in turn resulting in insufficient decrease of hippocampal activation, where face-picture associations have been stored during the learning phase. Alternatively, it has been suggested that inconsistent findings regarding the suppression of negative stimuli or suppression at all might be due to certain personality traits and/or genetic variables, found in the present work to contribute to thought inhibition in the TNT. Rumination, which is a key feature in MDD and describes the extent an individual is coping with depressive moods (Nolen-Hoeksema 2000), has been shown to be a valid predictor of thought suppression performance. Increased ruminative tendencies led to worse suppression performance, which is in line with data by Hertel and Gerstle (2003) and which in the present work has been linked to less effective recruitment of the dlPFC and in turn less effective down-regulation of hippocampal activity during no-think trials. Trait anxiety has also been shown to interrupt effective thought suppression despite higher, however inefficient recruitment of the dlPFC. Both, rumination and trait anxiety have been associated with disorders known to lead to decreased performance on tests of executive functions, strengthening the assumption that the TNT is a measure of an active mechanism exerting control over memory processes paralleling the top down executive control over motor responses in the Go/Nogo paradigm (Anderson & Green 2001). Complementing the findings regarding ruminative tendencies and decreased thought inhibition a functional polymorphism in the KCNJ6 gene, encompassing a G-to-A transition, has been shown to disrupt thought suppression despite increased activation of the dlPFC.

Limitations

While the current studies have added a lot of evidence concerning the existence and modulation of an active thought suppression mechanism which can be recruited to adapt the mental environment in response to certain cues and which can result in the weakening of pre-

established cue-target associations, some limitations have to be mentioned. The first and most prominent limitation is the lack of evidence for below-baseline suppression, which has been regarded as the indicator of effective suppression (Anderson & Green 2001). Lower findings of no-think than think stimuli could be described as an effect of simply practiced recall of only some of the items (i.e. think). In other words, worse recall of no-think than think items might be an effect of memory enhancement for practiced items (i.e. think) and not be viewed as reflecting a disruption of an existing memory trace due to voluntarily exerted cognitive control. In relation to this issue, it has to be remarked that the present work did not include an independent probe recall test due to practical reasons when using picture stimuli. Only the pilot study using word stimuli would have provided the opportunity to test recall by means of a semantically-related cue and the initial letter of the target word. It has been advocated by Anderson and Green (2001) that impaired recall of no-think relative to think or baseline targets might also be explained by alternative mechanisms such as the formation of new associations between the cue and a divisionary thought or, as already mentioned, simply a degradation of the association between cue and target due to the lack of practice. If, however, recall would be also shown to be impaired when presented with a semantically-related cue, interference by a newly formed association could be ruled out. One could thus argue that, in the current work, lower recall of suppressed relative to retrieved items might only reflect a practice or interference effect. Given, however, the vast amount of data on the TNT showing lower recall of no-think than think stimuli in both same and independent probe recall tests (e.g. Anderson & Green 2001; Anderson et al 2004; Bergström et al 2009b; Lambert et al 2010), the paradigm seems well-established as measuring cognitive control over thoughts by means of weakening cue-target associations during suppression and it can be assumed that the observed difference in recall of think and no-think items reflects these control processes. Furthermore, the current work could replicate findings of previous imaging and electrophysiological studies supporting the evidence of a fronto-hippocampal network which is activated during voluntary thought suppression and whose activation level is directly related to impaired recall at the behavioral level. Considering both, the paradigm being a well-established measure of cognitive inhibition and replication of the neural pattern previously observed by other groups, it can be assumed, even in the absence of testing with an independent probe, that results presented in the current work add to the status quo of thought suppression mechanisms.

Another factor to be mentioned is the use of a fixation baseline in the functional imaging studies. Contrasting a task to an unconstrained baseline may contain an element of

uncertainty due to the lack of knowledge about the cognitive processes the participant is engaging in at the time of the fixation. Additional analyses performed in the current work to clarify the underlying pattern of the think/no-think contrast in the dlPFC and hippocampus as well as to show hippocampal deactivation during no-think trials, have thus to be interpreted with caution. Future studies should attempt to include more constrained baseline trials in order to be able to non-mistakenly ascribe the causes of relative activation and deactivation in the ROIs investigated in the present work. Some certainty, however, that comparisons against the fixation baseline in the present studies accurately reflect relative changes during think and no-think trials respectively can be assumed given that both conditions would be evenly affected by unpredictable fluctuations during fixation.

Outlook

Supporting the role of the right dlPFC as the key structure exerting inhibitory control on the hippocampus, some beneficial effects of iTBS have been found. As already discussed in the according section, the evidence, however, is only indirectly indicative of a causal connection between iTBS and improved suppression performance. This has been assumed to be due to the within-subject design used in the present work. While normally in the TNT the recall test comes as a surprise, in the TBS study the subjects knew that they were to recall all pictures irrespective of previous task instructions. It has been orally reported by some subjects that, knowing this, they attempted to retrieve also the no-think items during the inter-trial interval following the face cue. Given that despite this potential non-compliance during the TNT more good suppressors were found in the verum-stimulated group, application of TBS as a measure of the contribution of the dlPFC to cognitive control provides an interesting tool in future studies using the TNT. It would, however, be important to use a more appropriate counter-balanced or between-subject design preventing obscuration of effects due to familiarity with the paradigm. Furthermore, it would be interesting to apply a cTBS protocol, which has been shown to temporarily disrupt activity in the underlying cortical region (Huang et al 2005), in order to investigate suppression performance in a state of diminished prefrontal functioning. This would be especially interesting, considering evidence in the current work suggesting inefficient activation of the dlPFC in subjects displaying high ruminative and anxious tendencies as well as evidence of impaired TNT performance in disorders linked to lowered prefrontal activation and dysfunctional executive control such as ADHD (Depue et al 2010) and depression (Hertel & Gerstle 2003).

Some success has been presented in the present work linking the electrophysiological correlates of thought suppression to the fronto-hippocampal network observed in fNIRS.

Source localization analyses[1] could provide further insight into the neural structures underlying the single ERP components showing suppression-related amplitude modulations and are needed to probe the hypothesized dissociation between general attentional and task-related processes both executed by the dlPFC and contributing to successful thought inhibition.

Future studies are needed to address these points. The current studies, however, provide an interesting new starting point for this research by further having outlined behavioral, neurophysiological and molecular features of the TNT, contributing to the evidence of a neurobiological model of memory control. Although very recently Meier et al. (2011) presented a study showing that impaired recall of suppressed items was only temporary, this work confirms the existence of a process by which people can actively prevent unwanted experiences from entering awareness and further specified the neural system underlying these processes.

By means of investigating thought suppression at different levels, the current work supports the idea of the TNT reflecting an executive control mechanism, which has been shown to be sensitive to alterations in stimulus valence to some extent, neurophysiological functioning as indicated by its sensitivity to iTBS as well as functional modulations at the molecular level and most importantly to personality traits, such as rumination and trait anxiety which have been linked to deficient executive functioning before.

[1] sLORETA was not performed in the current work due to the use of only 22 scalp electrodes.

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7. Appendix

Table A - 1: List of word stimuli from the BAWL used in the pilot study.

Label	Word	Valence	Arousal	Imageability	L	P	S	Frequency
neutral	Nachbar	-0.10 ± 0.57	2.38 ± 0.81	5.00 ± 1.50	7	6	2	43.50
	Reihe	0.00 ± 0.73	1.94 ± 0.87	3.27 ± 1.45	5	3	2	152.67
	Stelle	0.00 ± 0.55	2.22 ± 1.00	3.38 ± 1.86	6	5	2	265.00
	Zahl	0.06 ± 0.60	2.22 ± 1.06	5.81 ± 1.88	4	3	1	197.83
	Arbeit	0.05 ± 1.43	2.83 ± 0.79	3.41 ± 1.56	6	5	2	532.00
	Gekicher	0.00 ± 1.15	3.11 ± 0.96	5.11 ± 1.36	8	7	3	0.67
	Kuhle	-0.05 ± 0.89	1.80 ± 0.89	3.23 ± 1.57	5	4	2	0.67
	Magma	0.00 ± 0.94	3.05 ± 1.31	5.67 ± 2.00	5	5	2	1.33
	Organ	0.00 ± 0.92	2.74 ± 0.99	4.68 ± 1.81	5	5	2	55.00
	Ruecklage	0.03 ± 1.57	2.11 ± 0.96	1.96 ± 1.22	8	7	3	39.50
	Tatsache	0.00 ± 0.92	2.50 ± 0.70	1.88 ± 1.40	8	7	3	159,33
	Zeugin	0.00 ± 0.94	3.35 ± 1.17	4.11 ± 1.90	6	5	2	1.67
	Aussage	0.00 ± 0.47	2.22 ± 0.94	2.33 ± 1.22	7	6	3	53.33
	Gelenk	0.05 ± 0.60	2.32 ± 1.00	4.18 ± 1.79	6	6	2	2.00
	Kuppe	0.05 ± 0.83	2.22 ± 1.11	3.50 ± 1.92	5	4	2	2.17
positive	Harmonie	2.50 ± 0.71	1.76 ± 1.20	3.44 ± 1.13	8	7	3	9.50
	Urlaub	2.45 ± 0.51	2.56 ± 1.09	5.09 ± 1.82	6	5	2	45.67
	Idylle	2.50 ± 0.71	1.82 ± 1.07	5.33 ± 0.71	6	5	3	1.50
	Sommer	2.50 ± 0.69	2.22 ± 1.31	5.64 ± 1.40	6	5	2	68.33
	Wahrheit	2.50 ± 0.85	3.00 ± 1.27	2.22 ± 1.39	8	6	2	125.50
	Zuhause	2.50 ± 0.71	1.88 ± 1.11	5.33 ± 1.32	7	6	3	2.83
	Frieden	2.53 ± 0.71	1.61 ± 1.20	4.73 ± 1 85	7	6	2	186.00
	Freund	2.56 ± 0.61	2.05 ± 1.13	6.04 ± 1.18	6	5	1	206.17
	Natur	2.35 ± 0.75	1.89 ± 1.08	4.91 ± 1.57	5	5	2	118.33
	Heilung	2.60 ± 0.52	2.35 ± 1.27	3.22 ± 1 39	7	5	2	8.33
	Sonne	2.60 ± 0.060	2.89 ± 1.18	6.41 ± 1.10	5	4	2	90.33
	Glück	2.62 ± 0.65	2.93 ± 1.53	3.81 ± 1.92	5	4	1	94.50
	Freude	2.70 ± 0.57	3.41 ± 1.33	4.27 ± 1.55	6	5	2	86.33
	Paradies	2.80 ± 0.42	2.29 ± 1.65	5.33 ± 1.22	8	7	3	12.00
	Liebe	2.90 ± 0.31	3.63 ± 1.61	3.73 ± 2.14	5	4	2	113.50
negative	Giftgas	-3.00 ± 0.00	4.22 ± 1.00	3.78 ± 2.17	7	7	2	1.00
	Krieg	-2.90 ± 0.32	4.57 ± 0.60	5.44 ± 1.74	5	4	1	315.33
	Attentat	-2.40 ± 0.70	4.71 ± 0.59	4.67 ± 2.00	8	7	3	6.83
	Nazi	-2.90 ± 0.32	4.67 ± 0.69	4.89 ± 1.76	4	4	2	16.50
	Unfall	-2.35 ± 0.67	4.24 ± 0.70	4.32 ± 1.81	6	5	2	51.83
	Alptraum	-2.80 ± 0.63	4.53 ± 0.62	4.67 ± 1.94	8	7	2	2.67
	Folter	-2.80 ± 0.52	4.68 ± 0.58	4.23 ± 1.60	6	6	2	2.50
	Gefängnis	-2.26 ± 0.79	3.05 ± 1.39	6.58 ± 0.76	9	8	3	52.67
	Mord	-2.80 ± 0.42	4.44 ± 0.92	5.33 ± 1.12	4	4	1	42.00
	Pest	-2.80 ± 0.42	4.00 ± 1.08	4.67 ± 1.12	4	4	1	2.67
	Tod	-2.80 ±0.63	4.06 ±1.21	4.44 ± 1.94	3	3	1	169.83
	Atombombe	-2.79 ± 0.48	4.42 ± 1.12	6.15 ± 1.19	9	9	4	48.17
	Tyrann	-2.60 ± 0.84	3.81 ± 1.12	4.78 ± 0.97	6	5	2	1.67
	Leiche	-2.45 ± 0.76	4.14 ± 0.85	5.32 ± 1.49	6	4	2	24.67
	Sucht	-2.30 ± 0.48	4.00 ± 0.97	4.00 ± 1.58	5	4	1	2.00

Table A - 2: List of IAPS pictures used as target pictures in the emotion study, the fMRI and the TBS study

Label	IAPS picture no.	Description	Valence	Arousal	Study
neutral	2597	Market	5.61 ± 1.26	4.09 ± 2.10	Emotion; fMRI
	1935	Hermit crab	4.88 ± 1.44	4.29 ± 1.95	
	7041	Baskets	4.99 ± 1.12	2.60 ± 1.78	
	7640	Skyscraper	5.00 ± 1.31	6.03 ± 2.46	
	7546	Bridge	5.40 ± 1.13	3.72 ± 2.16	
	2570	Man	4.78 ± 1.24	2.76 ± 1.92	
	4000	Artist	4.82 ± 1.66	3.97 ± 2.15	
	2840	Chess	4.91 ± 1.52	2.43 ± 1.82	
	7207	Beads	5.15 ± 1.46	3.57 ± 2.25	
	2487	Musician	5.20 ± 1.80	4.05 ± 1.92	
	1675	Buffalo	5.24 ± 1.48	4.37 ± 2.15	
	2890	Twins	4.95 ± 1.09	2.95 ± 1.87	
	7036	Shipyard	4.88 ± 1.08	3.32 ± 2.04	
	2514	Woman	5.19 ± 1.09	3.50 ± 1.81	
	2191	Farmer	5.30 ± 1.62	3.61 ± 2.14	
	2518	Quilting	5.67 ± 1.66	3.31 ± 1.88	
	1121	Lizard	5.79 ± 1.61	4.83 ± 1.98	
	1670	Cow	5.82 ± 1.63	3.33 ± 1.98	
positive	1710	Puppies	8.34 ± 1.12	5.41 ± 2.34	Emotion
	2070	Baby	8.17 ± 1.46	4.51 ± 2.74	
	2091	Girls	7.68 ± 1.43	4.51 ± 2.28	
	2165	Father	7.63 ± 1.48	4.55 ± 2.55	
	2340	Family	8.03 ± 1.26	4.90 ± 2.20	
	2530	Couple	7.80 ± 1.55	3.99 ± 2.11	
	4626	Wedding	7.60 ± 1.66	5.78 ± 2.42	
	4660	Erotic Couple	7.40 ± 1.36	6.58 ± 1.88	
	5200	Flowers	7.36 ± 1.52	3.20 ± 2.16	
	5830	Sunset	8.00 ± 1.48	4.92 ± 2.65	
	5831	Seagulls	7.63 ± 1.15	4.43 ± 2.49	
	5833	Beach	8.22 ± 1.08	5.71 ± 2.66	
	7502	Castle	7.75 ± 1.40	5.91 ± 2.31	
	8170	Sailboat	7.63 ± 1.34	6.12 ± 2.30	
	8496	Water-Slide	7.58 ± 1.63	5.79 ± 2.26	
	1604	Butterfly	7.11 ± 1.41	3.30 ± 2.17	
	1750	Bunnies	8.28 ± 1.07	4.10 ± 2.31	
	2311	Mother	7.54 ± 1.37	4.42 ± 2.28	
negative	6415	Dead Tiger	2.21 ± 1.51	6.20 ± 2.31	Emotion; fMRI;
	9561	Sick Kitty	2.68 ± 1.92	4.79 ± 2.29	Modulation
	2799	Funeral	2.42 ± 1.41	5.02 ± 1.99	
	2683	War	2.62 ± 1.78	6.21 ± 2.15	
	9910	Car Accident	2.06 ± 1.26	6.20 ± 2.16	
	3181	Battered Female	2.30 ± 1.43	5.06 ± 2.11	
	6243	Aimed Gun	2.33 ± 1.49	5.99 ± 2.23	
	9340	Garbage	2.41 ± 1.48	5.16 ± 2.35	
	9320	Vomit	2.65 ± 1.92	4.93 ± 2.70	
	6940	Tank	3.53 ± 2.07	5.35 ± 2.02	
	9390	Dishes	3.67 ± 1.58	4.14 ± 2.52	
	9440	Skulls	3.67 ± 1.86	4.55 ± 2.02	
	9041	Scared Child	2.98 ± 1.58	4.64 ± 2.26	

9265	Hung Man	2.60 ± 1.52	4.34 ± 2.09	
2750	Bum	2.56 ± 1.32	4.31 ± 1.81	
9921	Fire	2.04 ± 1.47	6.52 ± 1.94	
1274	Roaches	3.17 ± 1.53	5.39 ± 2.39	
9560	Duck In Oil	2.12 ± 1.93	5.50 ± 2.52	
3230	Dying Man	2.02 ± 1.30	5.41 ± 2.21	Modulation
9220	Cemetery	2.06 ± 1.54	4.00 ± 2.09	
6831	Police	2.59 ± 1.50	5.55 ± 2.16	
9611	Plane Crash	2.71 ± 1.95	5.75 ± 2.44	
9620	Shipwreck	2.70 ± 1.64	6.11 ± 2.10	
2688	Hunters	2.73 ± 2.07	5.98 ± 2.22	
2981	Deer Head	2.76 ± 1.94	5.97 ± 2.12	
9415	Handicapped	2.82 ± 2.00	4.91 ± 2.35	
7380	Roach On Pizza	2.46 ± 1.42	5.88 ± 2.44	
9040	Starving Child	1.67 ± 1.07	5.82 ± 2.15	
9102	Heroin	3.34 ± 1.76	4.84 ± 2.50	
2718	Drug Addict	3.65 ± 1.58	4.46 ± 2.03	
2692	Bomb	3.36 ± 1.61	5.35 ± 2.19	
9181	Dead Cows	2.26 ± 1.85	5.39 ± 2.41	
9290	Garbage	2.88 ± 1.52	4.4 ± 2.11	
1050	Snake	3.46 ± 2.15	6.87 ± 1.68	
9230	Oil Fire	3.89 ± 1.58	5.77 ± 2.36	
9926	Flood	3.85 ± 1.59	4.83 ± 1.95	

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Affidavit
(Eidesstattliche Erklärung)

I hereby declare that my thesis entitled

Investigation of variables influencing cognitive inhibition: from the behavioral to the molecular level / Untersuchung der Einflußgrößen kognitiver Unterdrückung: Vom verhaltensorientierten zum molekularen Ansatz

is the result of my own work. I did not receive any help or support from commercial consultants. All sources and/or materials applied are listed and specified in the thesis.
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München, 25-07-2011 ……