Neurophysiological Effects of Hypnotherapy Compared to Cognitive Behavioral Therapy for Depression Measured with fNIRS

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List of Abbreviations

ACC	Anterior Cingulate Cortex
BOLD	Blood oxygen level dependent
CBT	Cognitive Behavioral Therapy
CEN	Central Executive Network
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
EBA	Extrastriate Body Area
EEG	Electroencephalography
ESP	Emotional Stroop Paradigm
FC	Functional Connectivity
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-infrared Spectroscopy
HT	Hypnotherapy
IFG	Inferior Frontal Gyrus
NIBB	Network Interaction Based Biotype Model
OFC	Orbitofrontal Gyrus
PCC	Posterior Cingulate Cortex
PCu	Precuneus
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PHQ-9	9-item Patient Health Questionnaire Depression Scale
SAC	Somatosensory Association Cortex
SN	Salience Network
STS	Superior Temporal Sulcus
WIKI-D	Wirksamkeit Aktivierend-Kognitionsfokussierter im Vergleich zu Hypnotherapeutischer Therapie bei leichten bis mittelgradigen Depressionen

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The effects of hypnotherapy compared to cognitive behavioral therapy in depression: a NIRS-study using an emotional gait paradigm	Haipt, A., Rosenbaum, D., Fuhr, K., Giese, M., Batra, A., & Ehlis, A.-C.	1	90	80	90	95
Differential Effects of Hypnotherapy and Cognitive Behavioral Therapy on the Default-Mode Network of Depressed Patients	Haipt, A., Rosenbaum, D., Fuhr, K., Batra, A., & Ehlis, A.-C.	1	90	80	92	95
How psychotherapy changes the depressed brain: activity in the left prefrontal cortex reduced after Hypnotherapy but not Cognitive Behavioral Therapy	Haipt, A., Geiger, N., Schunk, S., Fuhr, K., Batra, & A., Ehlis, A.-C.	1	90	80	97	95

Zusammenfassung

Hypnose und hypnotische Trance waren Teil von Heilungsritualen, seitdem es geschriebene Geschichte gibt. In der modernen Psychotherapie werden sie seit deren Ursprung genutzt; heutzutage meist als ein Element einer umfassenden Psychotherapie, der Hypnotherapie (HT). Ihre Wirksamkeit zeigte sich bei verschiedenen Störungen, wohingegen die ihr zugrundeliegenden Mechanismen noch weitgehend unerforscht sind. Auf neurophysiologischer Ebene wird Hypnose/Trance mit einem zerebralen Hauptnetzwerk, dem Default Mode Network (DMN), in Verbindung gebracht. Im psychiatrischen Kontext wurden die zerebralen Mechanismen der HT bisher bei zwei Störungen untersucht, welche sich stark voneinander unterscheiden und sehr spezifisch sind. Depression hingegen ist eine weiterverbreitete Krankheit, welche mit verschiedenen Mechanismen im Gehirn in Verbindung gebracht wird. Dazu gehört eine Störung des DMN, sowie des temporalen und präfrontalen Kortex (PFC). Kognitive Verhaltenstherapie (KVT) hat sich als erfolgreiche Behandlung bei Depressionen herausgestellt. In einer großen Studie haben wir erstmalig 75 depressive Patienten vor und nach einer HT oder KVT untersucht. Dazu führten wir mit funktioneller Nahinfrarotspektroskopie (fNIRS) Messungen der Gehirnaktivität während drei Paradigmen durch, jedes mit bestimmten Hypothesen verbunden. Die Ergebnisse zeigen eine signifikante Symptomverbesserung in beiden Therapiegruppen. Therapieeffekte wurden für zwei Komponenten des DMN gefunden: Die Konnektivität innerhalb posteriorer Mittelregionen nahm ab, eine interhemisphärische Verbindung nahm in der HT Gruppe zu. Weitere HT spezifische Effekte fanden wir für den linken PFC (Aktivitätszunahme) und den temporalen Kortex (Aktivitätsveränderung abhängig von Rumination). Diese Ergebnisse weisen stark auf eine Veränderung des DMN während einer HT hin, was mit dessen Rolle in hypnotischer Trance zusammenhängen könnte. Außerdem helfen sie uns dabei, sowohl das Phänomen „Hypnose“ als auch „Depression“ besser zu verstehen, um letztendlich präzisere Behandlungen entwickeln zu können. Unklar bleibt das Ausbleiben eines KVT spezifischen Effekts. Einschränkend für unsere Forschungsfrage ist der Mangel an Grundlagenforschung, welche, neben Replikationen unserer Ergebnisse, dringend gebraucht wird. Dennoch ist unsere Arbeit ein wichtiger erster Schritt in Richtung Passung von Patienten und Therapieoptionen, sowie deren grundlegendes Verständnis.

Abstract

Hypnosis and hypnotic trance have been used as parts of healing rituals since the earliest of recorded history. In modern times their application dates back to the beginnings of psychotherapy, where it is now most commonly used as one aspect in a comprehensive psychotherapy, namely Hypnotherapy (HT). Its efficacy has been shown for multiple disorders, whereas underlying processes have not yet been understood. On neurophysiological level, hypnosis/hypnotic trance has been connected to the involvement of a cerebral core network, the Default Mode Network (DMN). In a psychiatric context, the underlying cerebral processes of HT have only been investigated twice, for two very different and specific conditions. By contrast, depression is a widespread disorder and multiple cerebral mechanisms have been associated with it, including malfunctioning of the DMN, temporal and prefrontal cortex (PFC). Cognitive Behavioral Therapy (CBT) has proven itself as beneficial treatment for depressed patients. In a large, first-of-its-kind study we measured 75 depressed patients before and after psychotherapy, either HT or CBT. We used functional Near-infrared Spectroscopy (fNIRS) to assess cerebral activation during three different paradigms, of which each was associated with distinct hypotheses. Results show a significant symptom reduction in both therapy groups. Significant treatment effects were found for two components of the DMN: While the Functional Connectivity (FC) within posterior midline regions of the DMN decreased in both therapy groups, an interhemispheric connection increased only in the HT group. HT-specific effects were also found for the left PFC (activity decreased) and the temporal cortex (activity changed depending on the extent of the patient's rumination). These findings strongly hint towards an involvement of the DMN during HT which could be connected to its role during hypnotic trance. Furthermore, they help us gain a better understanding of the phenomena "hypnosis" as well as "depression" to finally develop more precise treatment. The lack of CBT-specific effects remains unclear. Limitations of our study lie in the lack of basic research in many areas combined in our research objective. Much more groundwork as well as replications are needed to validate our results. Still, this study serves as important first steppingstone in finding treatment options for different patients and understanding their mechanisms.

1. Introduction

Have you ever googled “hypnosis”? If so, you can divide the results into two categories: Either you get videos of people calling themselves hypnotists and promising to hypnotize you via YouTube, pictures of a pendulum swinging back and forth or of black and white swirls giving you the impression of being sucked into the screen. Or you find articles asking what hypnosis truly is. Many say it is a physiological state and offer definitions and characteristics of hypnotic states. A simple google search reflects the range of public approach to hypnosis: as a mystic phenomenon that has fascinated people for over 2000 years, and an area of scientific research, especially in the past centuries. Scientists have tried to find explanations and physiological correlates to this state of consciousness. Today, science acknowledges hypnosis as a deeply subjective state, and it attempts to objectify this state by finding common factors in hypnotized individuals. Despite and beyond this, hypnosis, or similar methods, have been successfully used in spiritual, religious and healing rituals from the earliest recorded history (Hammond, 2013). In this dissertation I examine the long-term effects of hypnosis on the brain and its effects in a therapeutic context. Specifically, I researched the effects of Hypnotherapy (HT) on the brain in depressed patients. We will first review hypnosis and hypnotic trance, where it comes from (historic perspective) and where it stands today, including its therapeutic application and its neurophysiology. Then I will review depression as a specific clinical condition with focus on its neurophysiology and treatment. Last, I will introduce the measurement method used in this study, prior to presenting the hypotheses.

1.1 Definitions

Hypnosis describes an altered state of consciousness as well as a procedure inducing this altered state (American Pschological Association, n.d.). In this thesis the term *hypnosis* is used to describe the procedure of inducing an altered state of consciousness, here called *hypnotic trance*[1], while the application of this procedure in a therapeutic context is called *HT*. The term *hypnosis* is derived from the Greek word “hypnos” (engl. “sleep”), evoking the image of a sleep-like state. Although it sometimes appears as sleep from the outside, hypnotic trance entails other specific

[1] In most studies no distinction is made between the induction (hypnosis) and the hypnotic trance itself; I chose to print both terms when the content demands it.

characteristics like “aroused, attentive focal concentration coupled with a relative suspension of peripheral awareness” (Spiegel and Moore, 1997; p. 1181). This definition includes 1) Absorption, or the intense involvement of a central object of concentration, 2) Dissociation in which certain perceptions are excluded from awareness and 3) Heightened suggestibility in which a person is more likely to accept outside input (e.g. instructions, guidance) without cognitive censor or criticism (Spiegel & Moore, 1997). In HT, hypnosis and hypnotic trance are used to facilitate changes desired by the patient (Revenstorf & Peter, 2009). In addition, the patient learns to control symptoms and physiological functions that are usually consciously inaccessible (Whorwell, 2011).

1.2 History

Phenomena that seem strikingly similar to what we consider hypnosis and hypnotic trance today have been part of healing or religious rituals since the earliest of recorded history (Hammond, 2013) and probably even preceded these times. Hypnotic rituals are found in many cultures, from ancient Hindu practices to ancient Rome and Greece, Egypt to pre-Columbian America (Hammond, 2013). In Europe hypnotic phenomena played a role for centuries in religious practices like exorcism, finding its way into the medical field since the middle ages, beginning with Paracelcus, and later with Franz Anton Mesmer, who used imaginative hypnotic methods and ideas about magnetism to heal others (Hammond, 2013). The priest Johann Gassner, a contemporary colleague of Mesmer, claimed to conduct exorcism with his “patients”. However, looking at his methods more closely shows, that he used hypnotic self-control techniques, which evoked criticism by the clergy (Peter, 2000). Thus, it seems the separation of hypnosis/hypnotic trance used in religious rituals and as a therapeutic tool started as early as 1775 (Hammond, 2013; Peter, 2000). Since then, it has been used as a tool by many well-known physicians and early “psychotherapists” like James Braid, Hippolyte Bernheim, Jean-Martin Charcot, Pierre Janet, and Sigmund Freud (Hammond, 2013). Supposedly, Freud abandoned the method of hypnosis for multiple reasons: His suggestive procedure was not equally successful in all patients, and he noticed the influence of the therapeutic relationship on the outcome, which both made the method unreliable. Further, society viewed the method quite negatively, and Freud found himself at risk of uncovering trauma too easily. The latter was said to be unwelcome, since he wanted to establish his theory that sexual content during the sessions resulted from childhood fantasies rather than uncovering sexual abuse (Hammond, 2013). With Freud's renunciation of hypnosis, the general interest in it also decreased until the US-psychiatrist Milton Erickson used hypnosis and hypnotic trance as one of several elements (i.e. storytelling, utilizing and reframing symptoms, etc.) to conduct a new type of psychotherapy – the modern Ericksonian HT (Revenstorf & Peter, 2009). This HT has been used mostly in the USA and Europe in the last decades. It integrates hypnosis, hypnotic trance, and other therapeutic elements and will be addressed in my work.

1.3 Efficacy of Hypnotherapy

Scientific validation is necessary for HT to be acknowledged as a serious treatment option. This can be done with evidence-based psychotherapy studies (randomized control trials) that show HT to be beneficial in treating various physiological and psychological disorders. Meta-analyses confirm the efficacy of HT for pain, tinnitus, insomnia (Flammer & Alladin, 2007), irritable bowel syndrome (Lee, Choi, & Choi, 2014), depression and depressive symptoms (Milling, Valentine, McCarley, & LoStimolo, 2018; Shih, Yang, & Koo, 2009), anxiety (Valentine, Milling, Clark, & Moriarty, 2019), trauma (O'Toole, Solomon, & Bergdahl, 2016; Rotaru & Rusu, 2016), and eating disorders (Barabasz, 2007). In 2006, the scientific advisory board of psychotherapy in Germany concluded HT should be considered a scientifically validated treatment of adults with somatic illnesses that are influenced by psychological and social factors and substance misuse (Wissenschaftlicher Beirat Psychotherapie nach § 11 PsychThG, 2006). These findings suggest that HT works, at least to some extent[2]. However, scientists and clinicians, including me, would like to understand *how* it works. Potential answers can be found in two fields: intrinsic and instrumental research.

1.4 Intrinsic Research

In the second half of the 19th century, physicians who used hypnosis and hypnotic trance as a therapeutic method also tried to find scientific explanations for the effects they observed in their patients. Even then, there was early controversy among famous neurologists over whether hypnotic state is physiological (advocated by Charcot) or psychological (proposed by Bernheim) (Hammond, 2013). Heidenhain

[2] A limiting factor is the differing quality of studies. Not all studies included in the above cited meta-analyses included randomized or intention-to-treat trials nor the same diagnostic criteria.

suggested a joint theory of behavioral and physiological factors in hypnotic trance (Windholz, 1996). With the emergence of neurophysiological research methods, hypnosis and hypnotic trance were researched with electroencephalography (EEG) (Gruzelier, 1998; Vanhaudenhuyse, Laureys, & Faymonville, 2014), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) (Oakley & Halligan, 2009; Vanhaudenhuyse, Laureys, & Faymonville, 2014). However, to this date intrinsic research on hypnosis is comparatively scarce (Oakley & Halligan, 2009).

One problem in researching the neurophysiology of hypnosis/hypnotic trance is the content itself. Since we are still lacking a precise physiological definition of hypnosis/hypnotic trance, the de facto examined state varies between studies. Some authors target the effect of hypnotic suggestions on motor control, pain perception, or cognitive functions, others compare it to pathological phenomena observed in schizophrenia, delusions, or conversion disorder (Halligan & Oakley, 2013). Further, only a few studies focus on hypnotic trance in contrast to a control condition like a “waking state”. Then, the factor “hypnotic state” is controlled for by giving a suggestion after hypnotic induction – ergo during hypnotic trance – or without induction – therefore during waking. In a review of these few neurophysiological studies including control conditions, the authors state that the existing data show specific neurophysiological changes in highly suggestible individuals during a hypnotic induction (Mazzoni, Venneri, McGeown, & Kirsch, 2013). Specifically, they conclude that the Default Mode Network (DMN) is involved.

Outside of hypnosis research, the DMN is one of the most studied networks in the brain and belongs to the so-called core networks, showing consistent coupling of spontaneous fluctuations (Greicius et al., 2008; Horovitz et al., 2009; Menon, 2011; Vanhaudenhuyse et al., 2010). Typically, the DMN is deactivated during attention demanding tasks but active during resting state (Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001). Its core nodes include the posterior cingulate cortex (PCC), including the precuneus (PCu), medial prefrontal cortex , nodes in the medial temporal lobe and the angular gyrus (Menon, 2011). The blood oxygen level dependent (BOLD) signal shows a pattern of very low frequency range (>0.1 Hz) (Sonuga-Barke & Castellanos, 2007). The DMN is associated with self-referential mental processes like theory of mind, thinking about one’s future, and affective decision making (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Menon, 2011) and spontaneous thoughts during these self-referential processes (Mason et al., 2007; Rosenbaum et al., 2016, 2017).

While earlier data suggest increased activity during hypnosis/hypnotic trance in main nodes of the DMN, namely the PCC, PCu, and prefrontal areas like the anterior cingulate cortex (ACC) (Cojan, Waber, Schwartz, et al., 2009; Egner, Jamieson, & Gruzelier, 2005; Pyka et al., 2011; Rainville, Hofbauer, Bushnell, Duncan, & Price, 2002), later data suggest decreased activity in DMN-associated regions, namely the ACC, PCC, and other prefrontal areas (Deeley et al., 2012; Dienes & Hutton, 2012; Jiang, White, Greicius, Waelde, & Spiegel, 2017; McGeown, Mazzoni, Venneri, & Kirsch, 2009). However, heterogeneity in the results might originate from different study designs, samples, contents of hypnosis and types of suggestion. Reviewing existing literature, the authors claim a relative consensus on the decrease of DMN functional connectivity (FC) during hypnosis/hypnotic trance while the changes in FC patterns across networks are divergent (Halsband & Wolf, 2021).

1.5 Instrumental Research/Experimental Psychopathology

In instrumental research hypnosis/hypnotic trance is used to learn more about psychological phenomena such as pain, memory, perception etc. and their underlying cognitive processes (Oakley & Halligan, 2009). Hypnotic suggestions (e.g. amnesia) are used as a tool to manipulate neurocognitive processes (e.g. memory) to then assess their effect on the outcome (e.g. memory performance)(Oakley & Halligan, 2009). When the psychological phenomena contain pathological criteria, this specific type of instrumental research is called “experimental psychopathology” (Oakley & Halligan, 2009). It teaches neuroscientists about maladaptive processes and their mechanisms as well as possible treatment. So far, hypnosis/hypnotic trance has been used to investigate the pathologies amnesia, pain, conversion, hallucinations, and delusions or misidentifications: During hypnotic trance healthy participants received suggestions of clinical symptoms - like pain (Derbyshire, Whalley, Stenger, & Oakley, 2004); then, their cerebral activity was compared to the activity of patients suffering from the clinical symptoms (Oakley & Halligan, 2009). From this information the scientists drew conclusions about the pathologies and their underlying processes.

A different approach to instrumental research is to use hypnosis/hypnotic trance as a tool to manipulate the brain of a person, who already suffers from a disorder, in attempt to heal. This can teach us about the cerebral mechanisms of a certain psychopathology and its possible treatment, as well as about the limits of the effects of hypnosis/hypnotic trance. To my knowledge, only two studies have been conducted following this research approach (Halsband & Wolf, 2015; Lowén et al., 2013) and we will take a closer look at them in the next section.

1.6 Neurophysiology of Hypnotherapy

In one fMRI study including patients with irritable bowel syndrome, the authors compared HT and an educational intervention and found decreased activity in the posterior insula in patients responding to HT compared to decreased prefrontal activity in patients who responded to the educational intervention (Lowén et al., 2013). In the other fMRI study, the authors investigated functional changes in the brain after hypnosis in patients with dental phobia (Halsband & Wolf, 2015). In the phobic patients the authors found fear-associated activity in the left amygdala, the ACC bilaterally, insula and hippocampus. In all of these areas activity was reduced during hypnotic trance. These two studies offer a first glimpse at how HT changes patients' cerebral activity. Yet, it should be noted that they included very particular pathologies (irritable bowel syndrome shows a prevalence of about 1.34 % in the German population (Häuser, Marschall, Layer, & Grobe, 2019) and dental phobia of about 3.7 % in the Dutch population[3] (Oosterink, De Jongh, & Hoogstraten, 2009) and varied greatly in their procedures. While in the first study patients received seven 1-hour HT treatments and their brains were scanned during a paradigm including rectal distension (Lowén et al., 2013), in the second study patients were scanned while viewing dental cues and either without hypnosis or after undergoing a short hypnotic induction (Halsband & Wolf, 2015). Further, the regions in which the activation changes occurred are quite specific to the investigated pathologies (Halsband & Wolf, 2015; Lowén et al., 2013). Therefore, generalizations of HT on other pathologies or the effect of hypnosis/hypnotic trance applied in therapy over a longer period of time seem untenable.

In the past years, colleagues from the University of Tübingen became interested in the controlled, randomized investigation of HT, in which hypnosis/hypnotic trance is

[3] Unfortunately, a more current number for the German population was unavailable.

applied frequently over a period of time and to a variety of patients sharing a common psychopathology. In the resulting so-called WIKI-D (Wirksamkeit Aktivierend-Kognitionsfokussierter im Vergleich zu Hypnotherapeutischer Therapie bei leichten bis mittelgradigen Depressionen) study (Fuhr, Schweizer, Meisner, & Batra, 2017) patients suffering from mild to moderate depression underwent either HT or the standard treatment for depression, Cognitive Behavioral Therapy (CBT).

1.7 Depression and its Neurophysiology

According to the Robert Koch-Institut, depression is a psychopathology affecting people of all ages, sexes, or educational background, reaching a one-year prevalence of 8.1 % in German adults in 2017 – number increasing (Thom, Kuhnert, Born, & Hapke, 2017). Main symptoms are persistent sad mood, feelings of worthlessness and a loss of joy and interests (American Psychological Association, 2013), as well as impaired affective cognition, e.g. the memory of emotional content (Elliott, Zahn, Deakin, & Anderson, 2011) and depressive rumination, which is defined as repetitive thoughts focusing on depressive symptoms and their implications, including thoughts about the past or one's shortcomings (Nolen-Hoeksema, 1991).

An important neurophysiological correlate of depressive symptoms is a malfunctioning of the DMN. It has been proposed to play a key role in the neurophysiology of depressive symptoms due to its activation during self-referential processes (Mason et al., 2007) and has been suggested to be a neurophysiological correlate of depressive rumination (Berman et al., 2011; Rosenbaum et al., 2017). However, the findings on altered DMN activity in depression are heterogeneous.

In early studies the DMN was found to be hyperactive in depressed participants (Anand et al., 2005; Greicius et al., 2007; Grimm et al., 2009; Sheline et al., 2009). On a symptomatic level, this increased activation is associated with impairments in emotional processing and cognitive performance (Drevets, Price, & Furey, 2008; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015) and automatic affective processing (Sheline et al., 2009). In contrast, later studies report a decrease in DMN FC during a depressive episode (Connolly et al., 2013; Rosenbaum et al., 2017). More specifically, in a large study, including over 1600 measured participants, DMN FC was decreased in depressed individuals. However, this decrease was observed only in recurrent, not in first-episode depressed patients (Yan et al., 2019). Other studies show mixed results hinting towards a general abnormal DMN functioning in depression (Guo et al., 2014; Zhu et al., 2012). Most recently, researchers found that especially midline cortical areas seem to play a key role in depression-specific DMN abnormalities (Scalabrini et al., 2020). Increased DMN FC in these regions seem to go along with abnormally high connections of the DMN to other brain networks and not to an increased intra-network connection. This finding might explain the impairment of so many cognitive, sensory and affective functions, which are not associated with the DMN and still affected in depression (Scalabrini et al., 2020).

Cognitive impairments in depression include attentional biases towards negative stimuli (Dalili, Penton-Voak, Harmer, & Munafò, 2015; Gotlib, Krasnoperova, Neubauer Yue, & Joormann, 2004; Suslow et al., 2004) and aberrant emotional recognition (Anderson et al., 2011; Surguladze et al., 2004). This, again, is connected to deficits in emotional regulation (Dryman & Heimberg, 2018). Functional imaging studies suggest a connection between these symptoms and depression-specific alterations in the cortico-limbic circuit (Price & Drevets, 2010). Generally, depressed individuals show hypoactivity in the prefrontal cortex (PFC) (DeRubeis, Siegle, & Hollon, 2008), while they show hyperactivity in prefrontal areas, including the orbitofrontal cortex (OFC), the dorsolateral prefrontal cortex (DLPFC), and the inferior frontal gyrus (IFG) when they had to react to emotionally negative stimuli (Canli et al., 2004; Kerestes et al., 2012). This aberrant functioning of the PFC is suggested to result from hyperactivation in limbic regions, which project onto the PFC (Anand et al., 2005; Price & Drevets, 2010). In other words, these limbic regions call for prefrontal regulation (Anand et al., 2005; Price & Drevets, 2010). This is in line with the finding that FC between limbic and prefrontal regions seems abnormal in depressed individuals (Carballedo et al., 2011). The regions connected to emotional recognition include temporal areas, that are consistently found to function abnormally in depression (Canli et al., 2004; Cullen et al., 2009; Fitzgerald, Laird, Maller, & Daskalakis, 2008; Takahashi et al., 2010).These findings on the neurophysiology of depression served as base for the definition of the cerebral regions we investigated, as will be discussed later.

1.8 Depression Treatment and its Effects

CBT or interventions including CBT elements show the strongest evidence in psychological treatments for depression (Treatment Target: Depression, 2022) CBT includes the identification of irrational beliefs and dysfunctional thought schemes entailing negative emotions or dysfunctional behavior (Beck, Rush, Shaw, & Emery, 1979), and learning the skill of checking the validity of (negative) beliefs and distancing oneself from them (DeRubeis et al., 2008). The neural effects of CBT have been researched far less, but hint towards a normalization of the PFC after CBT (Lueken & Hahn, 2016). Cognitive Therapy seems to increase prefrontal hypoactivity which inhibits limbic (amygdala) hyperactivation, whereas patients receiving medication directly showed decreased amygdala activity (DeRubeis et al., 2008). Still, the effects of CBT on specific parts of the PFC, the PCC, and the amygdala are not homogeneous enough to establish a model for the effects of CBT (Franklin, Carson, & Welch, 2016). Unfortunately, there still exists a considerable amount of patients who does not respond to CBT, and some authors even question the superiority of CBT due to weak empirical tests, limited study quality, and limited efficacy (response rate of about 50%) (Leichsenring & Steinert, 2017).

An alternate approach or promising addition to CBT in depression treatment is HT (Alladin, 2006; Alladin & Alibhai, 2007). CBT complemented by HT elements was more efficacious than CBT alone (Alladin & Alibhai, 2007). In direct comparison, depressed patients benefited equally from both, HT and CBT (Fuhr et al., 2021). In their study, HT included hypnotic inductions, self-hypnosis, the construction of inner mental images and future visions, the activation of inner resources and biographical work (Wilhelm-Goessling, Schweizer, Dürr, Fuhr, & Revenstorf, 2020). Yet, the neurobiological factors that might influence the patients' therapy response to either therapy, or neurobiological effects of HT in depression are yet to be found.

1.9 Functional Near-Infrared Spectroscopy (fNIRS)

Up to date, most studies on neuroimaging are conducted using fMRI. While this method offers great advantages, like its high spatial resolution and the possibility to map the entire brain, these advantages come at a high cost: the MRI machines are very loud and narrow, putting participants into a stressful measurement situation and exclusion criteria are quite strict. An alternate measurement method avoiding these disadvantages is fNIRS. It is based on the fact that near-infrared light penetrates bone and tissue and then spreads and is absorbed by the tissue. Depending on the oxygenation of hemoglobin in the examined brain tissue, the light is absorbed to a certain degree, which can be measured. From this relative concentration of chromophores conclusions about the activation of the tissue can be drawn. Even though its penetration depth (1-2 cm (Patil, Safaie, Moghaddam, Wallois, & Grebe, 2011)) and spatial resolution is smaller compared to fMRI, fNIRS offers the advantages of being easy to apply on the participants' heads, being robust to movement, producing less noise, and having less exclusion criteria. These advantages are of particular importance when examining a sample which might be more prone to potential stressful external stimuli – like psychiatric patients.

2. Objective of this work

As described above, hypnosis/hypnotic trance and their application in therapeutic contexts is as old as medical treatments have been reported in history. From the beginning of psychological research, scientists have tried to study hypnotic phenomena – the nature of the phenomena themselves, as well as their impact on the physis and psyche. However, researchers have been facing difficulties: a great part of the hypnotic experience is a subjective one, it seems important what kind of content is used during hypnosis and trance (suggestions, images, metaphors etc.). In addition, studies vary in their objectives: some authors look at the nature of hypnotic phenomena (intrinsic research), others at their impact on other phenomena (instrumental research) such as mental disorders (experimental psychopathology). In my work here I would like to bring intrinsic and experimental psychopathology closer together and therefore investigate the effects of repeated hypnotic trance in a therapeutic context. I wish to gain clues about the nature of hypnosis/hypnotic trance itself, but also see how HT is connected to a specific psychological disorder and a possible treatment. This comprehensive and joint approach has rarely been undertaken and inspired me to this challenging endeavor. When the WIKI-D study was developed to examine the efficacy of HT on a patient sample with a comparatively common disorder, namely depression, I raised the question whether HT changed the patients' brains and if so, whether this change was different from the effects of CBT. Interestingly, brain imaging studies have shown a connection between hypnosis/hypnotic trance and the DMN and this same network is also affected during depression. Further, depressed individuals show cognitive and emotional impairments that are linked to abnormalities in the fronto-limbic circuit and temporal areas. CBT has been found to normalize frontal hypoactivity in depressed patients when they received therapy. On a content level, this finding seems plausible since the work with cognitions is a central element of CBT. HT, on the other hand, includes the repeated use of hypnosis and hypnotic trance including emotional content. Based on this, I developed the following general main hypothesis:

1) Both, CBT and HT, affect the depressed patients' brains. I expected to see this in changed cerebral activity/FC after therapy compared to before therapy.

Specifically, I expected this therapy-induced cerebral change to look differently for the two therapies and developed these hypotheses:

2) HT affects the DMN and temporal lobe. Due to highly exploratory nature of this hypothesis and lack of previous findings, I did not assume a direction of these effects.

3) In line with previous research, CBT normalizes depression-specific prefrontal hypoactivity. I expected more prefrontal activity after therapy compared to before therapy in the CBT group.

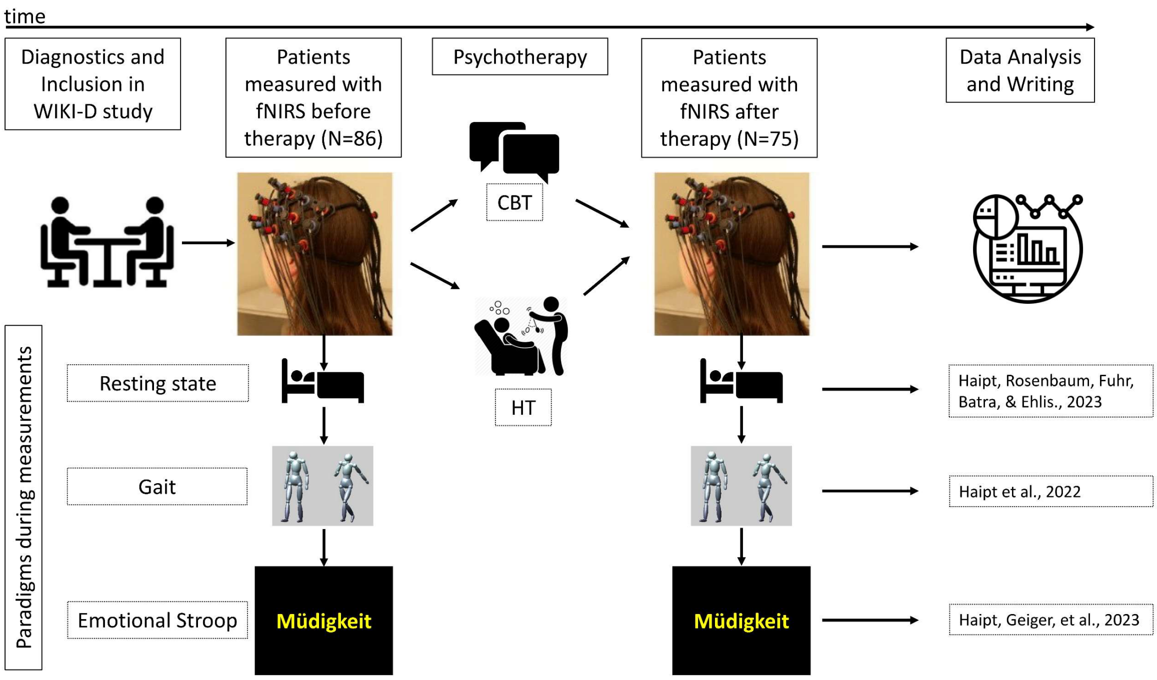
Additionally, I assumed these cerebral changes to be mirrored in behavioral data and propose the following hypothesis:

4) In association with the cerebral changes, reaction times and error rates decrease over time/therapy and show paradigm specific effects. Further, I assume symptom severity to decrease over time/therapy and to be related to the cerebral changes, as well as rumination.

To test these hypotheses, we conducted an experiment using three paradigms aiming at eliciting activity in three different regions/networks of interest (for an overview see Table 1): The first paradigm, a resting state measurement, was used to activate the DMN while parietal regions, including the PCu and somatosensory association cortex (SAC), as well as angular gyri and supramarginal gyri were investigated (mainly testing hypothesis 1, 2 and 4). The second paradigm portrayed human avatars walking neutrally or emotionally (gait paradigm) and evoked temporal activity which is associated with emotional recognition (focusing on hypothesis 1, 2 and 4). The third paradigm, an Emotional Stroop Paradigm (ESP), was used to raise activity in the prefrontal cortex (PFC) which is associated with affective cognition (focusing on hypothesis 1, 3 and 4). To test as many WIKI-D patients as possible, our measurement method of choice was fNIRS. Further, we recorded behavioral parameters during the gait paradigm and ESP: trait rumination and symptom severity. We examined 86 patients at baseline, and 75 patients returned to a second measurement after therapy. 39 patients completed CBT, 36 patients HT. To give you an overview of the experiment setup, see Figure 1. The analysis of each paradigm served as base for one manuscript, resulting in three articles on the effects of HT and CBT on 1) the DMN during a resting state measurement, 2) temporal regions during an emotional gait paradigm, and 3) the PFC during an ESP (Table 1 and Figure 1). Next, each article is presented in an own chapter, followed by a general discussion. Here, the results of our experiment will be summarized and connected to previous knowledge. They will be integrated into existing models for each intrinsic and instrumental research, and new model developments will be presented before I will list some limitations and conclude.

Figure 1

Procedure of study



Note. After inclusion in the WIKI-D study patients were measured before and after psychotherapy. They were randomly assigned to either CBT or HT. During each measurement three different paradigms were used, each associated with distinct hypotheses. The results of each paradigm were analyzed and discussed in one manuscript.

Table 1

Overview of manuscripts in this dissertation

Manuscript	Paradigm	Network/Regions of Interest	Analysis	Analyzed Patients	Tested Hypotheses	Results
Haipt, Rosenbaum, Fuhr, Batra, & Ehlis., 2023: Differential Effects of Hypnotherapy and Cognitive Behavioral Therapy on the Default Mode Network of Depressed Patients	Resting State	Parts of the DMN: partly PCu, SAC, angular gyri, supramarginal gyri	<u>Outcome:</u> FC, symptom severity	n = 75	1, 2 and 4	- Symptom reduction after HT and CBT - FC in SAC decreased in all patients - FC between right angular gyrus und left supramarginal gyrus increased in HT group - No results for PCu - No correlation between symptom severity and FC
Haipt et al., 2022: The effects of hypnotherapy compared to cognitive behavioral therapy in depression: a NIRS-study using an emotional gait paradigm	Gait	STS, EBA	<u>Outcome:</u> FC and cerebral activity, error rates, symptom severity before therapy <u>Covariate:</u> Rumination	n = 75	1, 2 and 4	- Decreased FC between right STS and EBA in HT group: activity in STS changed in HT group, depending on rumination - No results for error rates - Positive correlation between rumination and symptom severity
Haipt et al., 2023a: How psychotherapy changes the depressed brain: activity in the left prefrontal cortex reduced after Hypnotherapy but not Cognitive Behavioral Therapy	Emotional Stroop	DLPFC	<u>Outcome:</u> Cerebral activity, symptom severity, error rates, reaction times <u>Covariate:</u> Symptom change	n = 66	1, 3 and 4	- Symptom reduction after HT and CBT - Decreased activity in left DLPFC in HT group - No results for error rates or reaction times

3. Manuscript 1: Differential Effects of Hypnotherapy and Cognitive Behavioral Therapy on the Default Mode Network of Depressed Patients

3.1 Author Contributions

Study Design WIKI-D and Fundraising: Anil Batra and Kristina Fuhr.

Study Design of Neurophysiological Addition: Alina Haipt in consultation with Ann-Christine Ehlis.

Sample Recruitment and Data collection: Alina Haipt.

Data Analysis: Alina Haipt with help from David Rosenbaum.

Manuscript Drafting and Correcting: First draft written by Alina Haipt with revisions from Ann-Christine Ehlis, David Rosenbaum, Anil Batra, and Kristina Fuhr. Redrafting by Alina Haipt.

Journal Selection and Submission: Alina Haipt in consultation with Ann-Christine Ehlis and support from Kristina Fuhr.

3.2 Research Article 1

Differential Effects of Hypnotherapy and Cognitive Behavioral Therapy on the Default Mode Network of Depressed Patients.

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Abbreviations

[1]CBT	Cognitive Behavioral Therapy
[2]HT	Hypnotherapy
[3]FC	Functional Connectivity
[4]DMN	Default Mode Network
[5]fNIRS	Functional Near-Infrared-Spectroscopy
[6]PCC	Posterior Cingulate Cortex
[7]PCu	Precuneus
[8]BOLD	Blood Oxygen Level Dependent
[9]CT	Cognitive Therapy
[10]ACC	Anterior Cingulate Cortex
[11]ITT	Intention to Treat
[12]SKID-I	Structured Clinical Interview for DSM-IV
[13]PHQ-9	9 item Patient Health Questionnaire Depression Scale
[14]O2Hb	Oxygenated Hemoglobin
[15]HHb	Deoxygenated Hemoglobin
[16]ROIs	Regions of Interests
[17]SAC	Somatosensory Association Cortex
[18]supG	Supramarginal Gyrus
[19]angG	Angular Gyrus
[20]TDDR	Temporal Derivative Distribution Repair
[21]CEN	Central Executive Network
[22]fMRI	Functional Magnetic Resonance Imaging

Abstract

Depression is a widespread disorder for which Cognitive Behavioral Therapy (CBT[1]) is an effective treatment. Recently, Hypnotherapy (HT[2]) was found to be a promising alternative. At a neurophysiological level depression is associated with abnormal functional connectivity (FC[3]) of the Default Mode Network (DMN[4]); effects of CBT on DMN-related regions are heterogeneous. Hypnosis has been associated with parts of the DMN, but its effects on this network when induced in a treatment setting have never been investigated. In this first-of-its-kind study 75 depressed patients receiving either CBT or HT were included and measured during resting-state before and after therapy with functional near-infrared-spectroscopy (fNIRS[5]). Results show significant symptom reduction in both groups and significant treatment effects in two components of the DMN: while the FC within posterior midline regions of the DMN decreased in both therapy groups, an interhemispheric connection increased only in the HT group. Our findings suggest that psychotherapy for depressed patients affects the DMN and these effects seem to differ between approaches. We conclude from these findings that while patients profit from different types of therapy, their underlying neurophysiological processes might be quite different. These findings are crucial for developing more individualized and indication-driven treatments.

Keywords: Hypnotherapy, Cognitive Behavioral Therapy, Default Mode Network, depression, functional Near-infrared Spectroscopy

3.2.1 Introduction

General Introduction

In the past decades, the temporal co-activation of spatially distributed brain regions, i.e., functional connectivity (FC) has been increasingly investigated. One of the most studied networks that was found to show robust coupling of spontaneous fluctuations is the so-called “Default Mode Network” (DMN)(Greicius et al., 2008; Horovitz et al., 2009; Menon, 2011; Vanhaudenhuyse et al., 2010).

The DMN is typically deactivated during attention demanding tasks but active during resting state (Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001). Its core nodes include the posterior cingulate cortex (PCC[6]), including the precuneus (PCu[7]), medial prefrontal cortex , nodes in the medial temporal lobe and the angular gyrus (Menon, 2011). The blood oxygen level dependent (BOLD[8]) signal shows a pattern of very low frequency range (>0.1 Hz) (Sonuga-Barke & Castellanos, 2007). The DMN is associated with self-referential mental processes like thinking about one’s future, theory of mind, and affective decision making (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Menon, 2011) and spontaneous thoughts during these self-referential processes (Mason et al., 2007; Rosenbaum et al., 2016, 2017). One author (Menon, 2011) suggests an involvement of this network, besides other core networks, to explain cognitive and emotional alterations in different psychiatric and neurological disorders such as schizophrenia, autism, anxiety, Alzheimer’s disease, frontotemporal dementia, but also depression.

Depression and the DMN

Key symptoms in depression are a persistent sad mood, feelings of worthlessness and a loss of joy and interests (American Psychological Association, 2013). Additionally, depressed people were found to be impaired in affective cognition, e.g., the memory of emotional content (Elliott, Zahn, Deakin, & Anderson, 2011) and depressive rumination. The latter is defined as thoughts that focus on depressive symptoms and their implications (Nolen-Hoeksema, 1991). Due to its activation during self-referential processes, the DMN has been suggested to play a role in the neurophysiology of depressive symptoms (Berman et al., 2011; Rosenbaum et al., 2017). However, results on altered DMN activity in depression are slightly heterogeneous.

Hyperactivity in the DMN was found in depressed patients in several early studies (Anand et al., 2005; Greicius et al., 2007; Grimm et al., 2009; Sheline et al., 2009) and was discussed to account for impairments associated with depressive symptoms like emotional processing and cognitive performance (Drevets, Price, & Furey, 2008; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015) or automatic affective processing (Sheline et al., 2009). Yet, in contrast, a depression-specific DMN decrease of FC was also observed (Connolly et al., 2013; Rosenbaum et al., 2017). In an exceptionally large study with over 1600 measured participants the researchers also found decreased DMN FC in depressed subjects, but only in recurrent depression, not in first-episode depressed patients (Yan et al., 2019). Mixed results, revealing decreased as well as increased FC within the DMN, were also found, hinting towards abnormal DMN homogeneity in depression (Guo et al., 2014; Zhu et al., 2012). The heterogeneity of results concerning the abnormalities of DMN FC in depression calls for further investigation to fully understand the neurophysiology of this disorder and the role of the DMN. This understanding could help to possibly distinguish subtypes of depression and draw implications for treatment.

Depression treatment and its Neurophysiology

The most researched psychological treatment for almost all mental disorders, including depression, is CBT(Cuijpers et al., 2013). In CBT for depression patients are taught to identify irrational beliefs and dysfunctional thought schemes that entail negative emotions or dysfunctional behavior (Beck, Rush, Shaw, & Emery, 1979) and they are supported to learn the skill of checking the validity of their (negative) beliefs and distance themselves from these beliefs (DeRubeis, Siegle, & Hollon, 2008). The neural mechanisms that underlie a CBT treatment have been researched far less than the efficacy of CBT and until today have not been understood satisfyingly. In a review, DeRubeis et al. (2008) compared the neural changes in patients who received medication or Cognitive Therapy (CT[9]) and concluded: Amygdala hyperactivity in depressed patients decreased directly due to medication while in patients who received CT prefrontal hypoactivity increased due to therapy and since the prefrontal cortex inhibits the amygdala, amygdala activity decreased indirectly. In a more recent review, the authors conclude that there are indications for biological changes in the brain caused by CBT, but they are not as homogenously clear as one might wish (Franklin, Carson, & Welch, 2016). Most commonly, a change in prefrontal areas is observed after CBT (Lueken & Hahn, 2016), specifically a deactivation in the dorsal anterior cingulate cortex (ACC[10]) during resting state (Franklin et al., 2016). Less conclusive are the findings about changes in the PCC, parts of the prefrontal cortex and the amygdala (Franklin et al., 2016). They are still too heterogeneous to assume a model for the effects of CBT (Franklin et al., 2016). Despite the overwhelming amount of research that shows the healing effects of CBT on depression and its first attempts for neurobiological explanation, there are still patients who do not respond to CBT. Leichsenring and Steinert (2017) challenge the superiority of CBT compared to other psychotherapies and conclude that CBT should not be considered gold standard due to limited study quality, weak empirical tests and limited efficacy (response rate of about 50%) (Leichsenring & Steinert, 2017). The reasons why a considerable amount of patients does not respond to CBT and their possible correlates on a neurophysiological level are yet to be found. To meet the needs of as many patients as possible and to make individualized treatment possible, it is necessary to further investigate CBT and possible alternatives, such as hypnotherapy (HT).

In HT, states of trance, that are induced by hypnosis, are used to create an altered state of consciousness (Revenstorf, 2003), which is characterized by focused attention and reduced peripheral awareness (Griffiths, 2017). Used in therapy, the patients can learn to control symptoms and physiological functions that are usually not accessible consciously (Whorwell, 2011). Alladin and colleagues developed an approach adding hypnotherapeutic elements to depression specific CBT (Alladin, 2006; Alladin & Alibhai, 2007) and found that this hypnotherapeutic addition to CBT was more efficacious than CBT alone (Alladin & Alibhai, 2007). Fuhr et al. (Fuhr et al., 2021) were the first to compare HT only to CBT in depressed patients. In their study, HT included hypnotic inductions, self-hypnosis, the construction of inner mental images and future visions, the activation of inner resources and biographical work (Wilhelm-Goessling, Schweizer, Dürr, Fuhr, & Revenstorf, 2020). The authors show that depressed patients benefited equally from both therapies. HT was not inferior to CBT in terms of the extent of symptom reduction (Fuhr et al., 2021). Yet, the underlying neural mechanisms of HT in psychiatric disorders have only been investigated rarely and not in the field of depression (Halsband & Wolf, 2015; Lowén et al., 2013).

Neurophysiology of Hypnosis

However, more research in the field of hypnosis has been conducted on the neural correlates of hypnosis and trance itself, without a specific therapeutic aim. In several studies hypnosis has been connected to changes in the DMN. The results to whether DMN activity during hypnosis increases or decreases vary among the studies. Increases in DMN activity during hypnosis were mainly found in the PCC and PCu as well as prefrontal areas like the ACC (Cojan, Waber, Schwartz, et al., 2009; Egner et al., 2005; Pyka et al., 2011; Rainville et al., 2002). Decreased activity in DMN associated regions, namely the ACC, PCC, and other prefrontal areas, were found in two studies (Deeley et al., 2012; McGeown, Mazzoni, Venneri, & Kirsch, 2009). Heterogeneity in these studies could result from the dissimilarities in study designs, tested samples, contents of hypnosis and types of suggestion.

Summary and study objective

To sum up the presented literature, acutely depressed subjects show aberrant functioning of the DMN and this has been linked to cognitive processes during depression, like rumination. Studies on the neural effects of therapies for depression have only been conducted for CBT and suggest alterations through therapy in regions that are also part of the DMN, like the ACC as part of the medial prefrontal cortex. Hypnotherapy has not been investigated in its neural effects on depressed patients yet, but the state of hypnosis has been associated with changes in DMN activity. In this study, we aimed to shed some light on the little known field of neural effects of CBT and HT for depression, specifically regarding the DMN. To this end, we conducted a neuroimaging study using functional near-infrared spectroscopy (fNIRS) on 75 depressed patients undergoing either CBT or HT. Both therapies were successful in reducing the patients' symptoms when assessed in a clinician administered rating as reported by Fuhr et al. (2021). In this exploratory study, we assume a reduction throughout therapy in self-reported symptoms and no difference between groups, analogously to Fuhr et al. (2021). We hypothesize that this therapeutic effect is mirrored by a change in DMN associated FC over time. We further investigate the similarity of possible treatment effects between the therapy groups (CBT vs. HT). Lastly, we are interested in a direct connection between a therapy effect on symptom level and on a cerebral level by correlating the changes in symptom reduction and FC change.

3.2.2 Material and Methods

Subjects

We recruited our subject sample from the 152 depressed patients that were intended to treat (ITT[11]) in the WIKI-D study by Fuhr et al. (2021). All study participants suffered from an acute unipolar mild to moderate depressive episode. Inclusion criteria to the WIKI-D study required no change in antidepressant medication for the last three months and no psychotherapy in the last 12 months before the study. Trained staff used the German version of the Structured Clinical Interview for DSM-IV (SKID-I[12]; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) to diagnose patients. All participants of the WIKI-D study were contacted and asked to participate in our neurophysiological sub-study (Figure 1). Exclusion criteria for the neurophysiological measurements included pregnancy or nursing a child, severe neurological diseases (e.g. meningitis, epilepsy), untreated hypertension, diabetes, or other coronary diseases as well as social phobia and acute substance abuse. As a result, 75 patients (56 females, 19 males) between the age of 18 and 69 (M = 39.24, SD = 14.85) participated in both measurements, before and after therapy (Figure 1). 25 patients took at least one antidepressant substance (36% SSRIs or other including atypical antipsychotics, NaSSA, tricyclic antidepressants, hypericum, SSNRI, agomelatine, bupropion, anticonvulsive medication); 24 patients showed at least one acute comorbid disorder, 6 patients showed more than one acute comorbidity. Therapy group assignment was randomized (in CBT 39 subjects and in HT 36 subjects). The Ethics Committee at the Medical Faculty of the University of Tuebingen and University Hospital Tuebingen approved of this study (061/2015B02). All participants gave their written informed consent after reading the complete description of the study.

Measures and therapies

All patients completed the 9 item Patient Health Questionnaire Depression Scale (PHQ-9[13]) (Kroenke & Spitzer, 2002) to evaluate self-reported depressive symptom severity before and after therapy. The difference between pre therapy and post therapy scores were used as indicators for therapeutic change (decrease in symptoms indicate

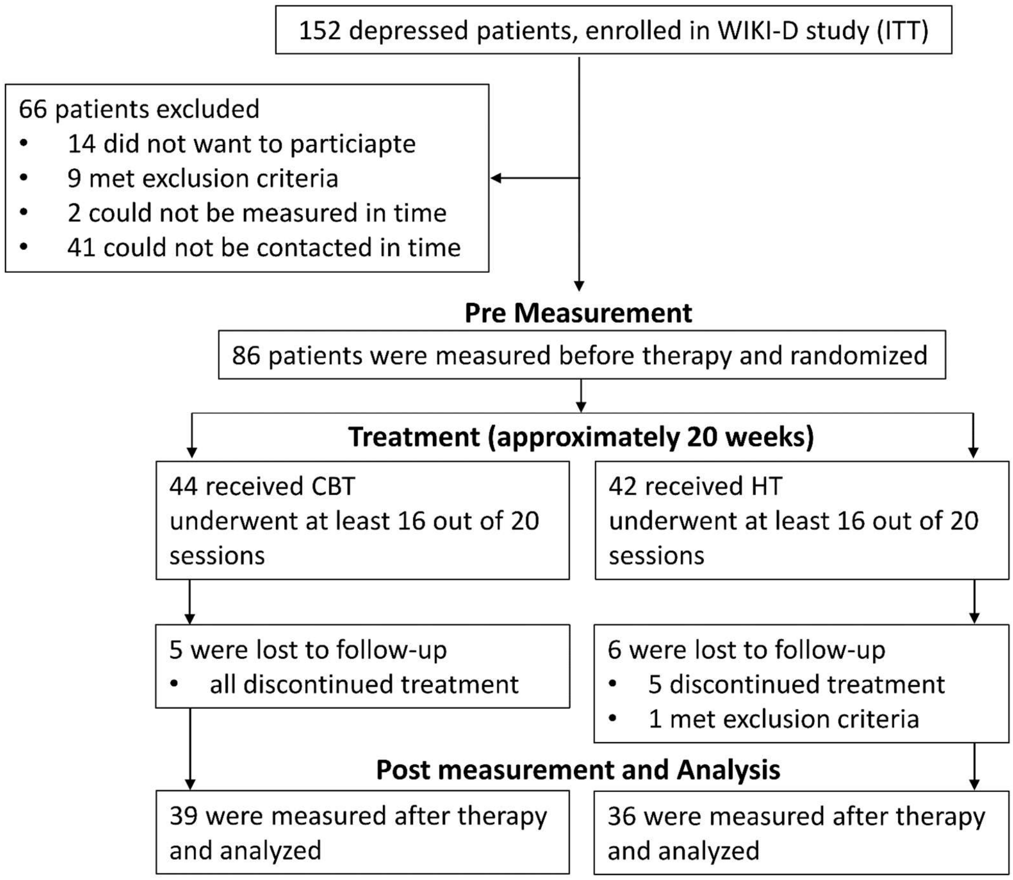

Figure 1. Procedure of including and measuring patients. WIKI-D study is by Fuhr et al. (2021), *ITT* intention to treat, *CBT* Cognitive Behavioral Therapy, *HT* Hypnotherapy.

positive therapeutic effect). CBT, as well as HT, consisted of 20 sessions, and patients were treated individually. The therapy was considered completed when patients visited at least 16 of the 20 sessions, which was accomplished by 76 patients. One patient became pregnant during therapy and could therefore not be measured a second time.

Procedure

The NIRS measurement took place between the time of diagnostic procedure of the WIKI-D study (Fuhr et al., 2021) and the beginning of the psychotherapy, the latest within one week after the first therapy session. After the end of therapy, the second measurement was conducted, the earliest one week before the last session, the latest four weeks after the end of therapy.

The NIRS measurement itself lasted around two hours, both at baseline and post treatment. After being seated 75 cm in front of a computer screen, the NIRS cap was placed on the subjects' heads according to their measurements. Resting state was measured first. All subjects were instructed to close their eyes, sit still and not fall asleep during the resting state measurement. The measurement lasted seven minutes. Afterwards the patients were asked to report their experiences during resting state in an open self-report form and rate the time they spend on specific processes (e.g. relaxation) on visual analogue scales (for results see Rosenbaum et al., 2017). After that, a second (gait) and third (Emotional Stroop) paradigm were presented, the results of which are to be reported elsewhere. During the measurement oxygenated (O2Hb[14]) and deoxygenated hemoglobin (HHb[15]) were recorded continuously after a 10 s baseline measurement. All subjects received a small monetary compensation for their participation.

Near-infrared spectroscopy and regions of interest

NIRS is a non-invasive method for optically-based functional imaging, offering many advantages. It is easy and quick to apply in a noise-free setting, is tolerant towards movement (Ernst, Schneider, Ehlis, & Fallgatter, 2012; Fallgatter, Ehlis, Wagener, Michel, & Herrmann, 2004) and has no specific exclusion criteria. NIRS is based on the ability of light in the near-infrared spectrum to penetrate the skull and tissue. The light's absorption depends on the oxygenation of hemoglobin in the investigated brain tissue and, therefore, the absorption rate indicates the relative concentration of O_2Hb and HHb. This leads to conclusions on activation changes in cortical areas of the brain. In our study we used an ETG-4000 Optical Topography System (Hitachi Medical Corporation, Tokyo, Japan) using a 52-channel array of 33 optodes (17 light emitters and 16 detectors) covering parietal and temporal brain areas with a temporal resolution of 10 Hz. The inter-optode distance was 3 cm and near-infrared light of two wavelengths (695 and 830 nm) was used. The optodes were arranged in a 3x11-rectangular shape on the subjects' heads according to the international 10/20 System. Channel 16 was placed over Pz, the anterior channels 43 (left) and 52 (right) were positioned on the temporal electrode positions T3 and T4, respectively. Even though the NIRS light does not penetrate the brain tissue further than 1-2 cm (Patil, Safaie, Moghaddam, Wallois, & Grebe, 2011) it is assumed that the cortical parts of the DMN are measured with NIRS, as shown in other studies (e.g. Bulgarelli et al., 2020; Duan, Van Dam, Ai, & Xu, 2020).

To execute hypothesis-based data analysis we focused on regions of interests (ROIs[16]) which are considered a sub-system of the DMN, found by Rosenbaum et al.

(2017) who analyzed a sub-sample of the participants presented in this study. The localized hub nodes of this sub-network were part of the middle somatosensory association cortex (SAC[17]), left supramarginal gyrus (supG[18]) and the right angular gyrus (angG[19]). We were interested in investigating these regions including the hub nodes as well as their hemispheric counterpart. Anatomic regions were assigned to channel positions using a neuronavigation system on a volunteer's head. This resulted in five ROIs: the SAC spreading over both hemispheres (channels 4, 5, 6, 7, 15, 16, 17, 25, 26, 27, 28, 35, 36, 37), the left angG (channels 2, 3, 12, 13, 23), right angG (channels 8, 9, 18, 19, 30), left supG (channels 14, 24, 34, 45) and right supG (channels 29, 39, 40, 50) as shown in Figure 2.

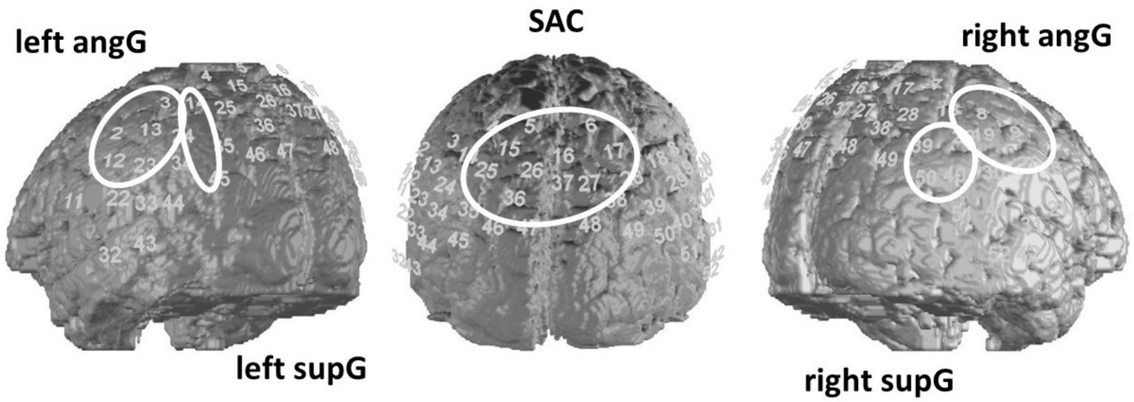

Figure 2. Regions of interest (ROI). We analyzed 5 ROIs, consisting of the portrayed channels, concerning the FC withing and between them. *angG* Angular Gyrus, *supG* Supramarginal Gyrus, *SAC* Somatosensory Association Cortex, *FC* Functional Connectivity.

Data analyses

Preprocessing. Firstly, the recorded data was preprocessed using MATLAB R2017b (MathWorks Inc, Natick, USA); brain plots were also generated with this software. This pre-processing included applying a temporal derivative distribution repair (TDDR[20]; Fishburn, Ludlum, Vaidya, & Medvedev, 2019), band-pass filtering (0.1–0.01 Hz) to minimize low- and high-frequency noise, as well as the algorithm of Cui, Bray, and Reiss (2010) for movement artefact reduction. Then all signals were visually inspected for local artefacts: In 15 of the 75 pre measurements and 13 post measurements, a total of 0.6 % and 0.02 % of the 52-channels per measurement were interpolated, respectively. In these cases, channels were interpolated from adjacent channels. To reduce the influence of global signal changes, a global signal reduction using a spatial gaussian kernel filter with a standard deviation of $\sigma = 40$ was applied. After preprocessing, FC-coefficients were computed with Pearson correlation after checking the variance of the channels for robustness and eliminating extreme values, then a Fishers r-to-z-transformation was conducted (Silver & Dunlap, 1987), each channel serving as seed. FC for the ROIs was computed by calculating the means of the FC coefficients belonging to this ROI.

Statistics. Further analyses were conducted using R Studio (R Studio Inc, Boston, USA). Non-brain graphs were also produced using this program. We used linear models to test our hypotheses regarding symptom reduction assessed with the PHQ-9 as well as changes in FC from pre to post and possible interaction with groups. Marginal sums of squares were used. To further explore main or interaction effects t-tests were used to conduct post-hoc testing; means (M) and standard deviations (SD) are reported. No testing for effects was corrected for multiple testing since we were interested in even small effects. According to our main hypotheses, PHQ-9 scores (pre and post treatment) and FC scores served as outcome variables. To explore network activity, we investigated the FC between all ROIs as well as within each ROI which sums up to 15 outcome variables. As predictors served the effect coded "time" (pre treatment = 1, post treatment = -1) and therapy approach ("group"; CBT = 1, HT = -1). In a last step, we correlated changes in symptoms and FC by using correlation tests on the change scores (post score – pre score) of the PHQ-9 and the relevant FC. For all analyses a level of significance $\alpha = 0.05$ was assumed.

3.2.3 Results

On a behavioral level we found a therapy effect over time for all patients, displaying a significant reduction in self-reported symptoms (*F*(1,146) = 129.31, $p < 0.001$, *M*(PHQ-9 pre therapy) = 14.69, *SD*(PHQ-9 pre therapy) = 3.99, *M*(PHQ-9 post therapy) = 6.70, *SD*(PHQ-9 post therapy) = 4.37. An interaction effect of time and group did not yield significance, implying that this symptom reduction over time did not differ between the therapy groups (*F*(3,146) = 0.07, *p* = .80). Post-hoc within-group t-testing showed significantly reduced symptoms in CBT (*t*(38) = 11.20, *p* < .001, *M*(PHQ-9 pre therapy) = 14.69, *SD*(PHQ-9 pre therapy) = 4.05, *M*(PHQ-9 post therapy) = 6.70, *SD*(PHQ-9 post therapy) = 3.99) and HT (*t*(35) = 8.63, *p* < .001, *M*(PHQ-9 pre therapy) = 14.89, *SD*(PHQ-9 pre therapy) = 3.99, *M*(PHQ-9 post therapy) = 7.25, *SD*(PHQ-9 post therapy) = 4.80).

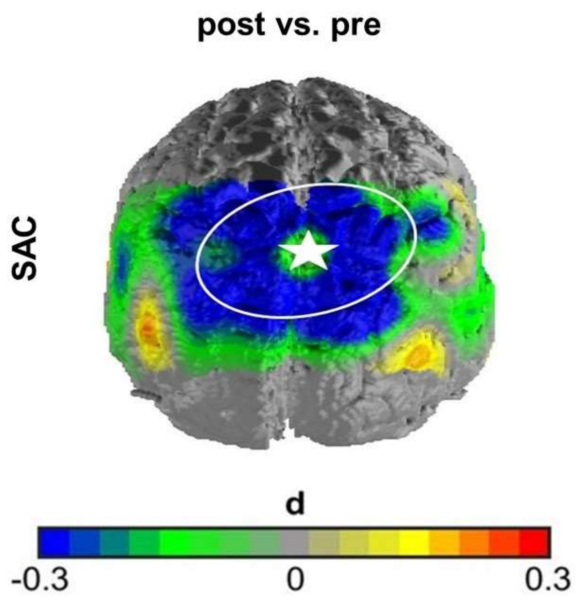

Figure 3. Effect size of main effect of time. The FC within the SAC decreased significantly over time comparing before therapy to after therapy. Channel 16 (marked with star) served as seed channel for this graph, displaying the contrast of correlations over time of all SAC channels to channel 16. *FC* Functional Connectivity, *SAC* Somatosensory Association Cortex.

On a neurophysiological level, we found a main effect of time within one ROI and an interaction effect between two ROIs out of the 15 possible intra- or inter-ROI connections. In the first case, namely the FC within the SAC, the time predictor yielded significance, implying a change in FC within the SAC throughout therapy ($F(1,146) = 7.00$, $p = 0.01$). FC significantly decreased after therapy (*M*(post therapy)=0.48, *SD*(post therapy) = 0.17) compared to before therapy (*M*(pre therapy) = 0.56 , *SD*(pre therapy)= 0.22), as displayed in Figure 3.

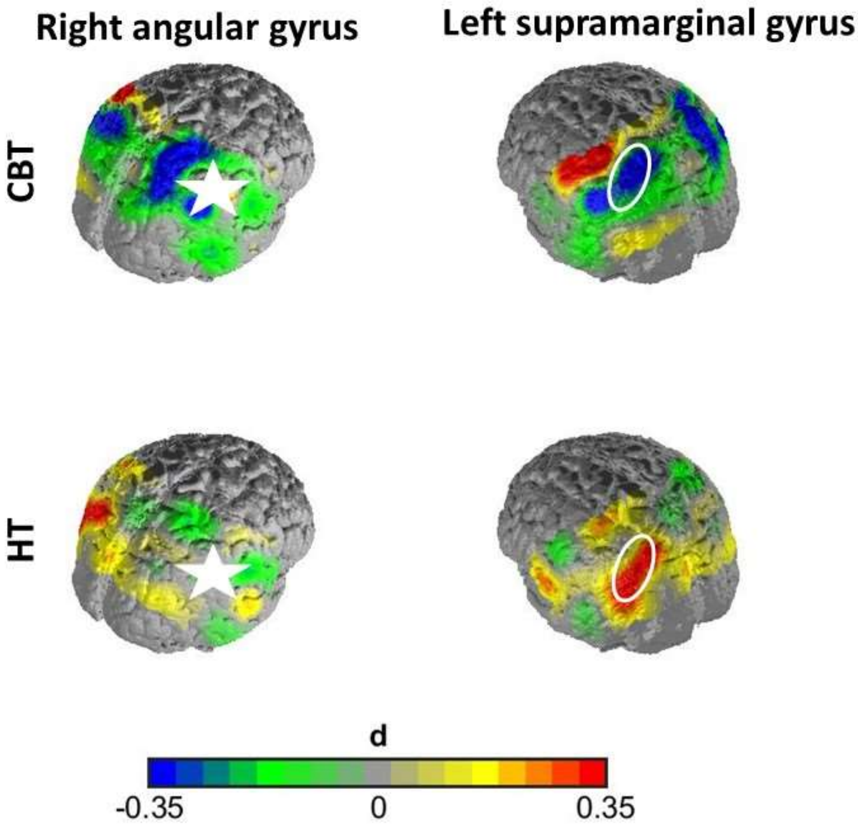

Figure 4. Effect size of interaction effect of time and group. The FC between the right angular gyrus and left supramarginal gyrus decreased non-significantly throughout therapy in the CBT group, while it increased in the HT group significantly. The right angular gyrus channels (marked with star) served as seed region for this graph, displaying the time-contrast of correlations of supramarginal gyrus channels to the seed region for both groups. *CBT* Cognitive Behavioral Therapy, *HT* Hypnotherapy, *FC* Functional Connectivity.

An interaction effect of time and group yielded significance ($F(1,146) = 3.83$, $p= 0.05$) implying a change in FC between the right angG and left supG, differing among the therapy groups. In CBT the FC between the right angG and left supG decreased throughout therapy (*M*(pre therapy) = 0.32, *SD*(pre therapy) = 0.28), *M*(post therapy)=0.26, *SD*(post therapy) = 0.14), while it increased in HT (*M*(pre therapy) = 0.26, *SD*(pre therapy) = 0.19), *M*(post therapy)=0.32, *SD*(post therapy) = 0.15), as displayed in Figure 4. We conducted an exploratory post-hoc within-group t-tests which showed his change to be only significant in the HT group ($t(35) = -2.15$, $p = 0.04$).

All means and SDs of the analyzed ROIs overall and separately for both groups are displayed in Table 1 (inline supplementary material Table 1).

Correlation tests between the change scores of symptoms and changes scores of the FC of the significant ROIs showed no significant correlation between the decrease of FC within the SAC throughout therapy and the symptom reduction overall ($r(73) = -0.87$, $p = 0.39$) nor between the increase of FC between the right angG and left supG throughout therapy and the symptom reduction in the HT group ($r(34) = 0.36$, $p = 0.72$).

To sum up the results: while treatment effects could be observed on the level of depressive symptoms, they were only tentatively found in two components associated with the DMN: the FC within the SAC changed throughout therapy, independent from the therapy patients received, and the FC between the right angG and left supG increased for HT patients. However, the symptom reduction did not correlate significantly with either of these neurophysiological changes.

3.2.4 Discussion

General Discussion

In this first of its kind study, we wanted to bring together the very different research objectives of DMN functioning in depression, its change throughout therapy, as well as hypnosis related DMN changes. Therefore, we investigated the neural effects of CBT and HT for depressed patients regarding key parts of the DMN. Results show that both therapies were effective in patients' symptom reduction. Further, a change in FC throughout therapy was observed in two components associated with the DMN: FC within the SAC decreased with time, indifferently of the therapy group, whereas an inter-hemispheric connection, namely between the right angG and left supG, increased only in the HT group. A correlation between these FC changes and the symptom reduction could not be found.

In this study, the ROI representing the SAC included a considerable amount of channels and spread over both hemispheres, accounting for the rather small spatial resolution of fNIRS (McCormick, Stewart, Lewis, Dujovny, & Ausman, 1992; Wabnitz et al., 2010). We assume that the parietal midline channels of this ROI include cortical parts of the PCu, which from the beginning of DMN research has been shown to be an important part of this network (Raichle et al., 2001). Most recent research shows that especially midline cortical areas seem to play an important role in depression-specific DMN abnormalities (Scalabrini et al., 2020). More specifically, the authors show that the depression-specific increase of DMN FC in these midline regions can be attributed to the abnormally high connection of the DMN to other brain networks and not to an increased intra-network connection: The abnormally active DMN midline regions were strongly connected to brain regions outside the DMN. The authors conclude that this could account for the many cognitive, sensory and affective functions, which are not associated with the DMN and still impaired in depression (Scalabrini et al., 2020). In line with this and previous research (Anand et al., 2005; Greicius et al., 2007; Grimm et al., 2009; Sheline et al., 2009), the here found decrease of FC within the SAC over time might mirror a normalization of this DMN midline component in depressed patients throughout therapy. Since this decrease was found for both therapy groups, it might reflect an overall treatment effect and not a specific component of either therapy program.

A therapy-specific effect was found in an interhemispheric DMN connection, which increased in FC over time in the HT group. Generally speaking, the strength of DMN FC follows an inverted u-shaped form across the life-span (i.e., it is higher in adulthood as compared to both childhood/adolescence and older age) and is positively correlated with cognitive functions (Mak et al., 2017). Further, while earlier studies seemed to suggest increased FC within the DMN in depressive patients as reported above, later studies showed both, increased and decreased DMN FC in depression (Guo et al., 2014; Zhu et al., 2012) and even more recent data indicate reduced FC in depression – at least in recurrent major depression (Connolly et al., 2013; Yan et al., 2019). Therefore, an increase of intra-DMN FC could reflect a therapy-specific normalization of DMN connectivity in the HT group. Why the therapeutic effect of CBT, which was clearly visible on a symptom level, was not reflected in DMN-related FC should be investigated in the future. Possibly, CBT specific effects can be found more easily in cerebral networks that are associated with high-level cognitive functioning like the Central Executive Network (CEN[21]) (Menon, 2011).

As Scalabrini et al. (2020) stress the role of the DMN midline regions in depression-specific over-activation, the role of rather lateral DMN regions and their connections remains unclear. Hypnosis was shown to be connected to parts of the DMN. However, which part of the DMN plays which role during hypnosis is still unknown. Consistently, involvement of prefrontal parts and the PCC during hypnotic trance has been reported (Cojan et al., 2009; Deeley et al., 2012; Egner et al., 2005; McGeown et al., 2009; Pyka et al., 2011; Rainville et al., 2002); lateral parts of the DMN were associated with hypnotic trance in one case (Pyka et al., 2011). Functionally, the DMN has been linked to a self-referential, introspective state, which may have very plausibly been fostered through the HT interventions. In HT, a major technique involved inducing pleasant emotions linked to personal experiences to make the patients feel strong, competent, and hopeful (Wilhelm-Goessling et al., 2020). Taken together, the group difference in FC changes between two of our DMN ROIs could be a first indication of a HT-specific impact on this network, which has been linked to self-referential processing. The specific effect of HT on the DMN though is not understood well enough and needs to be object to further research.

The lack of correlations between symptom reduction and DMN associated changes might hint towards a multifaceted connection between DMN activity on a cerebral level and symptoms on a behavioral level. As the authors of one study suggest (Scalabrini et al., 2020), many symptoms in depression are associated with processes of non-DMN networks like movement, memory, reward, perception and they might be connected to the DMN on a neurophysiological level through over-connections with the DMN. Therefore, it is plausible that symptoms and abnormal DMN activity in depression are both components of a very complex psychopathology but do not relate directly or linearly. Moderating or mediating factors such as subtypes of depression, amount of rumination, extent of somatic syndrome in depression, symptom severity or medication (see below) seem likely to be part of the equation. In a review, the authors report that in different studies up to six depression subtypes, which differed on a symptom as well as brain network FC level, were identified (Chahal, Gotlib, & Guyer, 2020; Williams, 2017). Also, non-linear relations could draw another connection between symptoms and DMN activity. In future research, variations in symptoms should be controlled for. Also, NIRS measurements should be conducted more often (e.g. weekly) to find possible non-linear relations.

Further, it remains unclear if psychotherapy and DMN changes relate directly or if they are also moderated or mediated by other factors. Psychotherapy, in the case of this study CBT and HT, includes many different techniques, aspects, a unique relationship between therapist and client and it is temporally spread – in our case over half a year – with weekly sessions, which leaves much time to process, learn and apply aspects of therapy. So far, few studies have been conducted on the effects of therapy on the DMN; in one, using functional magnetic resonance imaging (fMRI[22]), the authors investigated the effect of behavioral activation on the change of the DMN and found a reduction of FC in an anterior subnetwork of the DMN after the intervention (Yokoyama et al., 2017). In another study from the same year, the authors also found a reduction of frontal DMN FC, namely between the mPFC and ACC after CBT and correlating positively with symptom reduction (Yoshimura et al., 2017). Until now it is unclear, which role temporal and parietal parts of the DMN play in therapy related DMN changes and calls for further investigation. Furthermore, time itself probably plays a crucial role in the progression of depression and its effects on the DMN are yet to be investigated. Again, a clearer picture of the role of the DMN during a temporally spread therapy could be obtained by a higher temporal resolution of measurements by e.g., weekly measurements.

Limitations and future research

A clear limitation to fNIRS is the restricted penetration depth of 3–5 mm into the adult cortex (Gervain et al., 2011) and thus the inability to measure subcortical processes. Especially concerning the DMN, subcortical regions are of interest (Raichle et al., 2001), like the PCC and ACC. Therefore, data from alternative imaging methods, such as fMRI, should be analyzed to underpin our findings. Further, our data on a symptom level consisted of self-reports and not an objective measure on a behavioral level or clinician administered scales. In future research a measure mirroring DMN processes, like rumination scales, should be included in the analysis. Additionally, the self-report questionnaire PHQ-9 consisted of only 9 questions, which is too short and unprecise to draw a more differentiated picture of depression symptoms and possible connections to the DMN. Another factor to consider in future research is the influence of medication. As the authors find in their very large study, the medication treatment of depressed patients was associated with decreased DMN FC, while illness duration did not play a significant role (Yan et al., 2019). Also, symptom severity was associated with reduced DMN FC only in recurrent depression (Yan et al., 2019). These factors were not included in our analyses. We suggest including the factor “medication” and the number of earlier episodes in future research on depression-specific DMN FC. Another limitation is that we derived our hypotheses concerning HT from research on hypnosis, not hypnosis included in therapy. Hypnosis used in therapy might be a very different issue though: Most hypnotic trances used in neurophysiological hypnosis studies do not include personal, nor emotional content and they were not applied repeatedly over a longer period of time, nor with patients, but healthy controls. Instead they included e.g. relaxation (Deeley et al., 2012) or hand paralysis (Cojan et al., 2009; Pyka et al., 2011). So, in future studies hypnotic trances similar to the ones used in a therapeutic context containing personal, emotionally relevant content, should be investigated regarding their connection to the DMN. Also, the effect of hypnotic trances applied repeatedly over a longer period of time, should be researched.

Conclusion

This study is the first of its kind: We investigated 75 depressed patients receiving either CBT or HT regarding FC associated with the DMN. All patients reported significantly fewer symptoms after therapy and this treatment effect was also found in two components of the DMN, while one of these was only significant for the HT group. These findings could hint towards overall treatment effects of psychotherapy in depressed patients and more specifically towards differential effects of different types of psychotherapy. Even though both therapy approaches helped the patients (i.e., reduced depressive symptoms), they might have done so based on different neural mechanisms. With this study we hope to open up a whole new field of questions about the effects of hypnosis in a therapeutic context. On a level of symptoms HT seems to be a very effective alternative to CBT when treating depression, and with our research we hope to set a first stepstone to understanding the underlying processes of this fascinating method.

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Statement of Ethics

This study was approved with a positive ethics vote by the Ethics Committee of the University Hospital of Tuebingen (061/2015B02). All patients gave their written informed consent to participate in the study after they had read a study description.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Submission declaration

This study has not been published elsewhere, neither is it in consideration to be published elsewhere. In case of acceptance, it will not be published elsewhere. All authors approved this manuscript.

Authors' contributions

Alina Haipt: Original idea, conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Visualization. **David Rosenbaum**: Conceptualization, Software, Data Curation, Writing – Review & Editing. **Kristina Fuhr**: Resources, Writing – Review & Editing, Project administration. **Anil Batra**: Supervision, Funding acquisition, Writing – Review & Editing. **Ann-Christine Ehlis**: Original idea, Conceptualization, Methodology, Formal analysis, Resources, Validation, Supervision, Project administration, Funding acquisition, Writing – Review & Editing.

Literature

Alladin. (2006). Cognitive hypnotherapy for treating depression. In *The clinical use of hypnosis with cognitive behavior therapy: A practitioner's casebook* (pp. 139–187).

Alladin, A., & Alibhai, A. (2007). Cognitive hypnotherapy for depression: An empirical investigation. *International Journal of Clinical and Experimental Hypnosis*, *55*(2), 147–166. https://doi.org/10.1080/00207140601177897

American Pschological Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington: American Psychological Association.

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., … Lowe, M. J. (2005). Activity and connectivity of brain mood regulating circuit in depression: A functional magnetic resonance study. *Biological Psychiatry*, *57*(10), 1079–1088. https://doi.org/10.1016/j.biopsych.2005.02.021

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-Anatomic Fractionation of the Brain's Default Network. *Neuron*, *65*(4), 550–562. https://doi.org/10.1016/j.neuron.2010.02.005

Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive Therapy for Depression*. New York: Guilford.

Berman, M. G., Peltier, S., Nee, D. E., Kross, E., Deldin, P. J., & Jonides, J. (2011). Depression, rumination and the default network. *Social Cognitive and Affective Neuroscience*, *6*(5), 548–555. https://doi.org/10.1093/scan/nsq080

Bulgarelli, C., de Klerk, C. C. J. M., Richards, J. E., Southgate, V., Hamilton, A., & Blasi, A. (2020). The developmental trajectory of fronto-temporoparietal connectivity as a proxy of the default mode network: a longitudinal fNIRS investigation. *Human Brain Mapping*, *41*(10), 2717–2740. https://doi.org/10.1002/hbm.24974

Chahal, R., Gotlib, I. H., & Guyer, A. E. (2020). Research Review: Brain network connectivity and the heterogeneity of depression in adolescence – a precision mental health perspective. *The Journal of Child Psychology and Psychiatry*, *61*(12), 1282–1298. https://doi.org/10.1111/jcpp.13250

Cojan, Y., Waber, L., Schwartz, S., Rossier, L., Forster, A., & Vuilleumier, P. (2009). The brain under self-control: modulation of inhibitory and monitoring cortical networks during hypnotic paralysis. *Neuron*, *62*(6), 862–875. https://doi.org/10.1016/j.neuron.2009.05.021

Connolly, C. G., Wu, J., Ho, T. C., Hoeft, F., Wolkowitz, O., Eisendrath, S., … Yang, T. T. (2013). Resting-State Functional Connectivity of Subgenual Anterior Cingulate Cortex in Depressed Adolescents. *Biological Psychiatry*, *74*(12), 898–907. https://doi.org/10.1016/j.biopsych.2013.05.036.Resting-State

Cui, X., Bray, S., & Reiss, A. (2010). Functional near infrared spectroscopy (NIRS) signal improvement based on negative correlation between oxygenated and deoxygenated hemoglobin. *Neuroimage*, *49*(9), 3039–3046. Retrieved from http://www.sciencedirect.com/science/article/pii/S105381190901235X

Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., & Dobson, K. S. (2013). A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *Canadian Journal of Psychiatry*, *58*(7), 376–385. https://doi.org/10.1177/070674371305800702

Deeley, Q., Oakley, D., Toone, B., Giampietro, V., Brammer, M. J., Williams, S. C. R., & Halligan, P. W. (2012). Modulating the default mode network using hypnosis. *The International Journal of Clinical and Experimental Hypnosis*, *60*(2), 206–228. https://doi.org/10.1080/00207144.2012.648070

DeRubeis, R. J., Siegle, G. J., & Hollon, S. D. (2008). Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. *Nature Reviews. Neuroscience*, *9*(10), 788–796. https://doi.org/10.1038/nrn2345

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. *Brain Structure and Function*, *213*(1–2), 93–118. https://doi.org/10.1007/s00429-008-0189-x

Duan, L., Van Dam, N. T., Ai, H., & Xu, P. (2020). Intrinsic organization of cortical networks predicts state anxiety: an functional near-infrared spectroscopy (fNIRS) study. *Translational Psychiatry*, *10*(402), 1–9. https://doi.org/10.1038/s41398-020-01088-7

Egner, T., Jamieson, G., & Gruzelier, J. (2005). Hypnosis decouples cognitive control from conflict monitoring processes of the frontal lobe. *NeuroImage*, *27*(4), 969–978. https://doi.org/10.1016/j.neuroimage.2005.05.002

Elliott, R., Zahn, R., Deakin, J. F. W., & Anderson, I. M. (2011). Affective cognition and its disruption in mood disorders. *Neuropsychopharmacology*, *36*(1), 153–182. https://doi.org/10.1038/npp.2010.77

Ernst, L. H., Schneider, S., Ehlis, A. C., & Fallgatter, A. J. (2012). Functional Near Infrared Spectroscopy in Psychiatry: A critical review. *Journal of Near Infrared Spectroscopy*, *20*(1), 93–105. https://doi.org/10.1255/jnirs.970

Fallgatter, A. J., Ehlis, A. C., Wagener, A., Michel, T., & Herrmann, M. J. (2004). Nah-Infrarot-Spektroskopie in der Psychiatrie. *Nervenarzt*, *75*(9), 911–916. https://doi.org/10.1007/s00115-002-1457-2

Fishburn, F. A., Ludlum, R. S., Vaidya, C. J., & Medvedev, A. V. (2019). Temporal Derivative Distribution Repair (TDDR): A motion correction method for fNIRS. *NeuroImage*, *184*, 171–179. https://doi.org/10.1016/j.neuroimage.2018.09.025.Temporal

Franklin, G., Carson, A., & Welch, K. (2016). Cognitive behavioural therapy for depression: systematic review of imaging studies. *Acta Neuropsychiatrica*, *28*(2), 61–74. https://doi.org/10.1017/neu.2015.41

Fuhr, K., Meisner, C., Broch, A., Cyrny, B., Hinkel, J., Jaberg, J., … Batra, A. (2021). Efficacy of hypnotherapy compared to cognitive behavioral therapy for mild to moderate depression - Results of a randomized controlled rater-blind clinical trial. *Journal of Affective Disorders*, *286*, 166–173. https://doi.org/10.1016/j.jad.2021.02.069

Gervain, J., Mehler, J., Werker, J. F., Nelson, C. A., Csibra, G., Lloyd-Fox, S., … Aslin, R. N. (2011). Near-infrared spectroscopy: A report from the McDonnell infant methodology consortium. *Developmental Cognitive Neur*, *1*, 22–46. https://doi.org/10.1016/j.dcn.2010.07.004

Greicius, M. D., Kiviniemi, V., Tervonen, O., Vainionpa, V., Alahuhta, S., Reiss, A., & Menon, V. (2008). Persistent Default-Mode Network Connectivity During Light Sedation. *Human Brain Mapping*, *29*(7), 839–847.

https://doi.org/10.1002/hbm.20537

Greicius, M.D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences*, *100*(1), 253–258. https://doi.org/https://doi.org/10.1073/pnas.0135058100

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., … Schatzberg, A. F. (2007). Resting-State Functional Connectivity in Major Depression: Abnormally Increased Contributions from Subgenual Cingulate Cortex and Thalamus. *Biological Psychiatry*, *62*(5), 429–437. https://doi.org/10.1016/j.biopsych.2006.09.020

Griffiths, M. (2017). The role of hypnotherapy in evidence-based clinical practice. *Oral Dieseases*, *23*(4), 420–423. https://doi.org/10.1111/odi.12532

Grimm, S., Boesiger, P., Beck, J., Schuepbach, D., Bermpohl, F., Walter, M., … Northoff, G. (2009). Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects. *Neuropsychopharmacology*, *34*(4), 932–943. https://doi.org/10.1038/npp.2008.81

Guo, W., Liu, F., Zhang, J., Zhang, Z., Yu, L., Liu, J., … Xiao, C. (2014). Abnormal default-mode network homogeneity in first-episode, drug-naive major depressive disorder. *PLoS ONE*, *9*(3), 1–7. https://doi.org/10.1371/journal.pone.0091102

Halsband, U., & Wolf, T. G. (2015). Functional changes in brain activity after hypnosis in patients with dental phobia. *Journal of Physiology*, *109*(4–6), 131–142. https://doi.org/10.1016/j.jphysparis.2016.10.001

Horovitz, S. G., Braun, A. R., Carr, W. S., Picchioni, D., Balkin, T. J., Fukunaga, M., & Duyn, J. H. (2009). Decoupling of the brain’s default mode network during deep sleep. *Proceedings of the National Academy of Sciences*, *106*(27), 11376–11381. https://doi.org/10.1073/PNAS.0901435106

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. *JAMA Psychiatry*, *72*(6), 603–611. https://doi.org/10.1001/jamapsychiatry.2015.0071

Kroenke, K., & Spitzer, R. L. (2002). The PHQ-9: A new depression diagnostic and severity measure. *Psychiatric Annals*, *32*, 509–521. https://doi.org/10.3928/0048-5713-20020901-06

Leichsenring, F., & Steinert, C. (2017). Is Cognitive Behavioral Therapy the Gold Standard for Psychotherapy ? The Need for Plurality in Treatment and Research. *Jama*, *318*(14), 1323–1324. https://doi.org/10.1001/jama.2017.13737

Lowén, M. B. O., Mayer, E. a., Sjöberg, M., Tillisch, K., Naliboff, B., Labus, J., … Walter, S. a. (2013). Effect of hypnotherapy and educational intervention on brain response to visceral stimulus in the irritable bowel syndrome. *Alimentary Pharmacology and Therapeutics*, *37*(12), 1184–1197. https://doi.org/10.1111/apt.12319

Lueken, U., & Hahn, T. (2016). Functional neuroimaging of psychotherapeutic processes in anxiety and depression: from mechanisms to predictions. *Current Opinion in Psychiatry*, *29*(1), 25–31. https://doi.org/10.1097/YCO.0000000000000218

Mak, L. E., Minuzzi, L., MacQueen, G., Hall, G., Kennedy, S. H., & Milev, R. (2017). The Default Mode Network in Healthy Individuals: A Systematic Review and Meta-Analysis. *Brain Connectivity*, *7*(1), 25–33. https://doi.org/10.1089/brain.2016.0438

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science*, *315*(5810), 393–395. https://doi.org/10.1126/science.1131295

McCormick, P. W., Stewart, M., Lewis, G., Dujovny, M., & Ausman, J. I. (1992). Intracerebral penetration of infrared light. Technical note. *Journal of Neurosurgery*, *76*(2), 315–318. https://doi.org/https://doi.org/10.3171/jns.1992.76.2.0315

McGeown, W. J., Mazzoni, G., Venneri, A., & Kirsch, I. (2009). Hypnotic induction decreases anterior default mode activity. *Consciousness and Cognition*, *18*(4), 848–855. https://doi.org/10.1016/j.concog.2009.09.001

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in Cognitive Sciences*, *15*(10), 483–506. https://doi.org/10.1016/j.tics.2011.08.003

Nolen-Hoeksema, S. (1991). Responses to depression and their effects on the duration of depressive episodes. *Journal of Abnormal Psychology*, *100*(4), 569–582. https://doi.org/10.1037/0021-843X.100.4.569

Patil, A. V., Safaie, J., Moghaddam, H. A., Wallois, F., & Grebe, R. (2011). Experimental investigation of NIRS spatial sensitivity. *Biomedical Optics Express*, *2*(6), 1478–1493. https://doi.org/10.1364/boe.2.001478

Pyka, M., Burgmer, M., Lenzen, T., Pioch, R., Dannlowski, U., Pfleiderer, B., … Konrad, C. (2011). Brain correlates of hypnotic paralysis—a resting-state fMRI study. *NeuroImage*, *56*(4), 2173–2182. Retrieved from http://www.sciencedirect.com/science/article/pii/S1053811911003727

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*(2), 676–682.

Rainville, P., Hofbauer, R. K., Bushnell, M. C., Duncan, G. H., & Price, D. D. (2002). Hypnosis modulates activity in brain structures involved in the regulation of consciousness. *Journal of Cognitive Neuroscience*, *14*(6), 887–901. Retrieved from http://www.mitpressjournals.org/doi/abs/10.1162/089892902760191117

Revenstorf, D. (2003). *Expertise zur Beurteilung der wissenschaftlichen Evidenz des Psychotherapieverfahrens*. University Tuebingen.

Rosenbaum, D., Hagen, K., Deppermann, S., Kroczek, A. M., Haeussinger, F. B., Heinzel, S., … Ehlis, A. C. (2016). State-dependent altered connectivity in late-life depression: A functional near-infrared spectroscopy study. *Neurobiology of Aging*, *39*, 57–68. https://doi.org/10.1016/j.neurobiolaging.2015.11.022

Rosenbaum, D., Haipt, A., Fuhr, K., Haeussinger, F. B., Metzger, F. G., Nuerk, H. C., … Ehlis, A. C. (2017). Aberrant functional connectivity in depression as an index of state and trait rumination. *Scientific Reports*, *7*(1), 1–12. https://doi.org/10.1038/s41598-017-02277-z

Scalabrini, A., Vai, B., Poletti, S., Damiani, S., Mucci, C., Colombo, C., … Northoff, G. (2020). All roads lead to the default-mode network—global source of DMN abnormalities in major depressive disorder. *Neuropsychopharmacology*, *45*(12), 2058–2069. https://doi.org/10.1038/s41386-020-0785-x

Sheline, Y. I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., … Raichle, M. E. (2009). The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(6), 1942–1947. https://doi.org/10.1073/pnas.0812686106

Silver, N. C., & Dunlap, W. P. (1987). Averaging Correlation Coefficients: Should Fisher's z Transformation Be Used ? *Journal of Applied Psychology*, *72*(1), 146–148. https://doi.org/https://doi.org/10.1037/0021-9010.72.1.146

Sonuga-Barke, E. J., & Castellanos, F. X. (2007). Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. *Neuroscience & Biobehavioral Reviews*, *31*(7), 977–986.

Vanhaudenhuyse, A., Noirhomme, Q., Tshibanda, L. J., Bruno, M.-A., Boveroux, P., Schnakers, C., … Boly, M. (2010). Default network connectivity refelcts the level of consciousness in non-communicative brain-damaged patients. *Brain: A Journal of Neurology*, *133*(1), 161–171. https://doi.org/10.1093/brain/awp313

Wabnitz, H., Moeller, M., Liebert, A., Obrig, H., Steinbrink, J., & MacDonald, R. (2010). Time-resolved Near-Infrared Spectroscopy and Imaging of the Adult Human Brain. In E. Takahashi & D. Bruley (Eds.), *Oxygen Transport to Tissue XXXI. Advances in Experimental Medicine and Biology, vol. 662* (pp. 143–148). Boston: Springer.

Whorwell, P. J. (2011). IBS: Hypnotherapy—a wasted resource? *Nature Reviews Gastroenterology & Hepatology*, *9*(1), 12–13. https://doi.org/10.1038/nrgastro.2011.235

Wilhelm-Goessling, C., Schweizer, C., Dürr, C., Fuhr, K., & Revenstorf, D. (2020). *Hypnotherapie bei Depressionen: Ein Manual für Psychotherapeuten*. (A. Batra & F. Hohagen, Eds.) (1st ed.). Stuttgart: Kohlhammer Verlag.

Williams, L. M. (2017). Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. *Depression and Anxiety*, *34*(1), 9–24.

https://doi.org/10.1002/da.22556

Wittchen, H.-U., Wunderlich, U., Gruschwitz, S., & Zaudig, M. (1997). *SKID I. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen.* Göttingen: Hogrefe.

Yan, C.-G., Chen, X., Li, L., Castellanos, F. X., Bai, T.-J., Bo, Q.-J., … Zang, Y.-F. (2019). Reduced default mode network functional connectvity in patients with recurrent major depressive disorder. *Proceedings of the National Academy of Sciences*, *116*(18), 9078–9083.

Yokoyama, S., Okamoto, Y., Takagaki, K., Okada, G., Takamura, M., Mori, A., … Yamawaki, S. (2017). Effects of behavioral activation on default mode network connectivity in subthreshold depression: a preliminary resting-state fMRI study. *Journal of Affective Disorders*, *227*, 156–163. https://doi.org/10.1016/j.jad.2017.10.021

Yoshimura, S., Okamoto, Y., Matsunaga, M., Onoda, K., Okada, G., Kunisato, Y., … Yamawaki, S. (2017). Cognitive behavioral therapy changes functional connectivity between medial prefrontal and anterior cingulate cortices. *Journal of Affective Disorders*, *208*, 610–614. https://doi.org/10.1016/j.jad.2016.10.017

Zhu, X., Wang, X., Xiao, J., Liao, J., Zhong, M., Wang, W., & Yao, S. (2012). Evidence of a Dissociation Pattern in Resting-State Default Mode Network Connectivity in First-Episode, Treatment-Naive Major Depression Patients. *Biological Psychiatry*, *71*(7), 611–617. https://doi.org/10.1016/j.biopsych.2011.10.035

Inline supplementary material

FC between		*Mean* Pre FC	*Mean* Post FC	*SD* Pre FC	*SD* Post FC
angG left to angG left	Overall CBT HT	0.33 0.31 0.35	0.31 0.28 0.35	0.19 0.19 0.19	0.17 0.13 0.20
angG left to angG right	Overall CBT HT	0.30 0.29 0.30	0.30 0.28 0.31	0.17 0.18 0.17	0.14 0.14 0.14
angG left to supG left	Overall CBT HT	0.34 0.35 0.34	0.35 0.33 0.38	0.19 0.17 0.21	0.17 0.15 0.18
angG left to supG right	Overall CBT HT	0.23 0.22 0.24	0.25 0.23 0.27	0.19 0.17 0.21	0.15 0.15 0.15
angG left to SAC	Overall CBT HT	0.31 0.32 0.31	0.29 0.27 0.30	0.19 0.14 0.23	0.15 0.15 0.15
angG right to angG right	Overall CBT HT	0.34 0.35 0.33	0.29 0.29 0.28	0.19 0.21 0.17	0.15 0.15 0.15
angG right to supG left	Overall CBT HT	0.29 0.32 0.26	0.29 0.26 0.32	0.24 0.28 0.19	0.15 0.14 0.15
angG right to supG right	Overall CBT HT	0.36 0.37 0.34	0.32 0.30 0.35	0.22 0.26 0.17	0.15 0.16 0.14
angG right to SAC	Overall CBT HT	0.32 0.33 0.30	0.28 0.25 0.32	0.21 0.22 0.20	0.14 0.14 0.13

supG left to supG left	Overall CBT HT	0.43 0.45 0.41	0.44 0.43 0.44	0.21 0.23 0.19	0.16 0.16 0.17
supG left to supG right	Overall CBT HT	0.48 0.50 0.46	0.46 0.47 0.46	0.21 0.25 0.17	0.17 0.16 0.18
supG left to SAC	Overall CBT HT	0.46 0.46 0.46	0.44 0.43 0.45	0.20 0.22 0.18	0.15 0.15 0.15
supG right to supG right	Overall CBT HT	0.51 0.52 0.51	0.46 0.46 0.46	0.19 0.20 0.18	0.16 0.16 0.17
supG right to SAC	Overall CBT HT	0.43 0.42 0.44	0.41 0.39 0.44	0.20 0.23 0.17	0.14 0.14 0.13
SAC to SAC	Overall CBT HT	0.56 0.53 0.59	0.48 0.46 0.50	0.21 0.22 0.19	0.17 0.18 0.15

Table 1. All means and standard deviations for all 15 ROIs, overall and both groups separately. *FC* functional connectivity, *HT* Hypnotherapy, *CBT* Cognitive Behavioral Therapy, *angG* angular gyrus, *SAC* somatosensory association cortex, *supG* supramarginal gyrus.

4. Manuscript 2: The effects of hypnotherapy compared to cognitive behavioral therapy in depression: a NIRS-study using an emotional gait paradigm

4.1 Author Contributions

Study Design WIKI-D and Fundraising: Anil Batra and Kristina Fuhr.

Study Design of Neurophysiological Addition: Alina Haipt in consultation with Ann-Christine Ehlis.

Design of Paradigm: Martin Giese

Sample Recruitment and Data collection: Alina Haipt.

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Manuscript Drafting and Correcting: First draft written by Alina Haipt with revisions from Ann-Christine Ehlis, David Rosenbaum, Anil Batra, and Kristina Fuhr. Redrafting by Alina Haipt.

Journal Selection and Submission: Alina Haipt in consultation with Ann-Christine Ehlis.

4.2 Research Article 2

The Effects of Hypnotherapy compared to Cognitive Behavioral Therapy in depression: an fNIRS-study using an emotional gait paradigm

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Abstract

Hypnotherapy (HT) is a promising approach to treating depression, but so far, no data are available on the neuronal mechanisms of functional reorganization after hypnotherapy for depressed patients. Here, 75 patients with mild to moderate depression, who received either HT or Cognitive Behavioral Therapy (CBT), were measured before and after therapy using functional near-infrared spectroscopy. We investigated the patients' cerebral activation during an emotional human gait paradigm. Further, rumination was included as predictor. Our results showed a decrease of functional connectivity (FC) between two regions that are crucial to emotional processing, the Extrastriate Body Area (EBA) and the Superior Temporal Sulcus (STS). This FC decrease was traced back to an activation change throughout therapy in the right STS, not the EBA and was only found in the HT group, depending on rumination: less ruminating HT patients showed a decrease in right STS activation, while highly ruminating patients showed an increase. We carefully propose that this activation change is due to the promotion of emotional experiences during HT, while in CBT a focus lay on activating behavior and changing negative cognitions. HT seemed to have had differential effects on the patients, depending on their rumination style: The increase of right STS activation in highly ruminating patients might mirror the improvement of impaired emotional processing, whilst the decrease of activation in low ruminating patients might reflect a dismissal of an over-compensation, associated with a hyperactivity before therapy. We conclude that HT affects emotional processing and this effect is moderated by rumination.

Keywords: Hypnotherapy, Cognitive Behavioral Therapy, emotional processing, temporal lobe, depression

4.2.1 Introduction

Depression is a widespread mental disorder currently affecting an estimated number of 264 million people worldwide [1]. Besides somatic and emotional symptoms [2] depression is associated with self-referential thoughts of negative content about the past, future and self, called rumination [3,4]. Cognitive Behavioral Therapy (CBT) has been shown to be an effective treatment for depressed patients [5]. It seems to help normalize depression-specific aberrant prefrontal [6] and amygdala activity [7]. In a meta-analysis on the neurophysiological effects of depression treatment, the authors report effects in frontal areas bilaterally and the lingual gyrus, middle temporal gyrus and middle cingulate cortex left-hemispherically [8]. The effectiveness of CBT in treating depression might originate in an increase of prefrontal functioning, which is associated with cognitive control [9,10]. On the other hand, Hypnotherapy (HT), as one of the oldest techniques used in treating mental and somatic disorders [11], displays a promising alternative to CBT in reducing depressive symptoms [12]. Meta-analyses have substantiated the adjuvant effect of hypnotic interventions in treating depressed patients [13,14] and greater effect sizes in symptom reduction when HT is added to CBT compared to sole CBT elements [15]. Fuhr et al. [16] showed in their WIKI-D study that HT is similarly effective to CBT in reducing mild to moderate depression despite their obvious theoretical and conceptual differences. The neurophysiological effects of HT were investigated in patients with irritable bowel syndrome [17] and dental phobia [18]; in recent literature the neurophysiological effects of hypnosis and HT are reviewed and a biopsychosocial model of hypnosis was suggested [19,20]. However, so far, the underlying neurobiological processes of HT applied specifically for treating depressed patients have not been investigated.

Depressed patients show altered emotional processing on a behavioral and perceptional level, including aberrant emotional recognition [21,22], a negativity bias [23,24], as well as attention biases [25,26]. Strikingly, most studies on emotional recognition in general and affective perception during depression have been conducted with faces as stimulus material [27]. However, humans are often forced to use other clues than faces, such as posture or gait [28], to infer emotional states in others. Thus, in this study we focus on the ability of emotional recognition based on human gait.

Neuroanatomically, emotion recognition based on whole-body movements is related to the Extrastriate Body Area (EBA) in the posterior inferior temporal sulcus/middle temporal gyrus [29–32]. Another region of interest (ROI) is the superior temporal sulcus (STS), which is associated with the analysis of biological motion [33–39] and also theory of mind (ToM) processes [39] like understanding the actions [40–43] or mental states of others [44–48]. It was found to be active when presenting subjects with dynamic emotional body expressions [28,49–51]. Moreover, depression is associated with abnormalities in the superior temporal cortex (including the superior temporal gyrus (STG) and its lateral part, which is often referred to as STS region [52]). In a meta-analysis of functional magnetic resonance imaging (fMRI) studies, the authors found the STG to be one of the regions most consistently involved in depression [52–56].

In the past years, research has focused on investigating connections between cerebral areas (i.e., neural networks) rather than isolated brain regions. Consequently, in this study we concentrated on the functional co-activation of distinct brain areas – namely the STS and EBA – in terms of functional connectivity (FC). From a theoretical perspective, emotion recognition based on human gait should be reflected in an increased FC between STS and EBA, since both areas are associated with motion recognition as well as emotional processing (STS) and dynamic emotion recognition (EBA), as described above. A coupling of these two areas could reflect a process of the sensory perception of a dynamic emotional body expression (EBA activation) as well as its integration and interpretation (STS activation).

Based on previous own research including a subsample of patients used in this study, it seems that the extent to which depressed patients ruminate influences cerebral activation [57]. Depressed patients who react habitually with rumination to sad mood (trait rumination) showed less FC within the Default-Mode Network (DMN), a major cerebral network that is associated with processes relevant to depression [58–60].

Functional near-infrared spectroscopy (NIRS) is a non-invasive method for optically-based functional imaging, offering many advantages including its easy and quick applicability in a noise-free setting and its (relative) tolerance towards movement [61,62], as well as few exclusion criteria. fNIRS has been shown to be an apt method to measure activation changes in cerebral networks [57,58].

Based on the theoretical and empirical background outlined above, we focused on the effects of CBT vs. HT on neurophysiological correlates of emotional processing. We also explored potential moderating influences of rumination and additionally analyzed emotion recognition as a behavioral correlate of emotional processing. Therefore, we examined a subsample of depressed patients who participated in the WIKI-D study [16] before and after therapy (CBT or HT). Using a human gait paradigm [28], activation in cortical areas associated with emotional processing and depression (EBA, STS) was elicited and measured with NIRS. Due to the exploratory nature of this study, our main hypothesis was that changes in the STS-EBA network associated with emotional processing would occur over the study period and that these changes would differ between CBT and HT treatment. Due to previous own research, we further hypothesized that rumination would moderate this change in connectivity between and among the groups and that the cerebral effects would be mirrored in the patients' behavior.

4.2.2 Methods

Subjects

All participants were recruited from 152 patients (intended to treat) of the WIKI-D study [16] , all being diagnosed with an unipolar mild to moderate depressive episode by trained clinicians using the Structured Clinical Interview for DSM-IV (SKID-I; [63]). Exclusion criteria for our neurophysiological measurements were pregnancy or nursing a child, severe neurological diseases (e.g. meningitis, epilepsy), untreated hypertension, diabetes, or other coronary diseases as well as social phobia and acute substance abuse. In total, we included 75 patients (56 female, 19 male; 18–69 years, *M* = 39.24, *SD* = 14.85) participating in two NIRS measurements, one before and one after therapy (Figure 1). Nearly one third of the patient sample (n = 24) showed at least one acute comorbid disorder; 25 patients (n = 25) took at least one antidepressant medication (36 % SSRIs or other including atypical antipsychotics[4]), which had to been taken without changes for three months prior to the study. All participants gave their written informed consent to participate in the study.

[4] besides NaSSA, tricyclic antidepressants, hypericum, SSNRI, agomelatin, bupropion, anticonvulsive medication

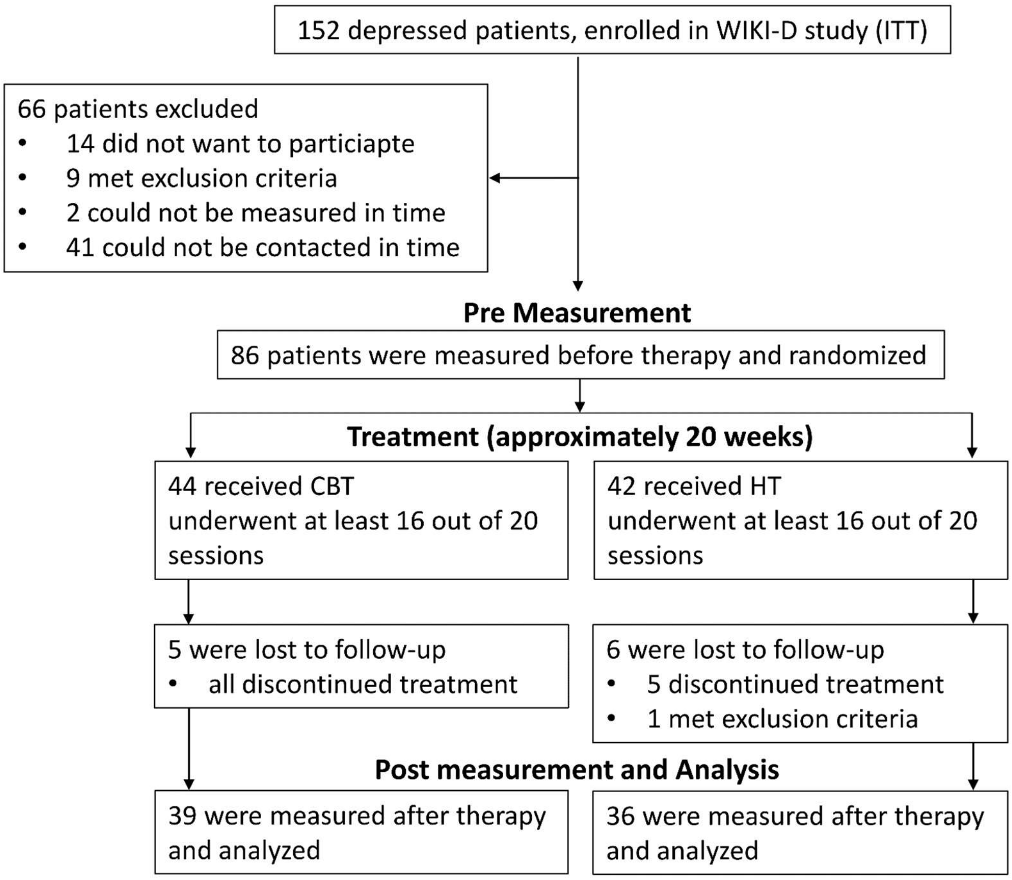

Fig. 1 Procedure of including and measuring patients throughout our study. Number of patients in the WIKI-D study [16] (N); intended to treat (ITT); Cognitive Behavioral Therapy (CBT); Hypnotherapy (HT)

Stimuli and materials

To test affective processing, we used an emotional gait paradigm [28,64], portraying sad, happy and neutral stimuli. We measured NIRS data as well as the reaction time and errors on a behavioral level. The happy gait was faster than the sad gait; the neutral walk was presented in three velocities (fast, medium, slow). The displayed video clips (3 s each) showed dark grey volumetric avatars walking across the screen from left to right or vice versa (at an angle of 22°). The avatars were uninformative about age, race or sex and still appeared human. The emotional videos (sad and happy) were presented 12 times each, the neutral videos (fast, medium, slow) four times each, once for each direction. This resulted in 72 videos total, intermitted by a break. Within blocks, the presentation of the videos was randomized. Rumination as a trait variable was assessed with the Rumination Response Scale [65].

Procedure

Measurements took place after diagnostics and before undergoing psychotherapy, and after therapy completion (Figure 1). Patients were randomly assigned to either CBT (n=39) or HT (n=36). The therapy was considered completed when patients underwent at least 16 of the 20 sessions, which applied to 76 patients. One patient became pregnant during therapy and was excluded from the second measurement. Each NIRS measurement lasted two hours and included two additional paradigms besides the gait paradigm, the results of which will be reported elsewhere. Moreover, RRS data were collected between paradigm presentation.

During the measurement, oxygenated (O2Hb) and deoxygenated hemoglobin (HHb) were recorded continuously after a 10 s baseline measurement. Subjects were asked to judge the portrayed emotion of a walking avatar by pressing the allocated response button (arrow buttons: left, down, and right). The down button always corresponded to neutral gait, the left and right buttons served as response buttons for sad or happy gait (balanced across subjects). Responses could be given as soon as the emotion was recognized. Subjects were not specifically asked to answer as quickly as possible to promote emotional processing over guessing. After a practice trial with feedback, the main experiment began. Each trial started with a fixation cross in the middle of the computer screen (400 ms), followed by a blank screen (100 ms) and an avatar video clip (2000 ms), which was followed by 200 ms blank screen. The duration of the inter-trial interval varied randomly among 5000 and 9000 ms. After 36 trials the subjects were given a break, which they could end themselves. The experiment lasted about 18–20 minutes. All subjects received a small monetary compensation for their time.

Near-infrared spectroscopy and regions of interest

Light in the near-infrared spectrum can penetrate the skull and other biological tissue. Depending on the O_2Hb and HHb in the underlying brain tissue, the light is absorbed differently and thus indicates the relative concentration of both chromophores. From this concentration conclusions can be drawn on cortical activation levels underneath the measurement probes. In our study we used an ETG-4000 Optical Topography System (Hitachi Medical Corporation, Tokyo, Japan) with a 52-channel array of 33 optodes (17 light emitters and 16 detectors) covering posterior-occipital and temporal brain areas (temporal resolution: 10 Hz). The inter-optode distance was 3 cm and near-infrared light with two wavelengths (695 and 830 nm) was used. The optodes were arranged in a 3×11-rectangular shape on the subjects' heads in respect to the international 10/20 System [66]. Channel 37 (middle channel in the lowest channel row) was placed over Oz; the anterior channels 43 (left) and 52 (right) were positioned on the temporal positions T3 and T4, respectively. To assign the channel positions to the anatomy, a neuronavigation system was used on a volunteer's head.

We selected ROIs according to previous findings [28]: namely the EBA and the STS region (including the STG; Figure 2). Due to limited spatial resolution in NIRS [67,68], we do not distinguish between activation due to motion perception or emotional perception – both evoking activation in the STS.

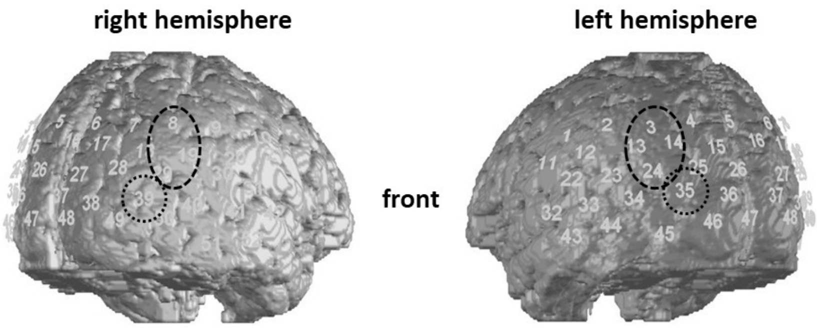

Fig. 2 Regions of Interest in the right and left cerebral hemisphere. The dashed circles portray the STS region (Channels: 8, 19, 29 (right); 3, 13, 14, 24 (left)) , the dotted circles the EBA region (Channels: 39 (right); 35 (left)). Superior Temporal Sulcus (STS); Extrastriate Body Area (EBA)

Data analyses

Preprocessing. The recorded NIRS data was preprocessed and brain plots were generated using MATLAB R2017b (MathWorks Inc, Natick, USA). Preprocessing included applying an algorithm for movement artefact reduction [69]. Then, all signals were visually inspected for local artefacts, 3% of the channels in the pre data and 4% in the post data were interpolated from adjacent channels. All signals were then scanned for biting artefacts and contaminated events were excluded from further analysis. We applied a band-pass filter (0.008–0.25 Hz) to minimize high- and low-frequency noise. Signals were z-transformed to compare between subjects, then the FC between STS and EBA was calculated. To explain the FC effects, post-hoc analyses were conducted on the ROIs separately. For this, the NIRS signals were fitted to a model hemodynamic response function in a general linear model based regression [28,70]. Based on previous studies using the same paradigm (e.g. [28]) as well as visual inspection of the current data set, peak time was set to 12 s with a peak dispersion of 2 s. In the behavioral data, responses given in under 300 ms were excluded because we do not expect them to result from cognitive processing.

Statistics. For the behavioral and NIRS data analyses, as well as non-brain figures, we used R Studio (R Studio Inc, Boston, USA). To account for the STS-EBA FC pre therapy and the therapy effect concurrently, we calculated the change score (CS): FC(post therapy) - FC (pre therapy), which served as dependent variable. Linear regression models were constructed consecutively adding fixed effects (first additively, then multiplicatively), in this order: FC(pre), therapy group (CBT = 0 vs. HT = 1), rumination (continuous variable) and portrayed emotion (neutral, sad, happy). The models were compared using F-Tests. The most complex model accounting for significantly more variance than the previous model was selected. The regression models were constructed in the following way:

$CS = ß_0 + ß_i * X + \varepsilon$

We applied the same regression analyses, including the significant predictors, on the behavioral data to capture changes in emotion recognition. We calculated the relative error rate (RER) (sum of errors divided by trial number) and its CS (RER post therapy – RER pre therapy), which served as dependent variable in regression analyses. Reaction times were looked at on a descriptive level, since they could not be interpreted: no instruction was given to answer as quickly as possible. Post-hoc two-tailed t-tests or correlation tests were conducted to further analyze interaction effects. Level of significance was $\alpha = 0.05$.

4.2.3 Results

In the left hemisphere the linear model containing pre FC as an additive term was the best fitting model for the CS, explaining a significant proportion of variance ($F(1,223) = 169.20$, $p < .001$, $r^2 = 0.43$). No further predictors contributed significantly. The FC before therapy significantly predicted the FC change in the left hemisphere ($ß = -0.78$, $t(223) = -13.01$, $p < .001$): The lower the FC between STS and EBA before therapy, the more it increased and vice versa (Online Resource 1). This effect could reflect a regression towards the mean effect, but also regulatory changes over time: patients who showed little EBA–STS coupling at baseline developed this coupling over therapy; patients who had lots of coupling between these two ROIs, possibly reflecting an overcompensation, showed decreased FC.

For the right hemisphere the model on the CS including pre FC as additive term and rumination and group as multiplicative predictors was the most complex model contributing significantly to the explained variance ($F(4, 220) = 42.30$, $p < .001$, $r^2 = 0.42$). This model revealed a significant influence of pre FC ($ß = -0.70$, $t(220) = -11.21$, $p < .001$), group ($ß = 0.37$, $t(220) = 2.60$, $p = .01$) and an interaction between rumination and group ($ß = -0.01$, $t(220) = -3.04$, $p = .003$). The pre FC effect implies, again, a negative connection between pre FC and the CS, thus portraying a regression to the mean on an analytical level and a possible compensation effect on a content level. The main effect for therapy group reflects a change in FC throughout therapy only in the HT group, while the interaction effect further specifies this change within the HT group, depending on rumination. To better understand this interaction

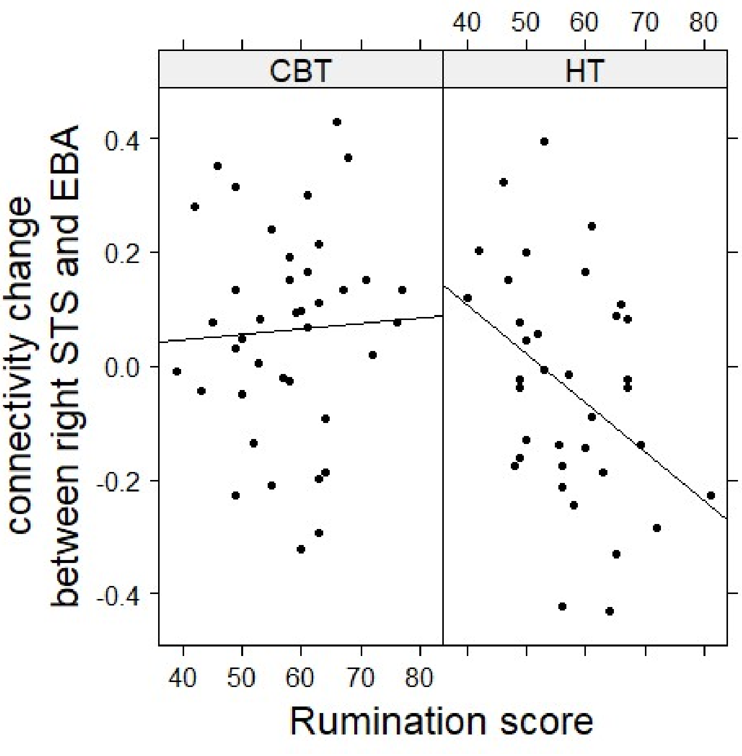

Fig. 3 Correlation between the change of connectivity between the right STS and EBA separately for the two therapy groups. Superior Temporal Sulcus (STS); Extrastriate Body Area (EBA); Cognitive Behavioral Therapy (CBT); Hypnotherapy (HT)

effect, we looked at the association between rumination and the CS separately for both groups. In the CBT group, there was a non-significant positive correlation between rumination and the CS (*r* (37) = .05, *p* = .77), while there was a significant negative correlation (*r*(34) = - .40, *p* = .02) in the HT group (Figure 3). Since the predictor “emotion”, accounting for the emotional valence of the portrayed gait, did not add significantly to the explanation of variance, the data were pooled across all conditions (affective and neutral) for further analyses.

To further uncover neurophysiological changes underlying the right hemispheric decrease of FC in the HT group, we conducted post-hoc analyses on the activation of the right STS and EBA separately in the HT group. For both ROIs we followed the same regression approach constructing the models consecutively, CS being the dependent variable and adding preactivation and rumination as fixed effects. As assumed, for the right STS the model including preactivation and rumination yielded significance ($F(2,33) = 13.84$, $p < .001$, $r^2 = 0.42$) and revealed main effects for preactivation ($ß = -0.64$, $t(33) = -4.50$, $p < .001$) as well as rumination ($ß = 0.14$, $t(33) = 3.01$, $p = .005$) on the CS (which results in a significant correlation between

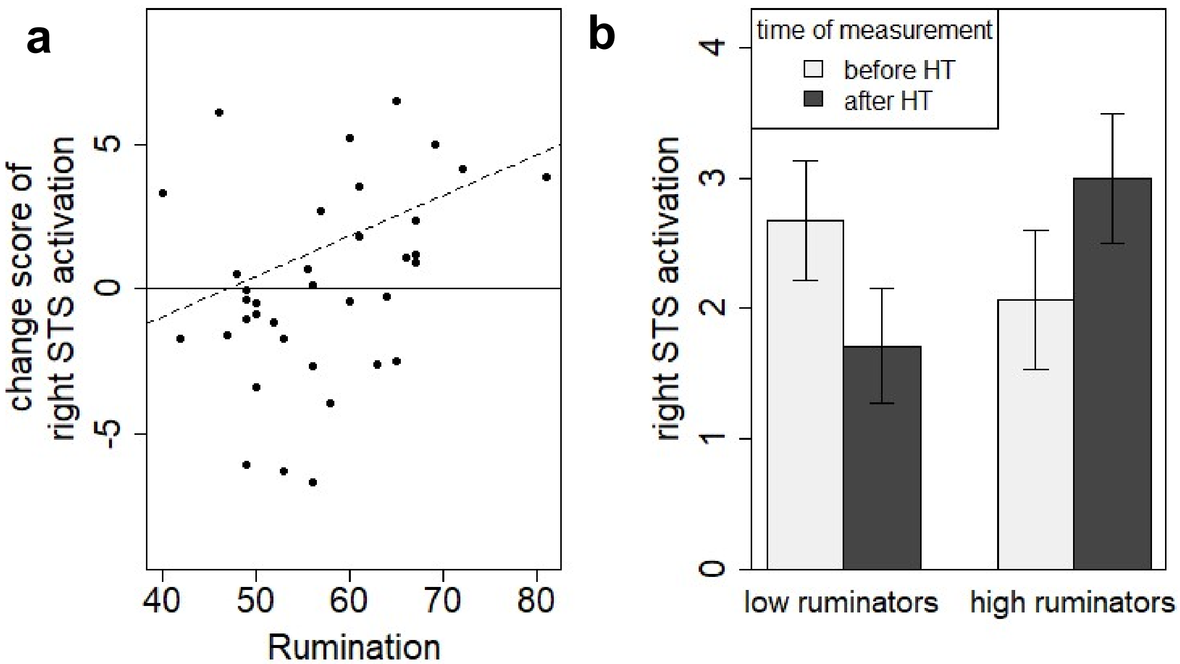

Fig. 4 a CS below and above zero (black line) and the regression line (dashed line) between the CS of right STS activation and rumination, the result of our regression analysis (including preactivation as additive predictor). **b** Categorial illustration of the association between rumination and the activation of the right STS in the HT group. Change Score (CS); Superior Temporal Sulcus (STS); Hypnotherapy (HT) rumination and CS of $r(34) = .35$, $p = .04$) indicating an increase in activation for those patients that showed less activation before HT and vice versa, equivalent to the previous analyses. This, again, could show a regression to the mean and possibly a compensation effect. The rumination effect indicates that higher levels of rumination were associated with a greater increase in right STS activation when patients received HT (Figure 4a). Considering the distribution of CS, it became apparent that negative changes (i.e. a decrease) in right STS activation occurred in a rather large subgroup of patients (who tended to show lower trait rumination scores; Figure 4a), while positive changes appeared more often in patients that tended to ruminate more. This might suggest a categorical relation between rumination and activation changes rather than a continuous one. For illustration purposes, this categorial relation is portrayed in Figures 4b and 5.

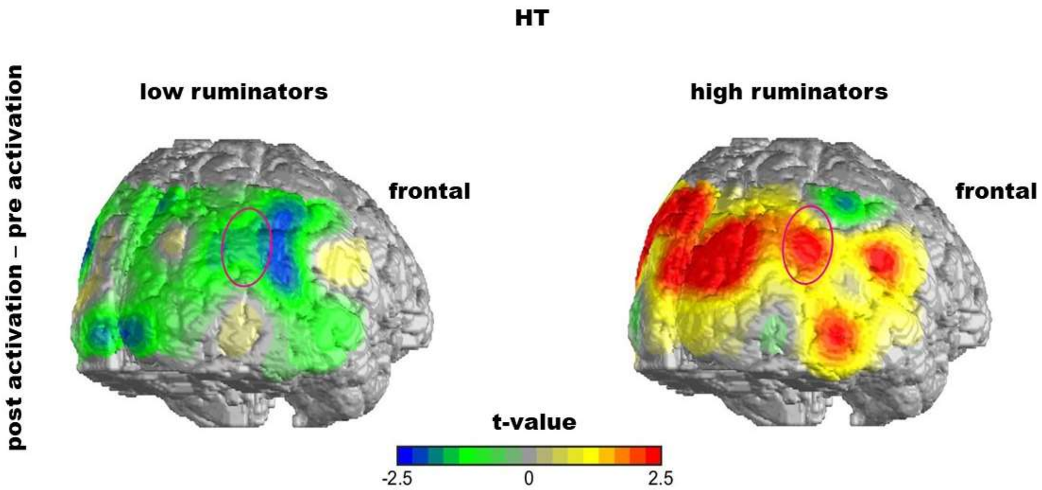

Fig. 5 The effect of rumination on the change of STS activation throughout therapy in the HT group. The figure portrays a t-test between activation before therapy (pre) compared to after therapy (post) (post-pre) in the HT group for either low or high ruminators. Superior Temporal Sulcus (STS); Hypnotherapy (HT)

For the activation in the right EBA in the HT group, no model including any predictors contributed to the explanation of variance implying no systematic change of activation in the right EBA in the HT group. We conclude that the decrease in right STS–EBA connectivity in the HT group could be derived from a change in activation in the right STS. Further, the STS activation change depended on rumination: while patients with rather low rumination scores showed decreased right STS activation after therapy, this effect was reverse for “high ruminators”. Therefore, we explain the decrease in right STS–EBA connectivity with this differential STS activation effect. Next, and for the purpose of completion, we checked for the activation in the right STS before therapy and whether it differentiated between the groups to rule out possible group effects due to different preactivation. We did not find a difference in right STS activation between groups before therapy (*M*(HT) = 2.24, *SD*(HT) = 3.02; *M*(CBT) = 2.53, *SD*(CBT) = 3.00; $t(73) = 0.41$, $p = .69$). Finally, as an additional post-hoc analysis, we correlated rumination with self-reported symptoms before therapy in both groups and found a significant correlation ($r(73) = 0.33$, $p = .004$). This offers an alternative explanation for the HT effect: The effect of HT could originate in initial symptom severity which is linked to rumination.

Behavioral data. On a descriptive level, reaction times decreased from before to after therapy, and in the HT group there is a slight positive correlation between reaction time and rumination (Online Resource 2). For the RER, descriptive parameters show a decrease over time (as can be seen in the tables, Online Resource 3). Further analysis revealed no systematic connection between RER, rumination, and groups. Applying the same regression method (stepwise regression, excluding the factor “emotion”), the model explaining a significant amount of variance ($F(1,65) = 92.75$, $p < .001$, $r^2 = 0.58$) included the RER before therapy to be the only predictor of the CS of RER (*ß* = -0.90, $t(65) = -9.63$, $p < .001$). This result was consistent, even when two outliers were excluded from the analysis ($F(1, 63) = 12.82$, $p = .001$, $r^2 = 0.12$, RER before therapy as predictor: *ß* = -0.52, $t(63) = -3.58$ $p = .001$). Thus, patients who either made very few or many mistakes at baseline showed a bigger change in their error rate after therapy (resulting in fewer mistakes for those who had many mistakes at first or more mistakes for those who had few mistakes before therapy). This seems to reflect a typical regression to the mean effect and partly a floor effect since the RER could not sink below zero. Since we did not find group- or rumination-specific effects in the behavioral data, we concluded that the activation change in the right STS in the HT group did not reflect the patients’ behavior.

4.2.4 Discussion

This study addressed the question whether two psychotherapies (CBT and HT) used in depression treatment affect the brain differently. Since the content of CBT and HT differs widely, particularly regarding the work with emotions, we hypothesized that these two therapies differ in their effect on a cerebral network – consisting of the STS and EBA – that is associated with emotional processing. Our main results show a decrease in right hemispheric STS–EBA connectivity in patients who received HT. This decrease in FC can mainly be explained by a change of activation in the STS while the EBA did not change in its activation. This activation change in the right STS in the HT group depended on rumination: while subjects with lower rumination scores showed a decrease in their right STS activation, subjects with higher rumination scores showed an activation increase. These specific neurophysiological changes were not mirrored in behavioral data and were independent from the type of displayed emotion.

These results have multiple implications. First, even though both the STS and EBA were previously found to be active during displayed biological motion [28,31,33,34,39,49,71,72], here, only the right STS showed activation changes throughout therapy. However, since we focus on the co-activation of the EBA and STS, we cannot make firm conclusions about the activation of the EBA during the gait paradigm by itself. Due to our analysis EBA activation did not change throughout therapy, suggesting it might not be involved in emotional processes changing in psychotherapy; the STS activation change, however, might be related to these emotional processes. The STS region has shown to be involved in pathological brain activation in depressed patients, when confronted with negative emotional stimuli, with clear lateralization, though [53]. The findings of STS activation in response to perceived body motion were heterogenous in regard to lateralization [28,33,34,39,72]. Thus, the STS seems to play a role in emotional processing influenced by depression-specific HT; the role of lateralization remains to be investigated.

Interestingly, this STS activation change throughout therapy was only found in the HT group. Since the groups did not differ in right STS activation before therapy, the group effect of the FC change is due to the differential activation after therapy. This difference could be due to the increased focus on emotional therapeutic work in HT compared to CBT. In CBT the focus lied on activating, analyzing and reviewing behavior and recognizing and changing negative cognitions [73]. This was implemented during therapy sessions and homework. In CBT emotions were mostly addressed on a conversational level. On the other hand, in HT a focus lied on using the patients' own strengths, positive experiences and memories to create alternatives to negative, wearing thoughts. Namely, pleasant emotions linked to positive personal experiences were induced during trance to make the patients feel competent, hopeful, and strong. The trances were recorded and handed to the patients to listen to them again at home. This might have led to a repetition of the emotional experiences. We argue that HT promoted changing one's perspective since multiple trances focused on putting oneself in a former or later self, possibly reflecting ToM processes. Since the STS region is associated with these emotional and ToM processes [39,53] it seems fitting that right STS activation changed throughout HT, but not CBT. CBT, on the other hand, has been shown to normalize aberrant amygdala [7] and prefrontal [6] activity, the latter being associated with cognitive control [9,10,74].

Interestingly, hypnosis has been shown to lead to decreased prefrontal activity [75,76] and disrupted prefrontal FC [77]. Therefore, the PFC seems to be important to consider when searching for the mechanisms underlying therapeutic effects of HT. Our research group investigated prefrontal areas in the same study sample as presented here (using a different paradigm and fNIRS cap placement); the results will be published elsewhere.

Secondly, we found that the right STS activation change after HT depended on the patients' rumination: Patients who tended to ruminate less before therapy showed a decrease while patients who tended to ruminate more showed an increase in right STS activation after HT suggesting a categorical division of patients in high and low ruminators. This is in line with previous research of our group, in which differential DMN activity was found for high versus low ruminating depressed patients [57]. In previous research, trait rumination was shown to be positively associated with depressive symptoms and their severity [78–80], mediating risk factors for depression [81], and predicting treatment success [82]. We, as well, found a correlation between rumination and self-reported symptoms. Further research has shown abnormal functioning of the DMN in depressed subjects [60] and decreased

FC within the DMN in depressed subjects who tended to ruminate [57]. The DMN also seems to be linked to ToM and thus emotional processes, which elicit increased activity in lateral regions like the STS and increased coupling with the medial prefrontal cortex, a core node of the DMN [83]. Furthermore, multiple authors suggested a link between hypnotic trance and the DMN [e.g. 78–81]. More detailed results on the connection between HT and the DMN will be derived from a resting-state measurement also conducted in the context of this study and published elsewhere. In line with this research, our results might indicate a greater degree of depression in highly ruminating patients whose decreased STS activity before therapy possibly reflected impaired emotional processing. The increase of STS activity throughout HT in these patients could be a neurophysiological correlate of normalized emotional processing induced by HT as described above. On the other hand, low ruminating depressed patients showed a decrease in STS activity throughout HT. Our results propose that low ruminators show less severe depressive symptoms and might therefore be less impaired in emotional processing. Opposed to the more severely impaired patients, the less impaired might still be capable to compensate abnormal emotional processing with a certain effort. This compensation effort could be associated with hyperactivity in the right STS. The benefit of HT for these patients could be linked to a decrease in right STS activity due to the reduction of over-compensation. Further research is needed to underpin this hypothesis and clarify the interaction of rumination and symptom severity on depression-related cerebral activity.

Thirdly, the absence of significant predictive value of the factors group and rumination for the error rate (RER) implies that activity changes in the right STS did not influence the behavioral data in a measurable way. A possible explanation is that the RER is based on the reaction as a consequence of emotional recognition. This reaction is rather a judgement than a mirror of the preceding emotional processing. Emotional judgement, though, is associated with prefrontal activity [88–90] and might not be correlated with temporal activity. To get to the core of this effect, further research with more specific hypotheses is needed.

Lastly, the portrayed emotion did not predict the FC change between EBA and STS throughout therapy nor did it predict the activity change in the right STS. In previous studies, differences in EBA activation occurred between negative emotional body expressions compared to neutral expressions [28,49,71,72], but all of these studies were conducted with healthy subjects. Indeed, depressed subjects have shown aberrant emotional processing on a behavioral level compared to healthy controls [21–24,26,91], but in these studies cerebral activation was not assessed. The cerebral processes measured in our study and the changes throughout HT do not seem to be emotion-specific.

4.2.5 Study limitations and future research

To our knowledge, no previous study has investigated the FC of these two regions even though they were found to be involved in the processing of dynamic, emotional body expressions, and none of them including depressed subjects [28,49,71]. This present study is of an exploratory nature and consequently more research is needed to investigate the FC between STS and EBA in depressed subjects. Moreover, other regions involved in the processing of emotional dynamic body expression, like the amygdala [49], cannot be measured with NIRS. Furthermore, due its relatively low spatial resolution, NIRS might not be an adequate method to distinguish motion perception and emotional perception, which are both associated with activation in the STG [e.g. 36,37]. Therefore, interpretations about emotional processing associated with STS activity need to be considered carefully. To further investigate the co-activation of other areas, including subcortical ones, and to distinguish intra-STS areas, fMRI data should be obtained. Another methodological restriction is that we could not perform a short-channel regression since our NIRS system does not allow to routinely include short-distance channels. Therefore, we cannot exclude the possibility that superficial perfusion changes contributed to our fNIRS data. A further limitation is that systemic effects were not controlled during data preprocessing which might have influenced the results.

The assumption that HT fosters more emotional processes than CBT was based on manuals used in the WIKI-D study [16] and interviews with experts. We do not claim this to be the only differentiating factor between HT and CBT; further research is required to clarify the differences. In the future, rumination should be continuously included when investigating depression as it seems to be linked to abnormal, depression-specific, cerebral functioning [57]. This would help to better understand depression in its many facets and to individualize treatment.

4.2.6 Conclusion

This first of its kind study explores the cerebral processes underlying differential effects of Hypnotherapy (HT) and Cognitive Behavioral Therapy (CBT) in treating depressed patients. In the treatment of depressed patients, HT was not inferior to CBT [16] . Still, how these treatments work (or which group pf patients responds well to either type of therapy) remained unclear. In our study, we investigated the effects of HT and CBT on cerebral activation associated with emotional processing. We found that activation in the right STS changed throughout therapy specifically in the HT group. Further, rumination played a crucial role in predicting activation changes in the HT group and thus seems to be an important factor to consider when drawing conclusions about depression treatment and differential indication. We conclude that HT affects emotional processing in depressed patients and this effect is moderated by the patients' rumination style. Depression-specific HT, its content, effects and underlying processes have rarely been investigated and therefore many of our assumptions were exploratory in nature. This paper was designed to be a first step in the direction of exploring HT and its differential effects.

Declarations

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Conflicts of Interests

The authors declare that they have no conflict of interest.

Availability of Data

The datasets from the current study are available upon request.

Code Availability

The codes of the current study are available upon request.

Authors' Contributions

Alina Haipt: Term, Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Visualization. **David Rosenbaum**: Conceptualization, Software, Data Curation, Writing – Review & Editing. **Kristina Fuhr**: Resources, Writing – Review & Editing, Project administration. **Martin Giese**: Methodology, Software, Writing – Review & Editing. **Anil Batra**: Supervision, Funding acquisition, Writing – Review & Editing. **Ann-Christine Ehlis**: Term, Conceptualization, Methodology, Formal analysis, Resources, Validation, Supervision, Project administration, Funding acquisition, Writing – Review & Editing.

Ethics Approval

This study was approved with a positive ethics vote by the Ethics Committee of the University Hospital of Tuebingen (061/2015B02).

Consent to participate

All participants gave their written informed consent to participate in the study.

References

[1] WHO. Depression 2020. https://www.who.int/news-room/fact-sheets/detail/depression.

[2] American Pschological Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychological Association; 2013.

[3] Nejad AB, Fossati P, Lemogne C. Self-Referential Processing, Rumination, and Cortical Midline Structures in Major Depression. Front Hum Neurosci 2013;7:1–9. https://doi.org/10.3389/fnhum.2013.00666.

[4] Nolen-Hoeksema S. Responses to depression and their effects on the duration of depressive episodes. J Abnorm Psychol 1991;100:569–82. https://doi.org/10.1037/0021-843X.100.4.569.

[5] Cuijpers P, Berking M, Andersson G, Quigley L, Kleiboer A, Dobson KS. A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. Can J Psychiatry 2013;58:376–85. https://doi.org/10.1177/070674371305800702.

[6] Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, et al. Modulation of Cortical-Limbic Pathways in Major Depression. Arch Gen Psychiatry 2004;61:34–41. https://doi.org/10.1001/archpsyc.61.1.34.

[7] DeRubeis RJ, Siegle GJ, Hollon SD. Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. Nat Rev Neurosci 2008;9:788–96. https://doi.org/10.1038/nrn2345.

[8] Boccia M, Piccardi L, Guariglia P. How treatment affects the brain: meta-analysis evidence of neural substrates underpinning drug therapy and psychotherapy in major depression. Brain Imaging Behav 2016;10:619–27. https://doi.org/10.1007/s11682-015-9429-x.

[9] Rosenbaum D, Leehr EJ, Rubel J, Maier MJ, Pagliaro V, Deutsch K, et al. Cortical oxygenation during exposure therapy – in situ fNIRS measurements in arachnophobia. NeuroImage Clin 2020;26:102219. https://doi.org/10.1016/j.nicl.2020.102219.

[10] Karlsson H. How Psychotherapy Changes the Brain. Psychiatr Times 2011;28:1–5. https://doi.org/10.0.3.249/S0033291709991607.

[11] Revenstorf D, Peter B. Hypnose in Psychotherapie, Psychosomatik und Medizin. Heidelberg: Springer; 2009.

[12] Kirsch I, Low CB. Suggestion in the Treatment of Depression. Am J Clin Hypn 2013;55:221–9. https://doi.org/10.1080/00029157.2012.738613.

[13] Milling LS, Valentine KE, McCarley HS, LoStimolo LM. A Meta-Analysis of Hypnotic Interventions for Depression Symptoms: High Hopes for Hypnosis? Am J Clin Hypn 2018;61:227–43. https://doi.org/10.1080/00029157.2018.1489777.

[14] Shih M, Yang YH, Koo M. A Meta-analysis of hypnosis in the treatment of depressive symptoms: A brief communication. Int J Clin Exp Hypn 2009;57:431–42. https://doi.org/10.1080/00207140903099039.

[15] Alladin A, Alibhai A. Cognitive hypnotherapy for depression: An empirical investigation. Int J Clin Exp Hypn 2007;55:147–66. https://doi.org/10.1080/00207140601177897.

[16] Fuhr K, Meisner C, Broch A, Cyrny B, Hinkel J, Jaberg J, et al. Efficacy of hypnotherapy compared to cognitive behavioral therapy for mild to moderate depression - Results of a randomized controlled rater-blind clinical trial. J Affect Disord 2021;286:166–73. https://doi.org/10.1016/j.jad.2021.02.069.

[17] Lowén MBO, Mayer E a., Sjöberg M, Tillisch K, Naliboff B, Labus J, et al. Effect of hypnotherapy and educational intervention on brain response to visceral stimulus in the irritable bowel syndrome. Aliment Pharmacol Ther 2013;37:1184–97. https://doi.org/10.1111/apt.12319.

[18] Halsband U, Wolf TG. Functional changes in brain activity after hypnosis in patients with dental phobia. J Physiol 2015;109:131–142. https://doi.org/10.1016/j.jphysparis.2016.10.001.

[19] Halsband U, Wolf TG. Current neuroscientific research database findings of brain activity changes after hypnosis. Am J Clin Hypn 2021;63:372–88. https://doi.org/10.1080/00029157.2020.1863185.

[20] Jensen MP, Adachi T, Tomé-Pires C, Lee J, Osman ZJ, Miró J. Mechanisms of hypnosis: Toward the development of a biopsychosocial model. Int J Clin Exp Hypn 2015;63:34–75. https://doi.org/10.1080/00207144.2014.961875.

[21] Anderson IM, Shippen C, Juhasz G, Chase D, Thomas E, Downey D, et al. State-dependent alteration in face emotion recognition in depression. Br J Psychiatry 2011;198:302–8. https://doi.org/10.1192/bjp.bp.110.078139.

[22] Surguladze SA, Senior C, Young AW, Brébion G, Travis MJ, Phillips ML. Recognition Accuracy and Response Bias to Happy and Sad Facial Expressions in Patients with Major Depression. Neuropsychology 2004;18:212–8. https://doi.org/10.1037/0894-4105.18.2.212.

[23] Milders M, Bell S, Platt J, Serrano R, Runcie O. Stable expression recognition abnormalities in unipolar depression. Psychiatry Res 2010;179:38–42. https://doi.org/10.1016/j.psychres.2009.05.015.

[24] Gur RC, Erwin RJ, Gur RE, Zwil AS, Heimberg C, Kraemer HC. Facial Emotion Depression Discrimination: II . Behavioral Findings in Depression. Psychiatry Res 1992;42:241–51.

[25] Gotlib IH, Krasnoperova E, Neubauer Yue D, Joormann J. Attentional Biases for Negative Interpersonal Stimuli in Clinical Depression. J Abnorm Psychol 2004;113:127–35. https://doi.org/10.1037/0021-843X.113.1.127.

[26] Suslow T, Dannlowski U, Lalee-mentzel J, Donges U, Arolt V, Kersting A. Spatial processing of facial emotion in patients with unipolar depression : a longitudinal study. J Affect Disord 2004;83:59–63. https://doi.org/10.1016/j.jad.2004.03.003.

[27] Gelder B De. Why bodies ? Twelve reasons for including bodily expressions in affective neuroscience. Philos Trans R Soc B Biol Sci 2009;364:3475–84. https://doi.org/10.1098/rstb.2009.0190.

[28] Schneider S, Christensen A, Häußinger FB, Fallgatter AJ, Giese MA, Ehlis AC. Show me how you walk and I tell you how you feel - A functional near-infrared spectroscopy study on emotion perception based on human gait. Neuroimage 2014;85:380–90. https://doi.org/10.1016/j.neuroimage.2013.07.078.

[29] Taylor JC, Downing PE. Division of labor between lateral and ventral extrastriate representations of faces, bodies, and objects. J Cogn Neurosci 2011;23:4122–37. https://doi.org/10.1162/jocn_a_00091.

[30] Downing PE, Jiang Y, Shuman M, Kanwisher N. A cortical area specialized for visual processing of the human body. Science (80-) 2001;293:2470–3. https://doi.org/10.1167/1.3.341.

[31] Lamm C, Decety J. Is the extrastriate body area (EBA) sensitive to the perception of pain in others? Cereb Cortex 2008;18:2369–73. https://doi.org/10.1093/cercor/bhn006.

[32] van de Riet W, Grèzes J, de Gelder B. Specific and common brain regions involved in the perception of faces and bodies and the representation of their emotional expressions. Soc Neurosci 2009;4:101–20. https://doi.org/10.1080/17470910701865367.

[33] Bonda E, Petrides M, Ostry D, Evans A. Specific Involvement of Human Parietal Systems and the Amygdala in the Perception of Biological Motion. J Neurosci 1996;16:3737–44. https://doi.org/10.1387/ijdb.113374sm.

[34] Allison T, Puce A, McCarthy G. Social perception from visual cues: role of the STS region. Trends Cogn Sci 2000;4:267–78. https://doi.org/10.1016/S1364-6613(00)01501-1.

[35] Grossman E, Donnelly M, Price R, Pickens D, Morgan V, Neighbor G, et al. Brain Areas Involved in Perception of Biological Motion. J Cogn Neurosci 2000;12:711–20. https://doi.org/https://doi.org/10.1162/089892900562417.

[36] Grossman ED, Blake R. Brain areas active during visual perception of biological motion. Neuron 2002;35:1167–75. https://doi.org/10.4324/9780203496190.

[37] Pelphrey K, Mitchell T, McKeown MJ, Goldstein J, Allison T, McCarthy G. Brain activity evoked by the perception of human walking: controlling for meaningful coherent motion. J Neurosci 2003;23:6819–25. https://doi.org/23/17/6819 [pii].

[38] Pelphrey KA, Morris JP, Michelich CR, Allison T, McCarthy G. Functional Anatomy of Biological Motion Perception in Posterior Temporal Cortex: An fMRI Study of Eye, Mouth and Hand Movements. Cereb Cortex 2005;15:1866–76. https://doi.org/10.1093/cercor/bhi064.

[39] Deen B, Koldewyn K, Kanwisher N, Saxe R. Functional organization of social perception and cognition in the superior temporal sulcus. Cereb Cortex 2015;25:4596–609. https://doi.org/10.1093/cercor/bhv111.

[40] Pelphrey KA, Singerman JD, Allison T, McCarthy G. Brain activation evoked by perception of gaze shifts: The influence of context. Neuropsychologia 2003;41:156–70. https://doi.org/10.1016/S0028-3932(02)00146-X.

[41] Pelphrey K, Morris J, McCarthy G. Grasping the Intentions of Others: The Perceived

Intentionality of an Action Influences Activity in the Superior Temporal Sulcus during Social Perception. J Cogn Neurosci 2004;16:1706–16. https://doi.org/10.1162/0898929042947900.

[42] Brass M, Schmitt RM, Spengler S, Gergely G. Investigating Action Understanding: Inferential Processes versus Action Simulation. Curr Biol 2007;17:2117–21. https://doi.org/10.1016/j.cub.2007.11.057.

[43] Vander Wyk BC, Hudac CM, Carter EJ, Sobel DM, Pelphrey KA. Action Understanding in the Superior Temporal Sulcus Region. Psychol Sci 2009;20:771–7. https://doi.org/http://doi.org/10.1111/j.1467-9280.2009.02359.x.

[44] Fletcher PC, Happe F, Frith U, Baker SC, Dolan RJ, Frackowiak RSJ, et al. Other minds in the brain: a functional imaging study of "theory of mind" in story comprehension. Cognition 1995;57:109–128. https://doi.org/10.1016/0010-0277(95)00692-R.

[45] Gallagher HL, Happé F, Brunswick N, Fletcher PC, Frith U, Frith CD. Spatial selectivity in the temporoparietal junction, inferior frontal sulcus, and inferior parietal lobule. Neuropsychologia 2000;38:11–21. https://doi.org/10.1167/15.13.15.

[46] Saxe R, Kanwisher N. People thinking about thinking people: The role of the temporo-parietal junction in "theory of mind." Neuroimage 2003;19:1835–42. https://doi.org/10.4324/9780203496190.

[47] Ciaramidaro A, Adenzato M, Enrici I, Erk S, Pia L, Bara BG, et al. The intentional network: How the brain reads varieties of intentions. Neuropsychologia 2007;45:3105–13. https://doi.org/10.1016/j.neuropsychologia.2007.05.011.

[48] Saxe R, Powell LJ. It's the Thought That Counts. Psychol Sci 2006;17:692–9. https://doi.org/10.1111/J.1467-9280.2006.01768.X.

[49] Grèzes J, Pichon S, de Gelder B. Perceiving fear in dynamic body expressions. Neuroimage 2007;35:959–67. https://doi.org/10.1016/j.neuroimage.2006.11.030.

[50] Kret ME, Pichon S, Grèzes J, De Gelder B. Similarities and differences in perceiving threat from dynamic faces and bodies. An fMRI study. Neuroimage 2011;54:1755–62. https://doi.org/10.1016/j.neuroimage.2010.08.012.

[51] Peelen M V., Atkinson AP, Vuilleumier P. Supramodal Representations of Perceived Emotions in the Human Brain. J Neurosci 2010;30:10127–34. https://doi.org/10.1523/JNEUROSCI.2161-10.2010.

[52] Takahashi T, Yücel M, Lorenzetti V, Walterfang M, Kawasaki Y, Whittle S, et al. An MRI study of the superior temporal subregions in patients with current and past major depression. Prog Neuro-Psychopharmacology Biol Psychiatry 2010;34:98–103. https://doi.org/10.1016/j.pnpbp.2009.10.005.

[53] Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ. A Meta-Analytic Study of Changes in Brain Activation in Depression. Hum Brain Mapp 2008;29:683–95. https://doi.org/10.1002/hbm.20426.A.

[54] Canli T, Sivers H, Thomason ME, Whitfield-Gabrieli S, Gabrieli JDE, Gotlib IH. Brain

activation to emotional words in depressed vs healthy subjects. Neuroreport 2004;15:2585–8. https://doi.org/10.1097/00001756-200412030-00005.

[55] Shah PJ, Glabus MF, Goodwin GM, Ebmeier KP. Chronic, treatment-resistant depression and right fronto-striatal atrophy. Br J Psychiatry 2002;180:434–40. https://doi.org/10.1192/bjp.180.5.434.

[56] Cullen KR, Gee DG, Klimes-Dougan B, Gabbay V, Hulvershorn L, Mueller BA, et al. A preliminary study of functional connectivity in comorbid adolescent depression. Neurosci Lett 2009;460:227–31. https://doi.org/10.1016/j.neulet.2009.05.022.

[57] Rosenbaum D, Haipt A, Fuhr K, Haeussinger FB, Metzger FG, Nuerk HC, et al. Aberrant functional connectivity in depression as an index of state and trait rumination. Sci Rep 2017;7:1–12. https://doi.org/10.1038/s41598-017-02277-z.

[58] Rosenbaum D, Hagen K, Deppermann S, Kroczek AM, Haeussinger FB, Heinzel S, et al. State-dependent altered connectivity in late-life depression: A functional near-infrared spectroscopy study. Neurobiol Aging 2016;39:57–68. https://doi.org/10.1016/j.neurobiolaging.2015.11.022.

[59] Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci 2011;15:483–506. https://doi.org/10.1016/j.tics.2011.08.003.

[60] Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, et al. Resting-State Functional Connectivity in Major Depression: Abnormally Increased Contributions from Subgenual Cingulate Cortex and Thalamus. Biol Psychiatry 2007;62:429–37. https://doi.org/10.1016/j.biopsych.2006.09.020.

[61] Ernst LH, Schneider S, Ehlis AC, Fallgatter AJ. Functional Near Infrared Spectroscopy in Psychiatry: A critical review. J Near Infrared Spectrosc 2012;20:93–105. https://doi.org/10.1255/jnirs.970.

[62] Fallgatter AJ, Ehlis AC, Wagener A, Michel T, Herrmann MJ. Nah-Infrarot-Spektroskopie in der Psychiatrie. Nervenarzt 2004;75:911–6. https://doi.org/10.1007/s00115-002-1457-2.

[63] Wittchen H-U, Wunderlich U, Gruschwitz S, Zaudig M. SKID I. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. Göttingen: Hogrefe; 1997.

[64] Roether CL, Omlor L, Christensen A, Giese MA. Critical features for the perception of emotion from gait. J Vis 2009;9:1–32.

[65] Nolen-Hoeksema S, Morrow J. A Prospective Study of Depression and Posttraumatic Stress Symptoms After a Natural Disaster: the 1989 Loma Prieta Earthquake. J Pers Soc Psychol 1991;61:115–21. https://doi.org/10.1037/0022-3514.61.1.115.

[66] Klem, G. H., Lüders, H. O., Jasper, H. H., & Elger C. The ten-twenty electrode system of the International Federation. Electroencephalogr Clin Neurophysiol Suppl 1999;52:19–22.

[67] McCormick PW, Stewart M, Lewis G, Dujovny M, Ausman JI. Intracerebral penetration of infrared light. Technical note. J Neurosurg 1992;76:315–8.

https://doi.org/https://doi.org/10.3171/jns.1992.76.2.0315.

[68] Wabnitz H, Moeller M, Liebert A, Obrig H, Steinbrink J, MacDonald R. Time-resolved Near-Infrared Spectroscopy and Imaging of the Adult Human Brain. In: Takahashi E, Bruley D, editors. Oxyg. Transp. to Tissue XXXI. Adv. Exp. Med. Biol. vol. 662, Boston: Springer; 2010, p. 143–8.

[69] Cui X, Bray S, Reiss A. Functional near infrared spectroscopy (NIRS) signal improvement based on negative correlation between oxygenated and deoxygenated hemoglobin. Neuroimage 2010;49:3039–46. https://doi.org/10.1016/j.neuroimage.2009.11.050

[70] Plichta MM, Heinzel S, Ehlis AC, Pauli P, Fallgatter AJ. Model-based analysis of rapid event-related functional near-infrared spectroscopy (NIRS) data: A parametric validation study. Neuroimage 2007;35:625–34. https://doi.org/10.1016/j.neuroimage.2006.11.028.

[71] Pichon S, de Gelder B, Grèzes J. Emotional modulation of visual and motor areas by dynamic body expressions of anger. Soc Neurosci 2008;3:199–212. https://doi.org/10.1080/17470910701394368.

[72] Sinke CBA, Sorger B, Goebel R, de Gelder B. Tease or threat? Judging social interactions from bodily expressions. Neuroimage 2010;49:1717–27. https://doi.org/10.1016/j.neuroimage.2009.09.065.

[73] Wilhelm-Goessling C, Schweizer C, Dürr C, Fuhr K, Revenstorf D. Hypnotherapie bei Depressionen: Ein Manual für Psychotherapeuten. 1st ed. Stuttgart: Kohlhammer Verlag; 2020.

[74] Rosenbaum D, Maier MJ, Hudak J, Metzger FG, Wells A, Fallgatter AJ, et al. Neurophysiological correlates of the attention training technique: A component study. NeuroImage Clin 2018;19:1018–24. https://doi.org/10.1016/j.nicl.2018.06.021.

[75] Gruzelier JH. A review of the impact of hypnosis, relaxation, guided imagery and individual differences on aspects of immunity and health. Stress 2002;5:147–63. https://doi.org/10.1080/10253890290027877.

[76] Jiang H, White MP, Greicius MD, Waelde LC, Spiegel D. Brain activity and functional connectivity associated with hypnosis. Cereb Cortex 2017;27:4083–93. https://doi.org/10.1093/cercor/bhw220.

[77] Fingelkurts AA, Fingelkurts AA, Kallio S, Revonsuo A. Cortex functional connectivity as a neurophysiological correlate of hypnosis: An EEG case study. Neuropsychologia 2007;45:1452–62. https://doi.org/10.1016/j.neuropsychologia.2006.11.018.

[78] Koval P, Kuppens P, Allen NB, Sheeber L. Getting stuck in depression: The roles of rumination and emotional inertia. Cogn Emot 2012;26:1412–27. https://doi.org/10.1080/02699931.2012.667392.

[79] Smith JM, Alloy LB. A roadmap to rumination: A review of the definition, assessment, and conceptualization of this multifaceted construct. Clin Psychol Rev 2009;29:116–28. https://doi.org/10.1016/j.cpr.2008.10.003.

[80] Ito T, Takenaka K, Tomita T, Agari I. Comparison of Ruminative Responses with Negative Rumination as a Vulnerability Factor for Depression. Psychol Rep 2006;99:763–772. https://doi.org/https://doi.org/10.2466/PR0.99.3.763-772.

[81] Spasojević J, Alloy LB. Rumination as a Common Mechanism Relating Depressive Risk Factors to Depression. Emotion 2001;1:25–37. https://doi.org/10.1037/1528-3542.1.1.25.

[82] Teismann T, Willutzki U, Michalak J, Schulte D. Bedeutung von Rumination und Ablenkung für den Therapieerfolg depressiver Patienten. Verhaltenstherapie 2008;18:215–22. https://doi.org/10.1159/000165687.

[83] Spreng RN, Grady CL. Patterns of Brain Activity Supporting Autobiographical Memory, Prospection, and Theory of Mind, and Their Relationship to the Default Mode Network. J Cogn Neurosci 2010;22:1112–23. https://doi.org/10.1162/jocn.2009.21282.

[84] Pyka M, Burgmer M, Lenzen T, Pioch R, Dannlowski U, Pfleiderer B, et al. Brain correlates of hypnotic paralysis—a resting-state fMRI study. Neuroimage 2011;56:2173–82. https://doi.org/10.1016/j.neuroimage.2011.03.078.

[85] Cojan Y, Waber L, Schwartz S, Rossier L, Forster A, Vuilleumier P. The brain under self-control: modulation of inhibitory and monitoring cortical networks during hypnotic paralysis. Neuron 2009;62:862–75. https://doi.org/10.1016/j.neuron.2009.05.021.

[86] Deeley Q, Oakley D, Toone B, Giampietro V, Brammer MJ, Williams SCR, et al. Modulating the default mode network using hypnosis. Int J Clin Exp Hypn 2012;60:206–28. https://doi.org/10.1080/00207144.2012.648070.

[87] McGeown WJ, Mazzoni G, Venneri A, Kirsch I. Hypnotic induction decreases anterior default mode activity. Conscious Cogn 2009;18:848–55. https://doi.org/10.1016/j.concog.2009.09.001.

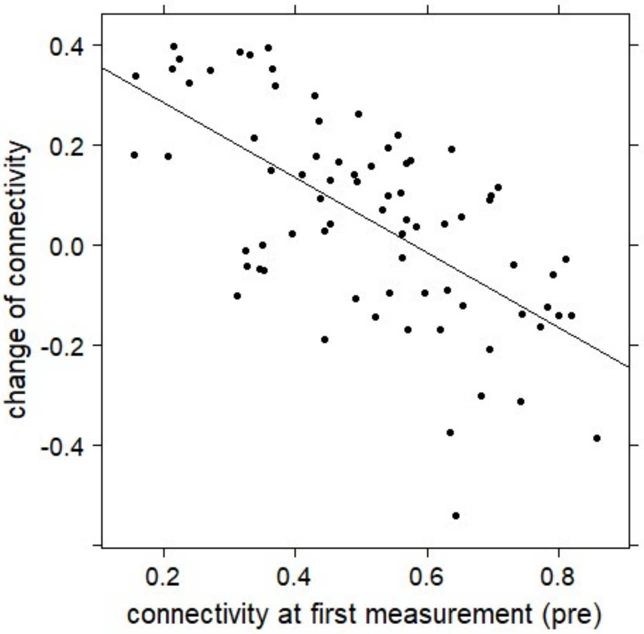
[88] Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, et al. Imbalance between Left and Right Dorsolateral Prefrontal Cortex in Major Depression Is Linked to Negative Emotional Judgment : An fMRI Study in Severe Major Depressive Disorder. Biol Psychiatry 2008;63:369–76. https://doi.org/10.1016/j.biopsych.2007.05.033.

[89] Grimm S, Schmidt CF, Bermpohl F, Heinzel A, Dahlem Y, Wyss M, et al. Segregated neural representation of distinct emotion dimensions in the prefrontal cortex — an fMRI study. Neuroimage 2006;30:325–40. https://doi.org/10.1016/j.neuroimage.2005.09.006.

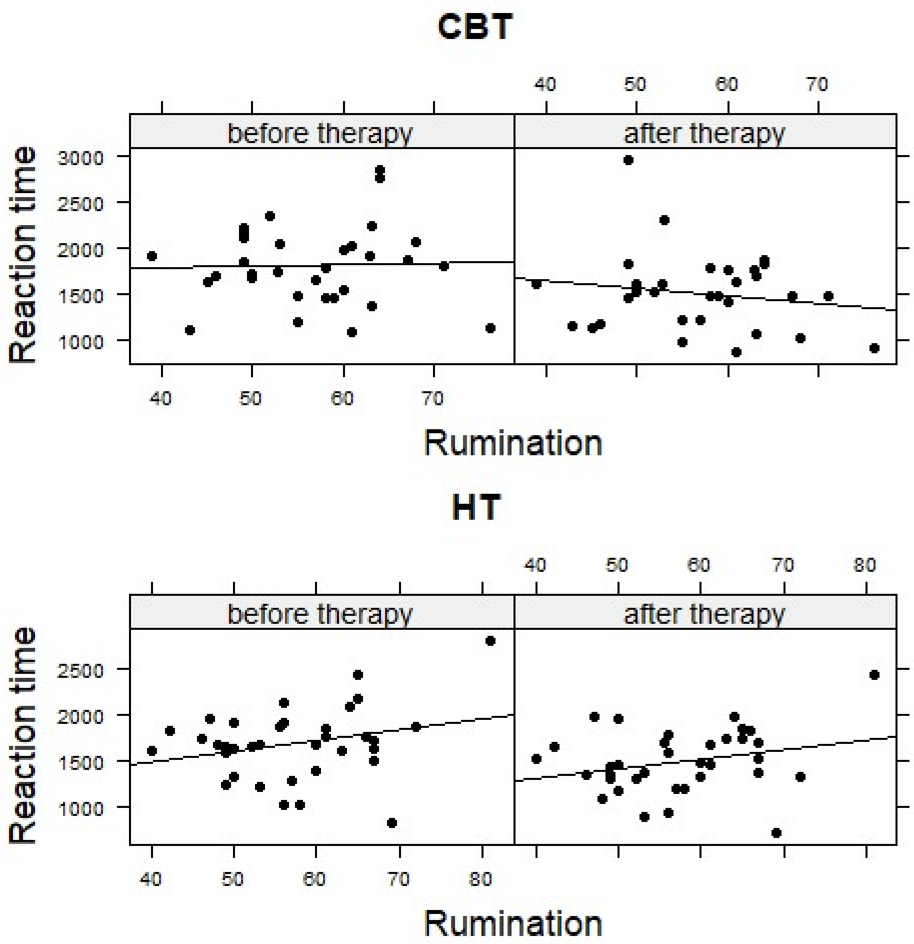
[90] Northoff G, Duncan NW, Hayes DJ. The brain and its resting state activity-Experimental and methodological implications. Prog Neurobiol 2010;92:593–600. https://doi.org/10.1016/j.pneurobio.2010.09.002.

[91] Gotlib IH, Kasch KL, Traill S, Joormann J, Arnow B a, Johnson SL. Coherence and specificity of information-processing biases in depression and social phobia. J Abnorm Psychol 2004;113:386–98. https://doi.org/10.1037/0021-843X.113.3.386.

Online Resources



Online Resource 1 Change of connectivity between the STS and EBA of the left hemisphere depending on the connectivity before therapy. Since “emotion” did not yield significance as predictor, this factor was excluded from this graph. Superior Temporal Sulcus (STS); Extrastriate Body Area (EBA)



Online Resource 2 Reaction times for patients in the different therapy groups CBT and HT depending on rumination. The line portrays the correlation between rumination and reaction time. Emotions where not considered here. Cognitive Behavioral Therapy (CBT); Hypnotherapy (HT)

5. Manuscript 3: How psychotherapy changes the depressed brain: activity in the left prefrontal cortex reduced after Hypnotherapy but not Cognitive Behavioral Therapy

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Study Design WIKI-D and Fundraising: Anil Batra and Kristina Fuhr.

Study Design of Neurophysiological Addition: Alina Haipt in consultation with Ann-Christine Ehlis.

Sample Recruitment and Data collection: Alina Haipt.

Data Analysis: Alina Haipt with support from Nina Geiger and Sonja Schunk.

Manuscript Drafting and Correcting: First draft written by Alina Haipt with revisions from Ann-Christine Ehlis, Anil Batra, and Kristina Fuhr. Redrafting by Alina Haipt.

Journal Selection and Submission: Alina Haipt in consultation with Ann-Christine Ehlis and support for submission from Nina Geiger and Sonja Schunk.

5.2 Research Article 3

How psychotherapy changes the depressed brain: activity in the left prefrontal cortex reduced after Hypnotherapy but not Cognitive Behavioral Therapy

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Abstract

Cognitive Behavioral Therapy (CBT) has been proven to be an apt treatment for depression. Yet, it has been shown that Hypnotherapy (HT) might offer additional or alternative benefits. The neurophysiological mechanisms underlying CBT have been investigated before, while HT has rarely been subject to neurophysiological research. Depression is associated with multiple affective and cognitive impairments, associated with aberrant activity in the prefrontal cortex (PFC). In this study we measured 66 depressed subjects either undergoing CBT or HT before and after therapy using functional near-infrared spectroscopy (fNIRS) during an Emotional Stroop Paradigm (ESP). On a behavioral level, reaction times and errors were measured. The results show that the patients' symptoms were reduced after therapy with both therapeutic approaches. However, an effect on a neurophysiological level was only found in the HT group: activity in the left dorsolateral PFC was reduced after therapy compared to before. This effect was not mirrored by the behavioral data, neither the relative error rate nor reaction times. The emotion displayed during the ESP did not have an effect on either the cerebral activity nor the behavioral data. We conclude that even though patients benefit from either therapy, HT and CBT, the underlying mechanisms might differ greatly between these two approaches. The roles of differentiating factors between patients remain unclear. In line with previous research, a connection between hypnosis and the dorsolateral PFC could be found, but its clear role needs to be objective to further investigation.

Keywords: Hypnotherapy, Cognitive Behavioral Therapy, Emotional Stroop Paradigm, prefrontal cortex, depression

List of Abbreviations

1	CBT	Cognitive Behavioral Therapy
2	HT	Hypnotherapy
3	fNIRS	Functional Near-infrared Spectroscopy
4	ESP	Emotional Stroop Paradigm
5	ACC	Anterior Cingulate Cortex
6	OFC	Orbitofrontal Cortex
7	DLPFC	Dorsolateral Prefrontal Cortex
8	IFG	Inferior Frontal Gyrus
9	RT	Reaction Time
10	BOLD	Blood Oxygen Level Dependent
11	PHQ-9	9-item Patient Health Questionnaire Depression Scale
12	O2Hb	Oxygenated Hemoglobin
13	HHb	Deoxygenated Hemoglobin
14	ROIs	Regions of Interest
15	TDDR	Temporal Derivative Distribution Repair
16	RER	Relative Error Rate
17	CS	Change Score
18	DMN	Default Mode Network
19	CEN	Central Executive Network
20	SN	Salience Network

5.2.1 Introduction

Depression is a widespread mental disorder which affects about 280 million people worldwide (WHO, 2021). Persistent sad mood, a loss of joy and interest in activities and feelings of worthlessness represent key symptoms of this disorder (American Psychological Association, 2013). Additionally, people with depression suffer from impaired affective cognition, e.g., the memory of emotional content (Elliott et al., 2011) and depressive rumination, which mirrors repetitive thoughts about the past or one's shortcomings (Nolen-Hoeksema, 1991). For the treatment of depression, cognitive behavioral therapy (CBT[1]), interpersonal therapy, short-term psychodynamic therapy and antidepressants (such as selective serotonin reuptake inhibitors, SSRIs) have been shown to be useful, especially when combined (Cuijpers et al., 2013, 2011; DeRubeis et al., 2008; Driessen et al., 2010). Still, remission rates after CBT are not as high as one would wish for compared to control conditions (Cuijpers et al., 2014); some authors even question the consideration of CBT as gold standard due to weak empirical tests, limited study quality and efficacy (response rate of about 50%) (Leichsenring and Steinert, 2017). An alternate therapy option, such as hypnotherapy (HT[2]), might be a promising addition to the treatment landscape of depression (Alladin and Alibhai, 2007). Fuhr et al. (2021) are the first authors to show that HT alone (not as an addition to CBT) is not inferior to CBT in reducing depressive symptoms, although the therapeutic approach is quite different. CBT focusses on addressing thoughts, decisions and behavior that contribute to a depressive state (Beck et al., 1979) as well as promoting the skill of checking the validity of (negative) beliefs and distancing oneself from these beliefs (DeRubeis et al., 2008). HT, on the other hand, includes formal hypnotic induction, that leads to an altered state of consciousness (Revenstorf, 2003) in which patients can learn to control symptoms and physiological functions that are usually not accessible consciously (Whorwell, 2011). Depression-specific HT includes techniques for ego-strengthening, expansion of awareness, positive mood inductions, posthypnotic suggestions and self-hypnosis (Alladin, 2006; Alladin and Alibhai, 2007). Emotions are addressed quite differently in these two therapy approaches. In the present study, we aim to assess these differences at the neurophysiological level. To this end, we used the functional imaging method of functional near-infrared spectroscopy (fNIRS[3]) in combination with an Emotional Stroop Paradigm (ESP[4]) (e.g. Williams and Broadbent, 1986) in order to capture cortical correlates of depression-specific emotional processing.

Mechanisms underlying the treatment of depression

Due to the high number of affected people across all age and social groups, the treatment of depression is object to a plethora of research. CBT is the most investigated psychological intervention for various mental disorders, not only regarding its efficacy, but also its underlying, neurophysiological mechanisms. Regarding depression, it seems that CBT can normalize depression-specific alterations in prefrontal (Goldapple et al., 2004) and amygdala activity (DeRubeis et al., 2008), which correlates with a decline of depressive symptoms. It is proposed that the effect of CBT is moderated by cognitive control, which is anatomically associated with prefrontal areas of the brain (Karlsson, 2011). These prefrontal control mechanisms might be influenced by CBT specifically addressing emotional regulation by focusing on the disruption of the interaction between depressed mood and negative cognitions by using suppression or reappraisal techniques (Yoshimura et al., 2014).

HT, on the other hand, deals with emotions quite differently. Trances, as an altered state of consciousness, are a rather old technique used in spiritual, religious, and healing rituals since the earliest recorded history (Hammond, 2013). Their healing effects have been investigated as early as the 18th century (Oon, 2008). Generally, HT includes these formal trances and other techniques and methods such as “pacing” and “leading”, metaphors and tales, utilization, and activation of resources to promote a different approach to dealing with problems (Revenstorf, 2017). In the treatment of depression, the HT used in this study included externalization, utilization and reframing of symptoms as well as biographical work, metaphors, formal trance inductions, time progression and other elements (Wilhelm-Goessling et al., 2020). As far as the efficacy of HT is concerned, there is only a very limited number of studies. Nevertheless, the existing studies show promising results, such as the study of Alladin and Alibhai (2007). The authors show that CBT including HT shows greater effect sizes in reducing symptoms of depression compared to CBT alone. Further, in a meta-analysis (Milling et al., 2018) the authors conclude that HT shows promising results in the treatment of depressive symptoms. In only two studies the neurophysiological effects of HT were investigated. In one of these, patients with irritable bowel syndrome were investigated and the authors found reduced activation in the Cortex Insularis after HT, whereas the cognitive intervention resulted in prefrontal changes (Lowén et al., 2013). The second study, on dental phobia, revealed reduced fear-related activity in the amygdala, anterior cingulate cortex (ACC[5]), insula and hippocampus during hypnosis (Halsband and Wolf, 2015). Recently, a biopsychosocial model of hypnosis has been suggested after reviewing the neurophysiological effects of hypnosis and HT (Halsband and Wolf, 2021; Jensen et al., 2015). Still, the question whether the data and resulting models can be applied to depression-specific therapy remains unanswered.

Neurophysiological alterations in depression

Individuals with depression often show attentional biases for stimuli of negative valence (Dalili et al., 2015; Gotlib et al., 2004), which is associated with impaired emotional regulation (Dryman and Heimberg, 2018). The latter is of clinical relevance for depression, as deficits in emotional regulation are an important marker for affective disorders and an indicator for relapse (Hardeveld et al., 2013). Functional imaging studies suggest depression-specific alterations in the cortico-limbic circuit, that are associated with depressive symptoms related to emotional regulation (Price and Drevets, 2010). As a reaction to emotional stimuli, depressed patients show higher activity in prefrontal areas, such as the orbitofrontal cortex (OFC[6]) (Kerestes et al., 2012), the dorsolateral prefrontal cortex (DLPFC[7]) (Lawrence et al., 2004), and the inferior frontal gyrus (IFG[8]) (Canli et al., 2004). The authors of one study propose that this hyperactivation is due to the hyperactivation of limbic regions to negative stimuli, which makes prefrontal regulation necessary (Anand et al., 2005). Further, functional connectivity between limbic and frontal regions seems to be impaired in individuals with depression (Carballedo et al., 2011). The DLPFC seems to play a prominent role in cerebral processes associated with emotional regulation. Apart from executive functions it is also associated with the regulation of negative emotions through reappraisal or suppression strategies (Ochsner et al., 2004; Phan et al., 2005), mediated through the top-down inhibition of the amygdala (Davidson, 2003). These insights show possible implications for depressive disorders: Reappraisal and suppression of negative affect are important protective factors in depression and are already successfully addressed in many CBT interventions (Denny and Ochsner, 2014; Dryman and Heimberg, 2018). And lastly, it has been shown that these interventions can go along with the normalization of prefrontal activity, as mentioned above (Goldapple et al., 2004).

Emotional Stroop Paradigm

A convenient paradigm to investigate interactions between emotion and cognition, e.g., the attentional bias towards emotional stimuli in depression, is the ESP (Williams & Broadbent, 1986; J. M. Williams, Mathews, & MacLeod, 1996). Similar to the classic Stoop Test (Stroop, 1935), participants are asked to ignore the semantic meaning of a presented word and name the color of the word. The time needed to name the color of the presented word is measured. In the classical test semantic color words are used and an interference between semantical meaning of the word and the task of naming the presented color can be observed. In the ESP, emotionally valanced words (instead of color words) are used. People with depression need more time to name the color of a word with sad valence compared to a neutral word (Mitterschiffthaler et al., 2008). The authors explain this effect with the attentional bias for negative content, which causes an interference with the actual task (naming the color). On a neurophysiological level the presentation of negatively valanced words causes a hyperactivation of the DLPFC, IFG and ACC, compared to neutral words (Hart et al., 2010; Mohanty et al., 2005). The left DLPFC might be involved in processing the conflicting information between two stimuli (e.g. semantic vs. color) due to its connection to selective attention processes (Nee et al., 2007), and the left IFG is associated with the top-down suppression of emotional contents, which facilitates focusing on the cognitive task (Swick et al., 2008). The hyperactivation of prefrontal control areas is more pronounced in individuals with depression than it is in healthy control subjects (Matsubara et al., 2014; Mitterschiffthaler et al., 2008; Mohanty et al., 2005; Nishizawa et al., 2019).

Objective, approach, and hypotheses

Taking together the results of the previously discussed literature, we tested how CBT and HT would differentially affect depression-specific prefrontal alterations in emotional processing, as for example tested with the ESP. Whereas the prefrontal normalization after CBT was already shown, there are no such investigations for HT. Furthermore, we investigated the association between possible prefrontal treatment effects and the patients' behavior. By investigating underlying processes of HT, we hope to contribute to understanding this promising alternative therapy option for patients with depression and possibly shed some light on specific factors that might advance personalization of therapy in depression. Therefore, we examined a sample of 66 individuals with depression, who participated in the study of Fuhr et al. (2021), before and after their HT or CBT intervention. Specifically, people were asked to name colors of emotionally valanced words in an ESP. Meanwhile, we measured prefrontal areas including the DLPFC and IFG bilaterally by using fNIRS. In line with previous research, we expected prefrontal normalization (decrease) of brain activity after CBT; we suspect a change in prefrontal activity in the HT group, a hypothesis for the direction of change (increase or decrease) cannot be made due to lacking research. Interaction effects of treatment (namely symptom change) and therapy group were investigated. We further hypothesized possible treatment and/or group effects should be mirrored in the behavioral data.

5.2.2. Materials and Methods

Subjects

All patients in this study were recruited from 152 participants (intended to treat) of the WIKI-D study (Fuhr et al., 2021), as shown in Figure 1. Trained clinicians diagnosed the participants with a unipolar mild to moderate depressive episode using the Structured Clinical Interview for DSM-IV (SKID-I) (Wittchen et al., 1997). In our neurophysiological measurements we additionally excluded WIKI-D patients if they were pregnant or nursing a child, had severe neurological diseases (e.g. meningitis, epilepsy), untreated hypertension, diabetes, or other coronary diseases as well as social phobia. In total, 75 patients (56 female, 19 male; 18–69 years, $M = 39.24$, $SD = 14.85$) participated in two fNIRS measurements, one before and one after therapy. The data sets of 9 patients were lost after the measurement due to problems during the saving process; thus, the data of 66 patients were analyzed in total (Figure 1). One third of the patient sample ($n = 22$) showed at least one acute comorbid disorder, 6 patients showed more than one comorbidity; 21 patients took at least one antidepressant medication (36 % SSRIs or other including atypical antipsychotics), which had to been taken without changes in dosage or intake for three months prior to study inclusion. Written informed consent to participate in the study was given by all participants.

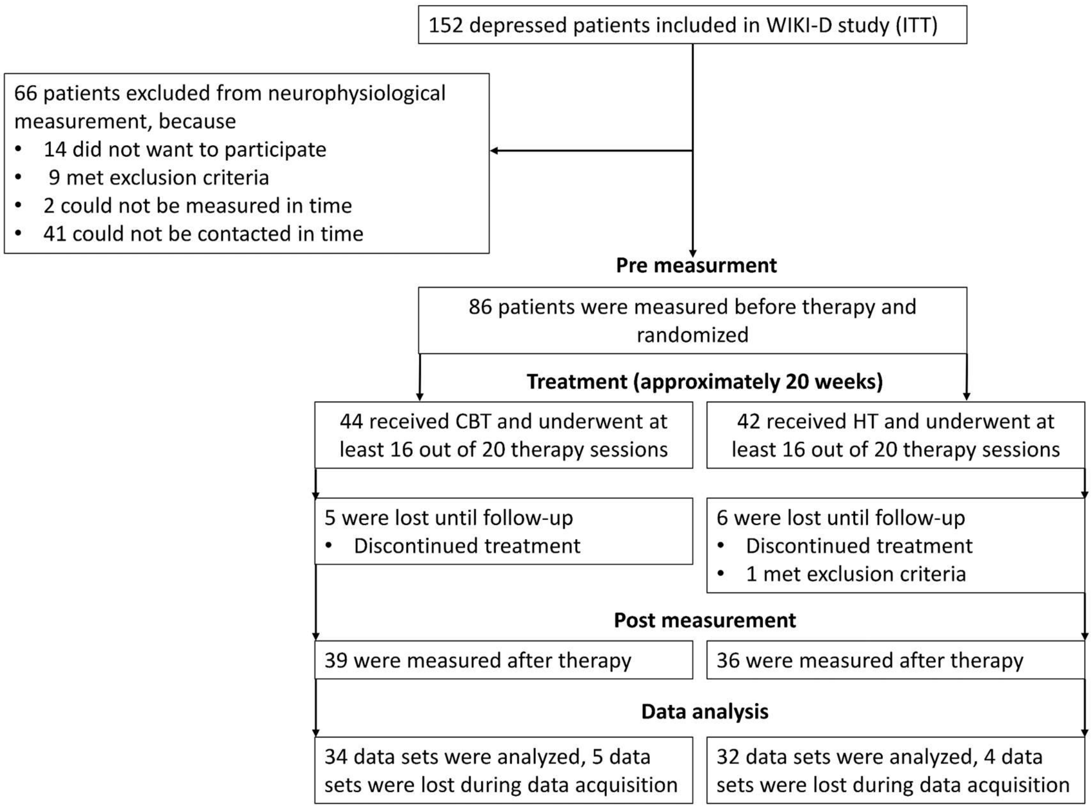

Figure 1. Inclusion and procedure of measuring patients throughout our study. The WIKI-D study was conducted by Fuhr et al. (2021); intended to treat (ITT); Cognitive Behavioral Therapy (CBT); Hypnotherapy (HT).

Stimuli, materials, and measures

The ESP we used in our study contained happy and neutral, as well as negatively valenced stimuli. To rule out a confounding of negative stimuli in general and depression-specific stimuli, we introduced two categories of negative stimuli: one category specific to depression and one specific to social phobia. The words were adapted from a German study on attentional biases in social phobia and depression (Rinck and Becker, 2005), since no study on depression included German words that were validated for the ESP. Each category included ten words, e.g. Gemütlichkeit[5] (= coziness), ausschneiden (= to cut out), Interessenlosigkeit (= absence of interest), Lampenfieber (=stage fright). The list of words is included in the Appendix A (Table 2). All words were displayed once in each color (red, blue and yellow), resulting in 120 trials in total. The colored words were presented on a black screen, in arial font,

[5] All German words used in the ESP were translated by authors.

size 25. The severity of symptoms was self-rated on the 9-item Patient Health Questionnaire Depression Scale (PHQ-9[9])(Kroenke and Spitzer, 2002). As behavioral data, we measured the errors the patients made and the reaction time (RT[10]). Also, the blood-oxygen-level-dependent (BOLD[11]) signal using fNIRS was measured.

Near-infrared spectroscopy and regions of interest

The mechanism of fNIRS is based on the fact that light in the near-infrared spectrum penetrates the skull and other biological tissue. Thereby, the amount of light which is absorbed depends on the concentration of oxygenated (O2Hb[12]) and deoxygenated hemoglobin (HHb[13]) in the underlying brain tissue, thus reflecting relative concentration changes of both chromophores. Concentration changes of O2Hb and HHb, in turn, allows for conclusions about cortical activation underneath the measurement probes. In our study we used an ETG-4000 Optical Topography System (Hitachi Medical Corporation, Tokyo, Japan) with a 52-channel array of 33 optodes (17 light emitters and 16 detectors) covering frontal brain areas (temporal resolution: 10 Hz). The inter-optode distance was 3 cm and near-infrared light with two wavelengths (695 and 830 nm) was used. The optodes were arranged in a 3×11-rectangular shape on the patients' heads in respect to the international 10/20 System (Jasper, 1958). Detector optode 26 (optode in the middle of the lowest channel row) was placed over Fpz; the posterior channels 43 (left) and 52 (right) were positioned towards the temporal positions T3 and T4, respectively. A neuronavigation system was used on a volunteer's head to assign the channel positions to the anatomy. The regions of interest (ROIs[14]) were selected according to previous findings on the cerebral activity of emotional processing in depressed subjects (Anand et al., 2005; Canli et al., 2004; Carballedo et al., 2011; Lawrence et al., 2004): namely the dorsolateral parts of the PFC and the IFG (Figure 2).

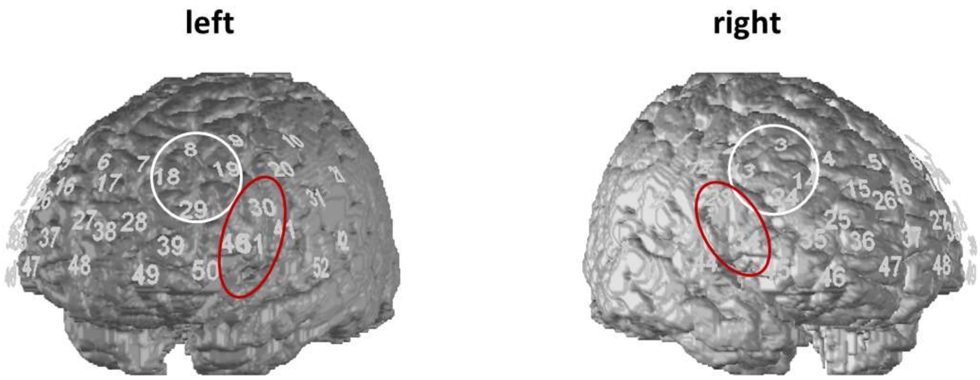

Figure 2. Regions of Interest. Here, the selected ROIs are displayed according to previous literature. The DLPFC region (white circle) included channels 8, 18, 19, 29 on the left and 3, 13, 14, 24 on the right and the IFG region (red circle) included channels 30, 40 and 51 on the left and 23 and 34 on the right. Regions of Interest (ROIs), Dorsolateral Prefrontal Cortex (DLPFC), Inferior Frontal Gyrus (IFG).

Procedure

After diagnostics and before undergoing psychotherapy, patients were measured for the first time, the earliest after being included in the WIKI-D study, the latest one week after therapy had started. The second measurement took place after therapy completion, the earliest one week before and the latest 4 weeks after the last session (Figure 1). Patients had been randomly assigned to either CBT (n=34) or HT (n=32). Therapy was considered completed, when the patients undertook at least 16 out of a maximum of 20 sessions over six months. Therapy was conducted individually. Each fNIRS measurement lasted two hours and included two additional paradigms besides the ESP, the results of which will be reported elsewhere (Haipt et al., 2022). In between the paradigms, patients filled out the PHQ-9 forms.

Using fNIRS, O2Hb and HHb were recorded continuously, after a 10 s baseline measurement. All patients were asked to name the color of the displayed word as fast as possible by pressing the allocated response button (arrow buttons left, down, and right). The allocation of the buttons and colors was balanced across all subjects. Responses could be given as soon as the color was identified. Due to the setup of the measurement material, all patients used their right hand regardless of handedness. During a practice trial with a number of “X” instead of words, the patients learned the color allocation to the buttons. During the practice as well as the measurement trials, first a white fixation cross was displayed in the middle of the black screen for 500 ms. After that a colored word appeared for 1500 ms. The time intervals between the words varied randomly between 4000 and 8000 ms. Words and colors were displayed randomly. After 60 trials the participants were given a break, which they could end themselves by pressing a button. The experiment lasted about 16 minutes. All patients received a small monetary compensation of 15 Euros for their time.

Data analyses

Preprocessing

MATLAB R2017b (MathWorks Inc, Natick, USA) was used for preprocessing the fNIRS data and plotting the brains. First, all signals were visually inspected for local artefacts, 0.52 % of all channels (across all subjects) of the pre-measurement were interpolated from adjacent channels, and 1.92 % of all channels of the post-measurement. Then, a temporal derivative distribution repair (TDDR[15]) (Fishburn et al., 2019) was applied, as well as band-pass filtering (0.1–0.01 Hz) to minimize low- and high-frequency noise. After that, movement artefacts were reduced by using a specific algorithm (Cui et al., 2010). Using a spatial gaussian kernel filter with a standard deviation of $\sigma = 40$, the influence of global signal changes was reduced. Then, all trials which were answered incorrectly (2 % of all trials across all subjects) were excluded from further analysis to ensure that possible ESP effects could be traced back to cognitive processing, not guessing or error processing. Then, the fNIRS signals were fitted to a model hemodynamic response function in a general linear model based regression (Plichta et al., 2007) with a peak time of 5.5 seconds and a peak dispersion of 2 seconds.

Statistics

For statistical analyses on the behavioral and fNIRS data, as well as bar charts, we used R Studio (R Studio Inc, Boston, USA). On a behavioral level we calculated the relative error rate (RER[16]; sum of errors divided by trial number) for each patient. Since the error trials were excluded from fNIRS data analyses, no direct connections between the RER and the neurophysiological data were made. RTs were also analyzed after the elimination of error trails. First, we tested the fNIRS and behavioral data for possible Stroop Effects over time. We calculated the change scores (CS[17]) of the fNIRS for all ROIs and behavioral data (post – pre) and then compared the different emotional categories with each other using an ANOVA. In former studies it has been shown that it was harder to find an interference effect when the ESP words were presented randomly compared to a block design (Bar-Haim et al., 2007), as well as that interference effects might not be influenced by therapy effects (Kampman et al., 2002). Therefore, we tested for possible Stroop Effects to determine the inclusion of the factor "emotion" in the following analyses to minimize the number of factors in favor of an increase of power.

We then tested for a therapy effect on the symptom level (PHQ-9) with a mixed ANOVA, time and group serving as independent variables. A significant time factor (therefore a significant therapy effect) was included in further fNIRS and behavioral data analyses by calculating the CS of the PHQ-9 (post – pre) and including it as covariate. The therapy group was included as independent variable (CBT = 0 vs. HT = 1). In a next step, we calculated the CS for the BOLD signal (post – pre) for all ROIs, the RERs and the RTs. These CSs served as dependent variables in further analyses. ANCOVAs were calculated for all dependent variables to test for therapy effects explained by therapy group and/or therapy effects on a symptomatic level, on a neurophysiological as well as behavioral level. Marginal sums of squares were used.

Post-hoc two-tailed t-tests were conducted to analyze significant group effects. The level of significance was $\alpha = 0.05$.

5.2.3 Results

First, we tested the neurophysiological and behavioral data for possible Stroop Effects. Since the displayed emotion did not affect the CS of the fNIRS data in neither the left nor right DLPFC nor left or right IFG, nor the RER nor the RT on behavioral level, we excluded the factor "emotion" from further analysis by pooling the data for each dependent variable.

Secondly, we tested for a treatment effect on the symptom level to see if patients reported less symptoms after therapy than before therapy. A mixed ANOVA on the PHQ score including time and therapy group as independent variables revealed a significant effect for time, but not for group ($F(1,128) = 47.32$, $p < 0.001$), indicating a significant decrease of self-reported symptoms over time in both patient groups

(M(pre) = 14.92, SD(pre) = 4.06, M(post) = 7.34 , SD(post) = 4.47). This therapy effect was included as a covariate (symptom change) in the further analyses of the CS of BOLD signals.

Thirdly, we tested the effects of the therapy group and therapy effect on symptom level on the change over time for all ROIs and the behavioral data. In the left DLPFC the ANCOVA on the CS of the BOLD signal revealed a significant main effect for the factor “group” ($F(1, 62) = 4.78$, $p = 0.03$), neither the symptom change alone ($F(1, 62) = 2.34$, $p = 0.13$) nor the interaction between symptom change and group ($F(1, 62) = 2.22$, $p = 0.14$) yielded significance. Post-hoc t-tests within the groups show no significant change in BOLD responses over time in the CBT group ($t(31) = -0.47$, $p = 0.64$, M(pre) = 0.03, SD(pre) = 0.21, M(post) = 0.04, SD(post) = 0.18), but a significant decrease of the BOLD response over time in the HT group ($t(33) = 2.12$, $p = 0.04$, M(pre) = 0.05; SD(pre) = 0.17; M(post) = -0.001; SD(post) = 0.24). This result is portrayed in Figure 3, 4 and 5. In no other ROI, neither the right DLPFC nor the left or right IFG, the ANCOVAs on the change of BOLD responses yielded significance, indicating no connection between the BOLD signal change over time and symptom change or therapy group (see Figure 3, 4, and 5). Descriptive data of the BOLD response for all ROIs is displayed in Table 1.

In the behavioral data we also did not find a group effect, nor an effect of symptom change on the CS for neither the RER nor the RTs using ANCOVAs indicating no systematic patterns in these outcome variables. On a numerical level, it should be noted that for the RER a ceiling effect could be observed. Descriptive values are portrayed in Table 3 (Appendix A).

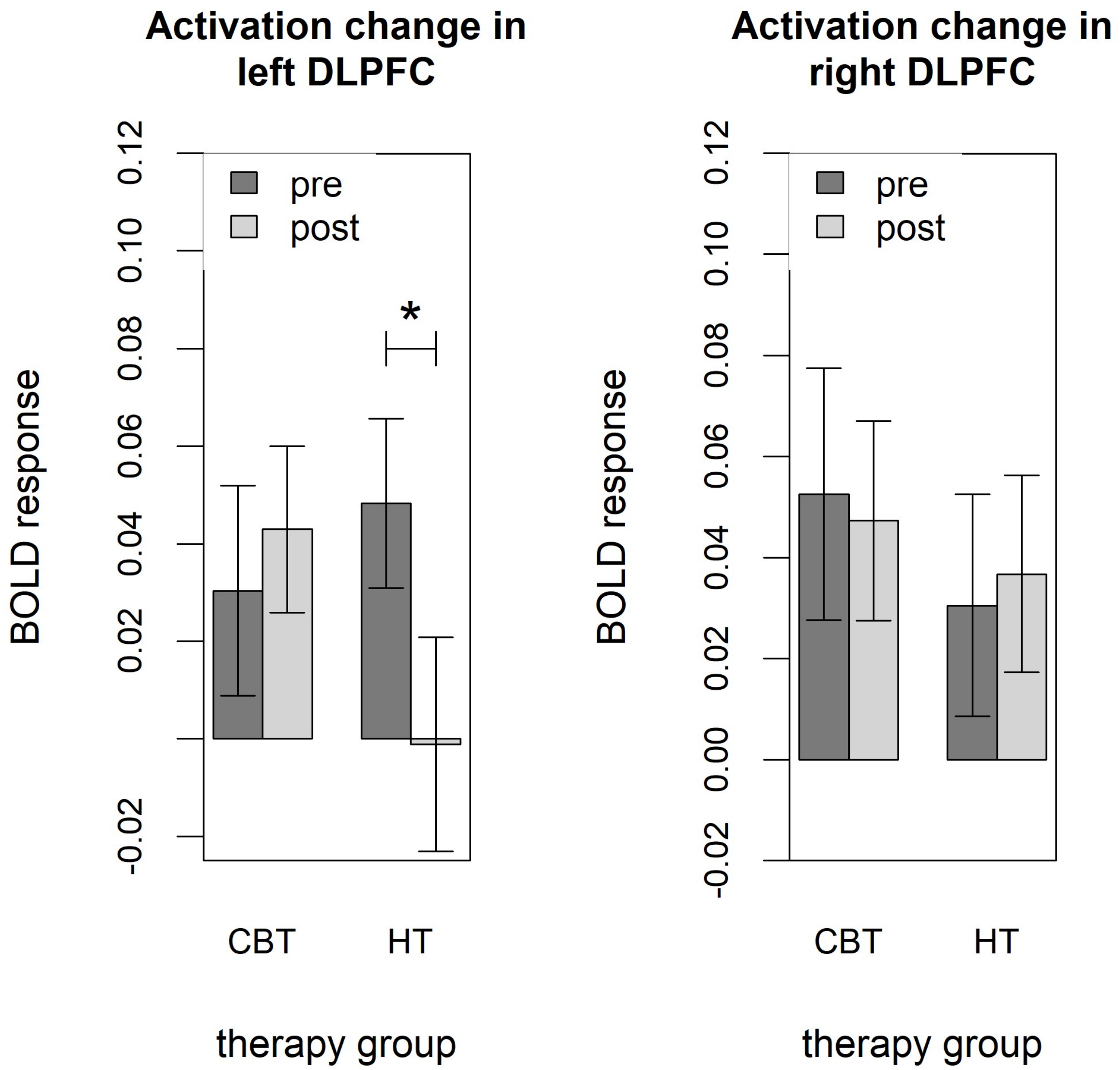

Figure 3. Activation effects in the Dorsolateral Prefrontal Cortices (DLPFC). This graph shows activation changes over time for each therapy group for the left and the right DLPFC. A significant effect was found in the HT group, where the BOLD response decreased after therapy (indicated by *). The bars indicate the confidence interval. Blood Oxygen Level Dependent (BOLD), Cognitive Behavioral Therapy (CBT), Hypnotherapy (HT).

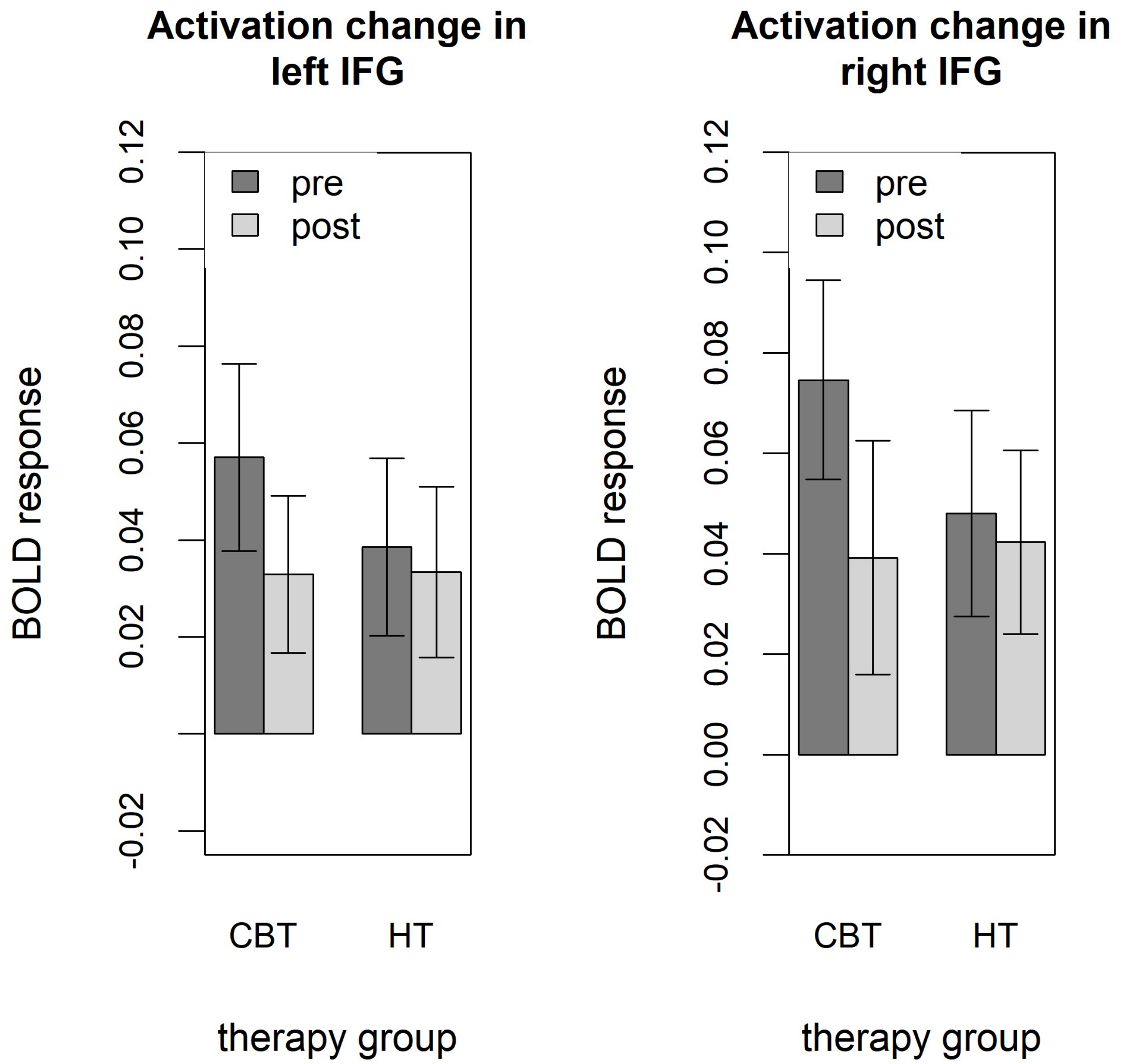

Figure 4. Activation effects in the Inferior Frontal Gyri (IFG). This graph shows activation changes over time for each therapy group for the left and the right IFG. No significant difference could be detected using ANOVAs. The bars indicate the confidence interval. Blood Oxygen Level Dependent (BOLD), Cognitive Behavioral Therapy (CBT), Hypnotherapy (HT).

Table 1

Descriptive data (beta-values of pre-processed fNIRS data) for all regions of interest.

ROI		*Mean* before therapy	*SD* before therapy	*Mean* after therapy	*SD* after therapy
	Overall	0.04	0.11	0.02	0.11
Left DLPFC	HT	0.05	0.10	-0.001	0.13
	CBT	0.03	0.12	0.04	0.10
	Overall	0.04	0.13	0.04	0.11
Right DLPFC	HT	0.03	0.13	0.04	0.11
	CBT	0.05	0.14	0.05	0.11
	Overall	0.05	0.11	0.03	0.10
Left IFG	HT	0.04	0.11	0.03	0.10
	CBT	0.06	0.11	0.03	0.09
	Overall	0.06	0.12	0.04	0.12
Right IFG	HT	0.05	0.12	0.04	0.11
	CBT	0.07	0.11	0.04	0.13

Note. Means and standard deviations (SD) were calculated for all ROIs, across therapy groups and for each group separately (and always averaged across affective categories of the Emotional Stroop Task). Regions of Interest (ROIs), Dorsolateral Prefrontal Cortex (DLPFC), Inferior Frontal Gyrus (IFG), Cognitive Behavioral Therapy (CBT), Hypnotherapy (HT).

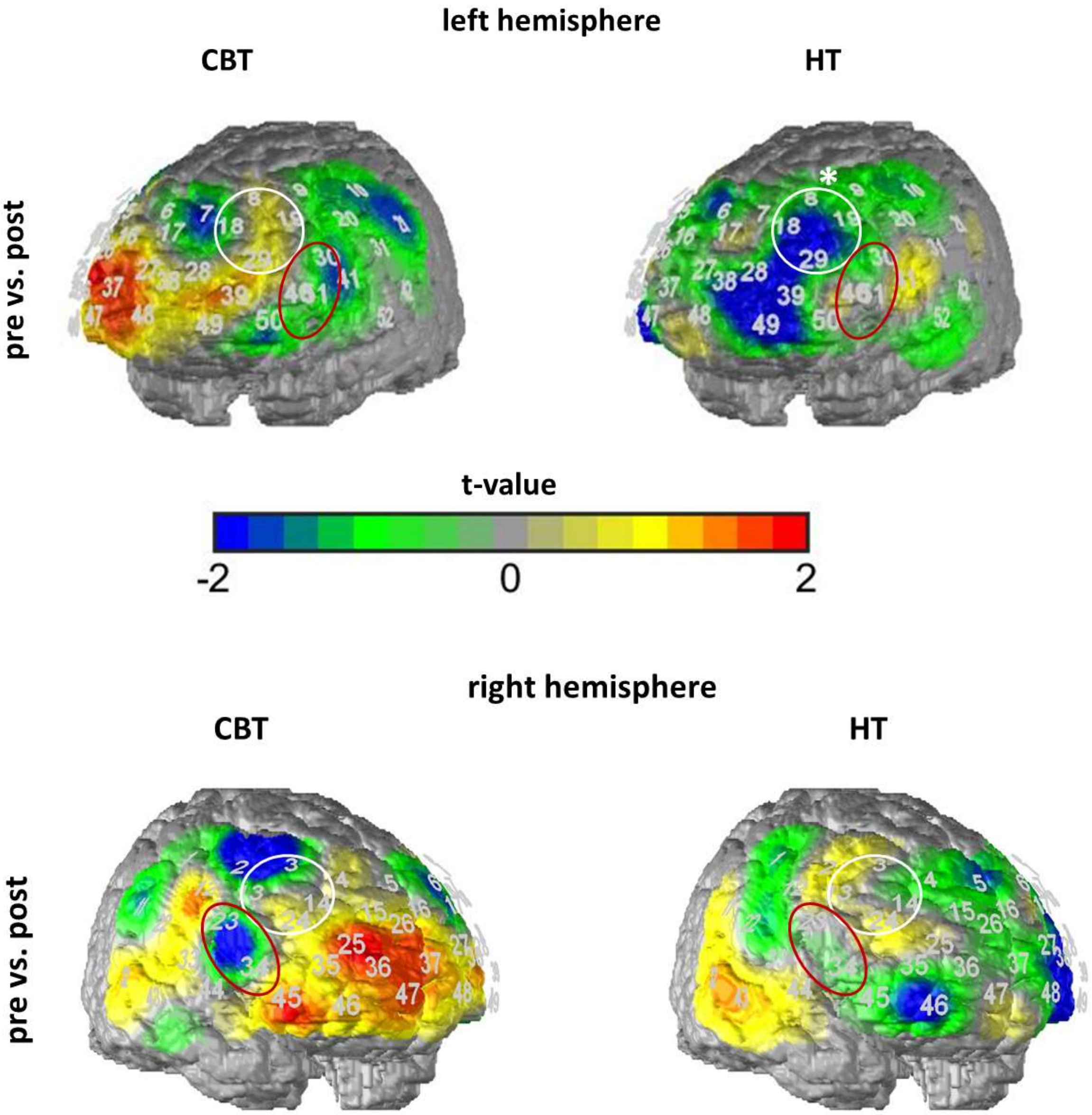

Figure 5. Therapy effects for both groups. This graph shows the change of BOLD signal over time (before and after therapy (post-pre)) for both therapy groups and both hemispheres. The white circles indicate the DLPFC, the red circles the IFG. A significant pre-post change was found for the left DLPFC, indicated with a white *. The colors indicate t-values resulting from pre-post comparisons for each channel. These t-values serve presentation purposes. Blood Oxygen Level Dependent (BOLD), Dorsolateral Prefrontal Cortex (DLPFC), Inferior Frontal Gyrus (IFG), Cognitive Behavioral Therapy (CBT), Hypnotherapy (HT).

5.2.4 Discussion

General Discussion

In this study we explored the question how the therapeutic effects of HT or CBT for depression differ on a neurophysiological level, specifically looking at the PFC. While patients profited from both therapies, the central finding of our study is the main effect of group on the change of BOLD response: Only the patients of the HT group showed a significant decrease in BOLD response in the left DLPFC over the treatment period. No changes in the right DLPFC nor IFG, nor for the CBT group were found. The symptom change did not predict the change of BOLD response nor behavioral data. A Stroop Effect could not be found for either measurement, neither on a neurophysiological level nor a behavioral level.

In line with our careful assumption, patients in the HT group showed changed activity in the DLPFC over time: the activity was reduced after therapy compared to before. Surprisingly and against our hypothesis, this effect was not found in the CBT group. However, our results suggest a possible normalization effect of activity in the DLPFC after HT. So far, the two studies on therapeutic effects of HT on the brain have not indicated a prominent role of the DLPFC (Halsband and Wolf, 2015; Lowén et al., 2013), so possible answers for this finding might lie in the investigation of hypnosis outside the therapeutic context. In various studies it was shown that subjects showed altered activity of the Default Mode Network (DMN[18]) during hypnosis. The DMN is one of the most studied cerebral networks showing robust coupling of spontaneous fluctuations (Greicius et al., 2008; Horovitz et al., 2009; Menon, 2011; Vanhaudenhuyse et al., 2010). Results of the studies of hypnosis and the DMN show activation changes of the DMN in major nodes of the DMN, like the ACC, and other prefrontal areas like the DLPFC (Cojan et al., 2009; Deeley et al., 2012; Egner et al., 2005; McGeown et al., 2009; Pyka et al., 2011; Rainville et al., 2002) which are closely connected to DMN activity (Menon, 2011; Sambataro et al., 2013; Sheline et al., 2009).

An involvement of the DMN in depression has been shown multiple times (Anand et al., 2005; Connolly et al., 2013;. Greicius et al., 2007; Grimm et al., 2009; Guo et al., 2014; Rosenbaum et al., 2017; Sheline et al., 2009; Yan et al., 2019; Zhu, Zhu, Shen, Liao, & Yuan, 2017). At a symptom level, the DMN has been discussed to account for impairments in emotional processing and cognitive performance (Drevets et al., 2008; Kaiser et al., 2015). In most recent literature it is suggested that especially the midline regions of the DMN are hyperactive during depression and show increased connectivity to other major brain networks (Scalabrini et al., 2020). DMN measurements conducted in the same context as this study will be reported elsewhere.

The DLPFC plays a major role in the Central Executive Network (CEN[19]), which is associated with cognitive functioning, and the Salience Network (SN[20]) which is linked to the detection, integration and filtering of interoceptive, automatic, and emotional information (Menon, 2011; Seeley et al., 2007). It has been noted that the CEN and SN are difficult to isolate due to the coactivation of prefrontal areas during cognitive processing (Menon, 2011). Summarizing these findings, we conclude that the DLPFC seems to play an important role in depression; also, changes in cognitive functioning and activation changes have been detected during hypnosis. Further, DLPFC activity has been shown to normalize after CBT (Goldapple et al., 2004; Yoshimura et al., 2014). Why the activation change in the DLPFC was only found in the HT in this study, remains unclear and calls for further investigation. Undoubtfully, the therapies do differentiate in their neurophysiological effects and this hints toward different mechanism the therapies are based on. This is in line with the results of a third study conducted in the context of the present work showing an activation change in posterior parts of the brain, which are associated with emotional processing, only in the HT group. This activation change was moderated by the degree of the patients' rumination (Haipt et al., 2022).

Limitations and future research

It remains unclear, why we did not find a Stroop Effect, neither on a behavioral nor a neurophysiological level. In a meta-analysis on the ESP the authors found a robust Stroop Effect on the attentional bias in depressed subjects (Epp et al., 2012). The lack of effect in our study might result from design decisions. One is the stimuli selection. Due to the unavailability of validated stimuli, namely emotional words in German relevant to depression, we included the verbal stimuli from a study on attentional biases and memory biases (Rinck and Becker, 2005). However, in this study only women were included and the verbal material contained a lot of household related words. Also, the study itself did not include neurophysiological measurements. In a second study on cognitive biases, these words were also used, but again, no neurophysiological data was obtained. Therefore, it is questionable if the words we used were apt to conduct an ESP. Thus, in future research, a gender-neutral set of ESP stimuli should be validated in a first step and then used in neurophysiological measurements. Further, we used a random event-related presentation of the stimuli and it has been shown that this presentation evokes less effects than a block-design (Bar-Haim et al., 2007). In a study on the neurophysiological differences between depressed subjects and healthy controls when performing a Stroop Task, the authors found a Stroop Effect in both subject groups, but differential activation in the DLPFC in the depressed subjects compared to healthy controls (Wagner et al., 2006). Unfortunately, this study did not use emotional words, but the classical Stroop color words. It remains unclear, if the ESP does in fact evoke interference effects of semantic content and color in depressed subjects or rather attentional biases. Due to a different focus in our study, we did not present specific hypotheses concerning a Stroop Effect – neither a neurophysiological nor a behavioral level - but in future research, these should be included. Also, a group of healthy control subjects should be included. Another question that remains open is, if the category of social phobic words was a suitable control category for negatively valenced words. Future studies could clarify these open questions.

Furthermore, the results we found on a neurophysiological level were not mirrored on a behavioral level. This might indicate that the processes changed by psychotherapy, specifically HT, might not be directly linked to the activity in the DLPFC or IFG, which we evoked with the ESP. Rather, they might be moderated or mediated by other factors, which are still unknown. Further research is needed to investigate the mechanisms.

On a descriptive level it can be noted that the variance of DLPFC activation varied greatly among the patients in our study. This could indicate that subjects react very differently to therapies and/or there might be other factors to consider when investigating depression. In the study by Haipt et al. (Haipt et al., 2022) rumination was a moderating factor for the effect of HT on temporal areas. Thus, in future research additional factors, like rumination, should be included. Further, some authors showed that medicated patients show different depression-related DMN activity than non-medicated patients (Yan et al., 2019). In our study, we included drug-naïve, as well as medicated subjects, but did not include this factor in our analysis. This should be considered in the future. This would pave the way to personalized medicine and treatment options.

Another limitation is that subcortical areas cannot be measured with fNIRS due to its low penetration depth. Therefore, areas that have been shown to be relevant when investigating HT (like the insula or the ACC (Halsband and Wolf, 2015; Lowén et al., 2013)), or CBT (like the amygdala (Goldapple et al., 2004)) were not measured here. In the future, fMRI data should be obtained to be able to observe subcortical areas.

A limitation in our study is also the vague assumptions we made about the differences between HT and CBT. Our assumptions on the different content of the two therapy approaches of the WIKI-D study (Fuhr et al., 2021) were based on the therapy manuals and interviews with experts, but we do not claim the therapy content to be the only differentiating factor between the therapy approaches. Other possible differentiating factors could be the expectations patients had (the word “hypnosis” alone might evoke specific expectations in patients) or the therapeutic relationship. The induction of a hypnotic trance by a therapist might entail specific relational factors (e.g. the patient is in a recipient role, the therapist is “doing” something “for” the patient). Medication effects could also play a role in the change of DLPFC activity and might differ between therapy approaches.

Conclusions

In this study on 66 depressed patients undergoing either CBT or HT we showed that these two therapy approaches yield a similar result in reducing symptoms, but seem to work differently on a neurophysiological level. Using an ESP, we investigated the patients’ prefrontal activity before and after therapy and showed a significant reduction of activity in the left DLPFC in the HT group, not the CBT group. This effect was not mirrored in the behavioral data. We conclude from these results, that these two beneficial therapies seem to be based on different neural mechanisms and that these mechanisms might not be directly linked to cognitive processes. The role of the DLPFC during hypnosis, especially used in a therapeutic context, remains unclear and calls for further investigation.

Declarations

Funding

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Conflicts of Interests

The authors declare that they have no conflict of interest.

Availability of Data

The datasets from the current study are available upon request.

Code Availability

The codes of the current study are available upon request.

Authors' Contributions

Alina Haipt: Term, Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Visualization. **Nina Geiger**: Methodology, data analysis, Writing - Review & Editing, Publication process. **Sonja Schunk:** Methodology, data analysis, Writing - Review & Editing. **Kristina Fuhr**: Resources, Writing – Review & Editing, Project administration. **Anil Batra**: Supervision, Funding acquisition, Writing – Review & Editing. **Ann-Christine Ehlis**: Term, Conceptualization, Methodology, Formal analysis, Resources, Validation, Supervision, Project administration, Funding acquisition, Writing – Review & Editing.

Ethics Approval

This study was approved with a positive ethics vote by the Ethics Committee of the University Hospital of Tuebingen (061/2015B02).

Consent to participate

All participants gave their written informed consent to participate in the study.

Appendix A

Table 2

List of words used in the ESP and their translation (Rinck and Becker, 2005)

Neutral words	**English**	**Positive words**	**English**	**Depression specific words**	**English**	**Social-phobia specific words**	**English**
ausschneiden	to cut out	Gemütlichkeit	coziness	Interessenlosigkeit	absence of interest	Lampenfieber	stage fright
Marmelade	jam	Waldesstille	forest silence	Erschöpfung	exhaustion	erröten	to blush
Dachluke	roof hatch	Schönheit	beauty	Leere	void	Peinlichkeit	embarrasment
Topflappen	pot holder	großartig	great	niedergeschlagen	dejected	verspottet	ridiculed
Dickwandig	thick-walled	genießen	to enjoy	verzweifeln	to dispair	stottern	to stutter
Einkleiden	to dress up	Harmonie	harmony	Konzentrations-probleme	concentration problems	Unsicherheit	insecurity

Salatschüssel	salad bowl	Blütenpracht	splendor of flowers	Müdigkeit	tiredness	schwitzen	to sweat
Lichtschalter	light switch	Wunder	miracle	Schwermut	melancholy	Blamage	embarrasment
Kanne	pot	gutgelaunt	being in a good mood	todunglücklich	deadly unhappy	ausgelacht	being laughed at
Gesalzen	salted	vergnügen	to enjoy oneself	grübeln	to ruminate	enttäuschen	to disappoint

Table 3

Descriptive data for all relative error rates (RER) and reaction times (RT).

		Mean before therapy	*SD* before therapy	*Mean* after therapy	*SD* after therapy
	Overall	1.65	2.84	1.88	3.73
	HT	1.43	2.49	1.83	4.12
	CBT	1.89	3.15	1.94	3.28
RER	Depressive	1.30	2.43	1.44	2.70
(in %)	Neutral	1.49	2.75	2.25	4.61
	Positive	1.89	3.06	1.98	3.42
	Social Phobic	1.93	3.07	1.85	3.96
	Overall	750.34	147.06	729.23	123.98
	HT	743.32	128.85	739.88	126.59
	CBT	757.81	164.40	717.92	120.60
Mean RT	Depressive	751.30	148.02	727.70	118.59
(in ms)	Neutral	758.23	150.09	729.43	124.29
	Positive	743.61	149.49	731.94	134.10
	Social Phobic	748.24	143.54	727.85	121.18

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References

Alladin, 2006. Cognitive hypnotherapy for treating depression, in: The Clinical Use of Hypnosis with Cognitive Behavior Therapy: A Practitioner's Casebook. pp. 139–187.

Alladin, A., Alibhai, A., 2007. Cognitive hypnotherapy for depression: An empirical investigation. Int. J. Clin. Exp. Hypn. 55, 147–166. https://doi.org/10.1080/00207140601177897

American Pschological Association, 2013. Diagnostic and statistical manual of mental disorders, 5th ed. American Psychological Association, Arlington.

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., Mathews, V.P., Kalnin, A., Lowe, M.J., 2005. Activity and connectivity of brain mood regulating circuit in depression: A functional magnetic resonance study. Biol. Psychiatry 57, 1079–1088. https://doi.org/10.1016/j.biopsych.2005.02.021

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M.J., Van Ijzendoorn, M.H., 2007. Threat-related attentional bias in anxious and nonanxious individuals: A meta-analytic study. Psychol. Bull. 133, 1–24. https://doi.org/10.1037/0033-2909.133.1.1

Beck, A.T., Rush, A.J., Shaw, B.F., Emery, G., 1979. Cognitive Therapy for Depression. Guilford, New York.

Canli, T., Sivers, H., Thomason, M.E., Whitfield-Gabrieli, S., Gabrieli, J.D.E., Gotlib, I.H., 2004. Brain activation to emotional words in depressed vs healthy subjects. Neuroreport 15, 2585–2588. https://doi.org/10.1097/00001756-200412030-00005

Carballedo, A., Scheuerecker, J., Meisenzahl, E., Schoepf, V., Bokde, A., Möller, H., Doyle, M., Wiesmann, M., Frodl, T., 2011. Functional connectivity of emotional processing in depression. J. Affect. Disord. 134, 272–279. https://doi.org/10.1016/j.jad.2011.06.021

Cojan, Y., Waber, L., Schwartz, S., Rossier, L., Forster, A., Vuilleumier, P., 2009. The brain under self-control: modulation of inhibitory and monitoring cortical networks during hypnotic paralysis. Neuron 62, 862–875. https://doi.org/10.1016/j.neuron.2009.05.021

Connolly, C.G., Wu, J., Ho, T.C., Hoeft, F., Wolkowitz, O., Eisendrath, S., Frank, G., Hendren, R., Max, J.E., Paulus, M.P., Tapert, S.F., Banerjee, D., Simmons, A.N., Yang, T.T., 2013. Resting-State Functional Connectivity of Subgenual Anterior Cingulate Cortex in Depressed Adolescents. Biol. Psychiatry 74, 898–907. https://doi.org/10.1016/j.biopsych.2013.05.036.Resting-State

Cui, X., Bray, S., Reiss, A., 2010. Functional near infrared spectroscopy (NIRS) signal improvement based on negative correlation between oxygenated and deoxygenated hemoglobin. Neuroimage 49, 3039–3046.

Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., Dobson, K.S., 2013. A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. Can. J. Psychiatry 58, 376–385. https://doi.org/10.1177/070674371305800702

Cuijpers, P., Geraedts, A.S., van Oppen, P., Andersson, G., Markowitz, J.C., van Straten, A., 2011. Interpersonal Psychotherapy for Depression: A Meta-Analysis. Am. J. Psychiatry 168, 581–592. https://doi.org/10.1176/appi.ajp.2010.10101411

Cuijpers, P., Karyotaki, E., Weitz, E., Andersson, G., Hollon, S.D., Van Straten, A., 2014. The effects of psychotherapies for major depression in adults on remission, recovery and improvement: A meta-analysis. J. Affect. Disord. 159, 118–126. https://doi.org/10.1016/j.jad.2014.02.026

Dalili, M.N., Penton-Voak, I.S., Harmer, C.J., Munafò, M.R., 2015. Meta-analysis of emotion recognition deficits in major depressive disorder. Psychol. Med. 45, 1135–1144. https://doi.org/10.1017/S0033291714002591

Davidson, R.J., 2003. Affective neuroscience and psychophysiology: Toward a synthesis. Psychophysiology 40, 655–665. https://doi.org/10.1111/1469-8986.00067

Deeley, Q., Oakley, D., Toone, B., Giampietro, V., Brammer, M.J., Williams, S.C.R., Halligan, P.W., 2012. Modulating the default mode network using hypnosis. Int. J. Clin. Exp. Hypn. 60, 206–228. https://doi.org/10.1080/00207144.2012.648070

Denny, B.T., Ochsner, K.N., 2014. Behavioral effects of longitudinal training in cognitive reappraisal. Emotion 14, 425–433. https://doi.org/10.1037/a0035276.Behavioral

DeRubeis, R.J., Siegle, G.J., Hollon, S.D., 2008. Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. Nat. Rev. Neurosci. 9, 788–796. https://doi.org/10.1038/nrn2345

Drevets, W.C., Price, J.L., Furey, M.L., 2008. Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. Brain Struct. Funct. 213, 93–118. https://doi.org/10.1007/s00429-008-0189-x

Driessen, E., Cuijpers, P., de Maat, S.C.M., Abbass, A.A., de Jonghe, F., Dekker, J.J.M., 2010. The efficacy of short-term psychodynamic psychotherapy for depression: A meta-analysis. Clin. Psychol. Rev. 30, 25–36. https://doi.org/10.1016/j.cpr.2009.08.010

Dryman, M.T., Heimberg, R.G., 2018. Emotion regulation in social anxiety and depression: a systematic review of expressive suppression and cognitive reappraisal. Clin. Psychol. Rev. 65, 17–42. https://doi.org/10.1016/j.cpr.2018.07.004

Egner, T., Jamieson, G., Gruzelier, J., 2005. Hypnosis decouples cognitive control from conflict monitoring processes of the frontal lobe. Neuroimage 27, 969–78. https://doi.org/10.1016/j.neuroimage.2005.05.002

Elliott, R., Zahn, R., Deakin, J.F.W., Anderson, I.M., 2011. Affective cognition and its disruption in mood disorders. Neuropsychopharmacology 36, 153–182. https://doi.org/10.1038/npp.2010.77

Epp, A.M., Dobson, K.S., Dozois, D.J.A., Frewen, P.A., 2012. A systematic meta-analysis of the Stroop task in depression. Clin. Psychol. Rev. 32, 316–328. https://doi.org/10.1016/j.cpr.2012.02.005

Fishburn, F.A., Ludlum, R.S., Vaidya, C.J., Medvedev, A. V, 2019. Temporal Derivative Distribution Repair (TDDR): A motion correction method for fNIRS. Neuroimage 184, 171–179. https://doi.org/10.1016/j.neuroimage.2018.09.025.Temporal

Fuhr, K., Meisner, C., Broch, A., Cyrny, B., Hinkel, J., Jaberg, J., Petrasch, M., Schweizer, C., Stiegler, A., Zeep, C., Batra, A., 2021. Efficacy of hypnotherapy compared to cognitive behavioral therapy for mild to moderate depression - Results of a randomized controlled rater-blind clinical trial. J. Affect. Disord. 286, 166–173. https://doi.org/10.1016/j.jad.2021.02.069

Goldapple, K., Segal, Z., Garson, C., Lau, M., Bieling, P., Kennedy, S., Mayberg, H., 2004. Modulation of Cortical-Limbic Pathways in Major Depression. Arch. Gen. Psychiatry 61, 34–41. https://doi.org/ 10.1001/archpsyc.61.1.34

Gotlib, I.H., Krasnoperova, E., Neubauer Yue, D., Joormann, J., 2004. Attentional Biases for Negative Interpersonal Stimuli in Clinical Depression. J. Abnorm. Psychol. 113, 127–135. https://doi.org/10.1037/0021-843X.113.1.127

Greicius, M.D., Flores, B.H., Menon, V., Glover, G.H., Solvason, H.B., Kenna, H., Reiss, A.L., Schatzberg, A.F., 2007. Resting-State Functional Connectivity in Major Depression: Abnormally Increased Contributions from Subgenual Cingulate Cortex and Thalamus. Biol. Psychiatry 62, 429–437. https://doi.org/10.1016/j.biopsych.2006.09.020

Greicius, M.D., Kiviniemi, V., Tervonen, O., Vainionpa, V., Alahuhta, S., Reiss, A., Menon, V., 2008. Persistent Default-Mode Network Connectivity During Light Sedation. Hum. Brain Mapp. 29, 839–847. https://doi.org/10.1002/hbm.20537

Grimm, S., Boesiger, P., Beck, J., Schuepbach, D., Bermpohl, F., Walter, M., Ernst, J., Hell, D., Boeker, H., Northoff, G., 2009. Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects. Neuropsychopharmacology 34, 932–943. https://doi.org/10.1038/npp.2008.81

Guo, W., Liu, F., Zhang, J., Zhang, Z., Yu, L., Liu, J., Chen, H., Xiao, C., 2014. Abnormal default-mode network homogeneity in first-episode, drug-naive major depressive disorder. PLoS One 9, 1–7. https://doi.org/10.1371/journal.pone.0091102

Haipt, A., Rosenbaum, D., Fuhr, K., Giese, M., Batra, A., Ehlis, A.-C., 2022. The effects of hypnotherapy compared to cognitive behavioral therapy in depression: a NIRS-study using an emotional gait paradigm. Eur. Arch. Psychiatry Clin. Neurosci. 272, 729–739. https://doi.org/10.1007/s00406-021-01348-7

Halsband, U., Wolf, T.G., 2021. Current neuroscientific research database findings of brain activity changes after hypnosis. Am. J. Clin. Hypn. 63, 372–388. https://doi.org/10.1080/00029157.2020.1863185

Halsband, U., Wolf, T.G., 2015. Functional changes in brain activity after hypnosis in patients with dental phobia. J. Physiol. 109, 131–142. https://doi.org/10.1016/j.jphysparis.2016.10.001

Hammond, D.C., 2013. A Review of the History of Hypnosis Through the Late 19th Century. Am. J. Clin. Hypn. 56, 174–191. https://doi.org/10.1080/00029157.2013.826172

Hardeveld, F., Spijker, J., Graaf, R. De, Nolen, W.A., Beekman, A.T.F., 2013. Recurrence of major depressive disorder and its predictors in the general population : results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Psychol. Med. 43, 39–48. https://doi.org/10.1017/S0033291712002395

Hart, S.J., Green, S.R., Casp, M., Belger, A., 2010. Emotional Priming Effects during Stroop Task Performance. Neuroimage 49, 2662–2670. https://doi.org/10.1016/j.neuroimage.2009.10.076.

Horovitz, S.G., Braun, A.R., Carr, W.S., Picchioni, D., Balkin, T.J., Fukunaga, M., Duyn, J.H., 2009. Decoupling of the brain's default mode network during deep sleep. Proc. Natl. Acad. Sci. 106, 11376–11381. https://doi.org/10.1073/PNAS.0901435106

Jasper, H.H., 1958. The ten-twenty electrode system of the International Federation. Electroencephalogr. Clin. Neurophysiol. 10, 371–375. https://doi.org/10.1213/00000539-192801000-00096

Jensen, M.P., Adachi, T., Tomé-Pires, C., Lee, J., Osman, Z.J., Miró, J., 2015. Mechanisms of hypnosis: Toward the development of a biopsychosocial model. Int. J. Clin. Exp. Hypn. 63, 34–75. https://doi.org/10.1080/00207144.2014.961875

Kaiser, R.H., Andrews-Hanna, J.R., Wager, T.D., Pizzagalli, D.A., 2015. Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. JAMA Psychiatry 72, 603–611. https://doi.org/10.1001/jamapsychiatry.2015.0071

Kampman, M., Keijsers, G.P.J., Verbraak, M.J.P.M., Näring, G., Hoogduin, C.A.L., 2002. The emotional Stroop: a comparison of panic disorder patients, obsessive-compulsive patients, and normal controls, in two experiments. J. Anxiety Disord. 16, 425–441. https://doi.org/10.1016/S0887-6185(02)00127-5

Karlsson, H., 2011. How Psychotherapy Changes the Brain. Psychiatr. Times 28, 1–5. https://doi.org/10.0.3.249/S0033291709991607

Kerestes, R., Ladouceur, C.D., Meda, S., Nathan, P.J., Blumberg, H.P., Maloney, K., Ruf, B., Saricicek, A., Pearlson, G.D., Bhagwagar, Z., Phillips, M.L., 2012. Abnormal prefrontal activity subserving attentional control of emotion in remitted depressed patients during a working memory task with emotional distracters. Psychol. Med. 42, 29–40. https://doi.org/10.1017/S0033291711001097

Kroenke, K., Spitzer, R.L., 2002. The PHQ-9: A new depression diagnostic and severity measure. Psychiatr. Ann. 32, 509–521. https://doi.org/10.3928/0048-5713-20020901-06

Lawrence, N.S., Williams, A.M., Surguladze, S., Giampietro, V., Brammer, M.J., Andrew, C., Frangou, S., Ecker, C., Phillips, M.L., 2004. Subcortical and Ventral Prefrontal Cortical Neural Responses to Facial Expressions Distinguish Patients with Bipolar Disorder and Major Depression. Biol. Psychiatry 55, 578–587. https://doi.org/10.1016/j.biopsych.2003.11.017

Leichsenring, F., Steinert, C., 2017. Is Cognitive Behavioral Therapy the Gold Standard for Psychotherapy ? The Need for Plurality in Treatment and Research.

Jama 318, 1323–1324. https://doi.org/10.1001/jama.2017.13737

Lowén, M.B.O., Mayer, E. a., Sjöberg, M., Tillisch, K., Naliboff, B., Labus, J., Lundberg, P., Ström, M., Engström, M., Walter, S. a., 2013. Effect of hypnotherapy and educational intervention on brain response to visceral stimulus in the irritable bowel syndrome. Aliment. Pharmacol. Ther. 37, 1184–1197. https://doi.org/10.1111/apt.12319

Matsubara, T., Matsuo, K., Nakashima, M., Nakano, M., Harada, K., Watanuki, T., Egashira, K., Watanabe, Y., 2014. Prefrontal activation in response to emotional words in patients with bipolar disorder and major depressive disorder. Neuroimage 85, 489–497. https://doi.org/10.1016/j.neuroimage.2013.04.098

McGeown, W.J., Mazzoni, G., Venneri, A., Kirsch, I., 2009. Hypnotic induction decreases anterior default mode activity. Conscious. Cogn. 18, 848–55. https://doi.org/10.1016/j.concog.2009.09.001

Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn. Sci. 15, 483–506. https://doi.org/10.1016/j.tics.2011.08.003

Milling, L.S., Valentine, K.E., McCarley, H.S., LoStimolo, L.M., 2018. A Meta-Analysis of Hypnotic Interventions for Depression Symptoms: High Hopes for Hypnosis? Am. J. Clin. Hypn. 61, 227–243. https://doi.org/10.1080/00029157.2018.1489777

Mitterschiffthaler, M.T., Williams, S.C.R., Walsh, N.D., Cleare, A.J., Donaldson, C., Scott, J., Fu, C.H.Y., 2008. Neural basis of the emotional Stroop interference effect in major depression. Psychol. Med. 38, 247–256. https://doi.org/10.1017/S0033291707001523

Mohanty, A., Herrington, J.D., Koven, N.S., Fisher, J.E., Wenzel, E.A., Webb, A.G., Heller, W., Banich, M.T., Miller, G.A., 2005. Neural Mechanisms of Affective Interference in Schizotypy. J. Abnorm. Psychol. 114, 16–27. https://doi.org/10.1037/0021-843X.114.1.16

Nee, D.E., Wager, T.D., Jonides, J., 2007. Interference resolution: Insights from a meta-analysis of neuroimaging tasks. Cogn. Affect. Behav. Neurosci. 7, 1–17.

Nishizawa, Y., Kanazawa, T., Kawabata, Y., Matsubara, T., Maruyama, S., Kawano, M., Kinoshita, S., Koh, J., Matsuo, K., Yoneda, H., 2019. fNIRS Assessment during an Emotional Stroop Task among Patients with Depression: Replication and Extension. Psychiatry Investig. 16, 80–86.

Nolen-Hoeksema, S., 1991. Responses to depression and their effects on the duration of depressive episodes. J. Abnorm. Psychol. 100, 569–582. https://doi.org/10.1037/0021-843X.100.4.569

Ochsner, K.N., Ray, R.D., Cooper, J.C., Robertson, E.R., Chopra, S., Gabrieli, J.D.E., Gross, J.J., 2004. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. Neuroimage 23, 483–499. https://doi.org/10.1016/j.neuroimage.2004.06.030

Oon, Z., 2008. A critical presentation of the life and work of Franz Anton Mesmer MD and its Influence on the development of hypnosis. Eur. J. Clin. Hypn. 8, 32–40.

Phan, K.L., Fitzgerald, D.A., Nathan, P.J., Moore, G.J., Uhde, T.W., Tancer, M.E.,

2005. Neural Substrates for Voluntary Suppression of Negative Affect : A Functional Magnetic Resonance Imaging Study. Biol. Psychiatry 57, 210–219. https://doi.org/10.1016/j.biopsych.2004.10.030

Plichta, M.M., Heinzel, S., Ehlis, A.C., Pauli, P., Fallgatter, A.J., 2007. Model-based analysis of rapid event-related functional near-infrared spectroscopy (NIRS) data: A parametric validation study. Neuroimage 35, 625–634. https://doi.org/10.1016/j.neuroimage.2006.11.028

Price, J.L., Drevets, W.C., 2010. Neurocircuitry of Mood Disorders. Neuropsychopharmacology 35, 192–216. https://doi.org/10.1038/npp.2009.104

Pyka, M., Burgmer, M., Lenzen, T., Pioch, R., Dannlowski, U., Pfleiderer, B., Ewert, A.W., Heuft, G., Arolt, V., Konrad, C., 2011. Brain correlates of hypnotic paralysis—a resting-state fMRI study. Neuroimage 56, 2173–2182. https://doi.org/10.1016/j.neuroimage.2011.03.078

Rainville, P., Hofbauer, R.K., Bushnell, M.C., Duncan, G.H., Price, D.D., 2002. Hypnosis modulates activity in brain structures involved in the regulation of consciousness. J. Cogn. Neurosci. 14, 887–901. https://doi.org/10.1162/089892902760191117

Revenstorf, D., 2017. Hypnotherpie und Hypnose. Psychotherapie-Verlag, Tübingen.

Revenstorf, D., 2003. Expertise zur Beurteilung der wissenschaftlichen Evidenz des Psychotherapieverfahrens. University Tuebingen.

Rinck, M., Becker, E.S., 2005. A comparison of attentional biases and memory biases in women with social phobia and major depression. J. Abnorm. Psychol.

Rosenbaum, D., Haipt, A., Fuhr, K., Haeussinger, F.B., Metzger, F.G., Nuerk, H.C., Fallgatter, A.J., Batra, A., Ehlis, A.C., 2017. Aberrant functional connectivity in depression as an index of state and trait rumination. Sci. Rep. 7, 1–12. https://doi.org/10.1038/s41598-017-02277-z

Sambataro, F., Wolf, N.D., Giusti, P., Vasic, N., Wolf, R.C., 2013. Default mode network in depression: A pathway to impaired affective cognition? Clin. Neuropsychiatry 10, 212–216.

Scalabrini, A., Vai, B., Poletti, S., Damiani, S., Mucci, C., Colombo, C., Zanardi, R., Benedetti, F., Northoff, G., 2020. All roads lead to the default-mode network—global source of DMN abnormalities in major depressive disorder. Neuropsychopharmacology 45, 2058–2069. https://doi.org/10.1038/s41386-020-0785-x

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349–2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Sheline, Y.I., Barch, D.M., Price, J.L., Rundle, M.M., Vaishnavi, S.N., Snyder, A.Z., Mintun, M.A., Wang, S., Coalson, R.S., Raichle, M.E., 2009. The default mode network and self-referential processes in depression. Proc. Natl. Acad. Sci. U. S. A. 106, 1942–1947. https://doi.org/10.1073/pnas.0812686106

Stroop, J.R., 1935. Studies of interference in serial verbal reactions. J. Exp. Psychol.

18, 643–662. https://doi.org/https://doi.org/10.1037/h0054651

Swick, D., Ashley, V., Turken, A.U., 2008. Left inferior frontal gyrus is critical for response inhibition. BMC Neurosci. 9, 1–11. https://doi.org/10.1186/1471-2202-9-102

Vanhaudenhuyse, A., Noirhomme, Q., Tshibanda, L.J., Bruno, M.-A., Boveroux, P., Schnakers, C., Soddu, A., Perlbarg, V., Ledoux, D., Moonen, G., Maquet, P., Greicius, M.D., Laureys, S., Boly, M., 2010. Default network connectivity refelcts the level of consciousness in non-communicative brain-damaged patients. Brain a J. Neurol. 133, 161–171. https://doi.org/10.1093/brain/awp313

Wagner, G., Sinsel, E., Sobanski, T., Köhler, S., Marinou, V., Mentzel, H.J., Sauer, H., Schlösser, R.G.M., 2006. Cortical Inefficiency in Patients with Unipolar Depression: An Event-Related fMRI Study with the Stroop Task. Biol. Psychiatry 59, 958–965. https://doi.org/10.1016/j.biopsych.2005.10.025

WHO, 2021. Depression [WWW Document]. URL https://www.who.int/news-room/fact-sheets/detail/depression (accessed 2.18.21).

Whorwell, P.J., 2011. IBS: Hypnotherapy—a wasted resource? Nat. Rev. Gastroenterol. Hepatol. 9, 12–13. https://doi.org/10.1038/nrgastro.2011.235

Wilhelm-Goessling, C., Schweizer, C., Dürr, C., Fuhr, K., Revenstorf, D., 2020. Hypnotherapie bei Depressionen: Ein Manual für Psychotherapeuten, 1st ed. Kohlhammer Verlag, Stuttgart.

Williams, J.M., Mathews, a, MacLeod, C., 1996. The emotional Stroop task and psychopathology. Psychol. Bull. 120, 3–24. https://doi.org/Doi 10.1037/0033-2909.120.1.3

Williams, J.M.G., Broadbent, K., 1986. Distraction by emotional stimuli: Use of a Stroop task with suicide attempters. Br. J. Clin. Psychol. 25, 101–110. https://doi.org/10.1111/j.2044-8260.1986.tb00678.x

Wittchen, H.-U., Wunderlich, U., Gruschwitz, S., Zaudig, M., 1997. SKID I. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. Hogrefe, Göttingen.

Yan, C.-G., Chen, X., Li, L., Castellanos, F.X., Bai, T.-J., Bo, Q.-J., Cao, J., Chen, G.-M., Chen, N.-X., Chen, W., Cheng, C., Cheng, Y.-Q., Cui, X.-L., Duan, J., Fang, Y.-R., Gong, Q.-Y., Guo, W.-B., Hou, Z.-H., Hu, L., Kuang, L., Li, F., Li, K.-M., Li, T., Liu, Y.-S., Liu, Z.-N., Long, Y.-C., Luo, Q.-H., Meng, H.-Q., Peng, D.-H., Qiu, H.-T., Qiu, J., Shen, Y.-D., Shi, Y.-S., Wang, C.-Y., Wang, F., Wang, K., Wang, L., Wang, X., Wang, Y., Wu, X.-P., Wu, X.-R., Xie, C.-M., Xie, G.-R., Xie, H.-Y., Xie, P., Xu, X.-F., Yang, H., Yang, J., Yao, J.-S., Yao, S.-Q., Yin, Y.-Y., Yuan, Y.-G., Zhang, A.-X., Zhang, H., Zhang, K.-R., Zhang, L., Zhang, Z.-J., Zhou, R.-B., Zhou, Y.-T., Zhu, J.-J., Zou, C.-J., Si, T.-M., Zuo, X.-N., Zhao, J.-P., Zang, Y.-F., 2019. Reduced default mode network functional connectvity in patients with recurrent major depressive disorder. Proc. Natl. Acad. Sci. 116, 9078–9083.

Yoshimura, S., Okamoto, Y., Onoda, K., Matsunaga, M., Okada, G., Kunisato, Y., Yoshino, A., Ueda, K., Suzuki, S. ichi, Yamawaki, S., 2014. Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. Soc. Cogn. Affect.

Neurosci. 9, 487–493. https://doi.org/10.1093/scan/nst009

Zhu, X., Zhu, Q., Shen, H., Liao, W., Yuan, F., 2017. Rumination and Default Mode Network Subsystems Connectivity in First-episode , Drug-Naive Young Patients with Major Depressive Disorder. Sci. Rep. 7, 1–10. https://doi.org/10.1038/srep43105

6. General Discussion

6.1 Summary of Results

We compared the cerebral effects of HT and CBT, measuring 75 depressed patients twice, before and after the respective therapy spanning about 4 months. We used fNIRS to examine various brain regions during three different paradigms. Each paradigm was associated with distinct hypotheses. Simultaneously, we recorded behavioral data including symptom severity and reaction times/error rates. The data of each paradigm was analyzed and discussed in one manuscript (Table 1).

In our first manuscript (Haipt, Rosenbaum, et al., 2023), we focus on changes in DMN functioning, which is related to depression, as well as to hypnosis/hypnotic trance. Therefore, we investigated parts of the DMN before and after therapy during resting state, and changes in symptom severity. Results show that both therapies were effective in patients' symptom reduction. Further, a change in FC throughout therapy was observed in two components associated with the DMN: FC within the SAC decreased with time, indifferently of the therapy group, whereas an inter-hemispheric connection, namely between the right angular gyrus and left supramarginal gyrus, increased only in the HT group. A correlation between these FC changes and symptom reduction could not be found, no FC changes were found for the PCu.

In the second manuscript (Haipt et al., 2022), we report the results of the human gait paradigm, which elicits emotional processing. The hypotheses predicted stimuli-induced activity in temporal areas, namely the superior temporal sulcus (STS) and extrastriate body area (EBA). Our main results show decreased FC between the right hemispheric STS and EBA in patients who received HT. This decrease in FC results from changed activation in the STS, while activation in the EBA did not change. This change in activation in the right STS in the HT group depended on trait rumination: while patients with lower rumination scores showed a decrease in right STS activation, patients with higher rumination scores demonstrated an activation increase. Behavioral data (error rate) did not mirror these specific neurophysiological changes and were independent from the type of displayed emotion.

In the third manuscript (Haipt, Geiger, et al., 2023), we focused on the possible effects of HT or CBT for depression on the PFC using the ESP. Due to recording problems, this data analysis only contained 66 datasets. Again, symptom severity was assessed before and after therapy and showed that patients profited from both therapies equally. On the neurophysiological level we found a main effect for group: Only the HT patients showed significantly decreased activity in the left DLPFC after the treatment period. The symptom change did not predict this change in activity. A Stroop Effect could not be found for either measurement, neither on a neurophysiological level nor a behavioral level (error rates and reaction times). Interestingly, and against our hypotheses, we only found therapy-specific cerebral activation changes in the HT group, not the CBT group. Further, none of the changes of cerebral activity were mirrored in the behavioral data.

In reference to the hypotheses, I conclude: Hypothesis 1 was confirmed, therapy – CBT and HT – affected the patients' brains. Hypothesis 2 was also confirmed: HT influenced the DMN and temporal lobe. Surprisingly, one component of the DMN was affected by therapy in general (not specifically HT). We could not confirm Hypothesis 3; CBT did not specifically affect the patients' brain – not even the PFC. Hypothesis 4 was mostly not confirmed. Therapy effects were not mirrored in the behavioral data meaning reaction times or error rates. However, rumination did predict some cerebral activity changes and on a symptom level the overall therapy effect was observed (symptoms reduced). Interestingly, this symptom reduction was not significantly related to activation changes.

In the following, these results will be discussed in regard to my hypotheses with implications for the neurophysiological level as well as regarding therapy content.

6.2 Therapy and Hypnotherapy-specific effects

One main result (in respect to Hypothesis 1) is an overall therapy effect, regardless of therapy group, for midline structures of the DMN (Haipt, Rosenbaum, et al., 2023). As recently shown, especially midline structures of the DMN seem to play an important role for depression (Scalabrini et al., 2020). In detail, the authors report a depression-specific increase of FC in DMN midline regions which can be attributed to the abnormally high connection of the DMN to other brain networks, outside of the DMN, instead of an increased intra-network connection. The authors conclude that this hyperconnection to other networks could account for the many sensory, cognitive, and affective functions, which are not associated with the DMN and still impaired in depression (Scalabrini et al., 2020). In line with this and previous research (Anand et al., 2005; Greicius et al., 2007; Grimm et al., 2009; Sheline et al., 2009), our result of decreased FC in a DMN midline structure (SAC) might mirror a normalization of this DMN component in depressed patients throughout therapy. Since this decrease was found regardless of the therapy group, it might reflect an overall treatment effect and not a specific aspect of either therapy.

Further main results (in respect to Hypothesis 2) imply specific cerebral changes through HT. HT seems to affect the DMN (Haipt, Rosenbaum, et al., 2023), the STS in the temporal lobe (Haipt et al., 2022), and the PFC (Haipt, Geiger, et al., 2023). This suggests that this specific type of therapy elicits specific effects. Regarding the DMN the therapy effect could originate from hypnosis/hypnotic trance itself, which was an integral part of HT. As displayed in the introduction, an involvement of the DMN during hypnosis/hypnotic trance has been repeatedly shown, namely a decrease in DMN FC (Halsband & Wolf, 2021). However, in our case the FC of an interhemispheric DMN component increased throughout therapy. This allows for several possible implications: While DMN FC decreases during the state of hypnosis/hypnotic trance itself, it could be affected differently (namely in terms of an increase in FC) when hypnosis/hypnotic trance is practiced repeatedly over time. Possibly, the brain undergoes some type of training effect: During hypnosis/hypnotic trance the DMN is brought down and boots up again afterwards. This happens again and again in therapy and at home when practicing, resulting in the increasing ability of the brain to shut down and boot up the DMN. This could be reflected in increased FC of a certain DMN component over time. However, this idea is highly speculative.

Another explanation for our results could lie in the constitution of our sample. Most studies on DMN FC during hypnosis/hypnotic trance have been conducted with highly suggestible individuals (Halsband & Wolf, 2021). In our study, we did not include the factor “suggestibility” in the analysis. As hypnotic suggestibility is a normally distributed trait (Oakley, Walsh, Mehta, Halligan, & Deeley, 2021), it can be assumed that our study sample included the whole range of suggestibility. Possibly, the decrease in DMN FC during hypnosis/hypnotic trance is specific to “high suggestibles”, but a set of individuals across all levels of suggestibility shows the opposite development when hypnosis/trance is practiced over time. The same argument extents to the field of clinical application. The studies on hypnosis/hypnotic trance and the DMN include healthy participants (Halsband & Wolf, 2021) whereas our sample suffered from depression. It may well be that healthy subjects show a decrease of DMN FC during hypnosis/hypnotic trance, while depressed patients (who already show DMN malfunctioning, as reported above (e.g., Scalabrini, 2020)) show an increase of DMN FC when hypnosis/hypnotic trance is practiced regularly. In both cases, as the study sample did not consist of the typically studied highly suggestible and healthy participants, more research is needed to clarify the direction of change in DMN FC.

Lastly, another difference between our study setup and the setup of the previous studies on hypnosis and the DMN is that in our study no hypnosis/hypnotic trance was induced during the measurement. In other studies (e.g., Cojan et al., 2009a; McGeown et al., 2009) hypnotic trance was induced during the experiment while our resting state measurement took place without any induction. Thus, it is possible that the DMN FC shows an increase over time undergoing HT when the brain is measured at rest, while it decreases at rest during or right after hypnosis/hypnotic trance. In future research, both cases (resting state without induction but regular hypnosis training outside the experiment, and resting state after hypnotic induction) should be investigated and compared directly to clarify the role of the DMN and the direction of its FC change.

Interestingly, our results on the STS as well as the PFC further strengthen the association between the DMN and HT. In our study on the STS (Haipt et al., 2022), rumination moderated the change of STS activity over time and rumination is suggested to be correlated to depression-specific DMN malfunctioning (Berman et al., 2011; Rosenbaum et al., 2017). Thus, the existence of rumination as moderator variable on STS activity suggests a connection to the DMN even though the DMN was not directly measured. This connection between the STS and DMN also makes sense on a content level, since both are associated with theory of mind processes (Andrews-Hanna et al., 2010; Deen, Koldewyn, Kanwisher, & Saxe, 2015). Further, our analysis of DLPFC activity also showed a specific therapy effect of HT. The DLPFC is an integral component of the Central Executive Network (CEN) and also involved in the Salience Network (SN), next to the DMN two core networks that are involved in many psychopathologies (Menon, 2011). The CEN is associated with cognitive functioning, the SN with detection, integration and filtering of automatic, interoceptive, and emotional information (Menon, 2011; Seeley et al., 2007). Indeed, these three core networks are closely connected and cannot be observed independently as they are active proportionally and often antagonistically (Menon, 2011). With respect to hypnosis, the DLPFC has been shown to be connected to it and an involvement of the CEN and SN as well as cross-network connections between these core networks have also been reported, though findings are heterogenous (Halsband & Wolf, 2021). Accordingly, we found an HT-specific effect on the DLPFC (Haipt, Geiger, et al., 2023). Since this structure is so prominent for two core networks (CEN and SN) which, again, are closely connected to the DMN, our results imply indirectly an involvement of the DMN.

To summarize the previous arguments, our results point out the importance of the DMN for hypnosis/hypnotic trance. As Halsband and Wolf (2021) report a relative consensus about the connection between hypnosis/hypnotic trance and the DMN, the actual interpretation of the role of the DMN for hypnosis/hypnotic trance varies among the studies. Some authors suggest the involvement of the DMN to mirror the suspension of spontaneous cognitive activity, possibly connected to a decrease of inferences from self-referential thoughts, like a state of "readiness to respond" to suggestions that might follow (McGeown et al., 2009). Two other groups of authors showed a significant involvement of the PCu (a main node of the DMN) during hypnotically induced paralysis and share the suggestion that during hypnosis/hypnotic trance the internal representation of the self is changed according to the given suggestion (Cojan, Waber, Schwartz, et al., 2009; Pyka et al., 2011). Thus, the involvement of the DMN could mirror changed self-representation in hypnotized individuals. Beyond these specific suggestions, the authors of these studies agree that the exact role of the DMN during hypnosis/hypnotic trance probably depends on the given suggestion during hypnosis/hypnotic trance (Cojan, Waber, Schwartz, et al., 2009; McGeown et al., 2009; Pyka et al., 2011).

Besides the DMN, the above mentioned groups of authors showed an involvement of prefrontal areas (the DLPFC (Pyka et al., 2011) and inferior frontal gyrus (Cojan, Waber, Schwartz, et al., 2009)), which hints at an involvement of the CEN and SN – in line with our results. The authors propose this prefrontal involvement might reflect increased general self-monitoring processes, so to speak a state of "hypercontrol", allowing internal mental representation to change according to the given suggestion (Cojan, Waber, Schwartz, et al., 2009). These suggestions on the roles of the DMN and prefrontal areas during hypnosis/hypnotic trance are very promising, but it is important to note that they were given in a different context, namely studies on resting state (McGeown et al., 2009) and hand paralysis *during* hypnosis/hypnotic trance (Cojan, Waber, Schwartz, et al., 2009; Pyka et al., 2011). To what extent these explanations can account for changes in the DMN or prefrontally rooted networks evoked by HT, as in our case, remains unanswered and calls for further investigation.

Similarly opaque stays the role of the STS, for which we found changes in activity in the HT group (Haipt et al., 2022). As research has consistently shown, the STS region is often involved in depression-specific cerebral alterations (Fitzgerald et al., 2008). On a behavioral level, it is associated with theory of mind processes (Deen et al., 2015). Although there are studies showing its malfunctioning in depression during resting state, it has also been aberrantly active during emotional tasks (Fitzgerald et al., 2008). Until now, it remains unclear if the STS is possibly part of an emotional network that is affected by depression and if it is to what extent. Also, its role during therapy is not known yet. Future research is needed for clarification.

Now, I want to come back to the effects of CBT – or rather the lack thereof. Surprisingly, we did not find a *specific* effect of CBT, even though we did expect an increase in PFC activity (Hypothesis 3) after therapy. Previous studies have shown a normalization of PFC hypoactivity in depression after CBT (Karlsson, 2011). This normalization is explained by the specific content of CBT, in which problem solving, self-representation and affective regulation are promoted, thus influencing the PFC as the putative “center” of cognitive control (Karlsson, 2011). Why we did not find a CBT-specific effect is unclear. That it did affect the brain to some degree became apparent in the overall therapy effect of decreased SAC FC – one DMN component. But the lack of a specific CBT effect raises questions: Should we have measured another region of interest? Would you see some other results with an fMRI or different experimental tasks (e.g. tasks involving cognitive control in a more classical sense or executive functions such as inhibitory control or working memory)? Are there moderating or mediating factors that we do not know of? The answer to all these questions is: possibly. And: more research is needed to shed some light onto these questions.

So far, I discussed our results mainly at a neurophysiological level. But what could our results mean on a content level, or rather what was the difference between the therapies applied in the WIKI-D study that could have led to these neurophysiological differences? It was very specific to this WIKI-D study that the content of the HT manual was based on psychodynamic ideas, not behavioral ones (Wilhelm-Goessling et al., 2020). As very briefly presented in the introduction, HT is a therapeutical approach that is comprised of hypnosis/hypnotic trances, but also includes suggestions, storytelling, symptom utilization and other tools outside an explicit hypnotic state. HT is very flexible regarding the context of application – it can be integrated into CBT, and psychodynamic therapies alike. HT does not have its own theoretical framework of pathogenesis, but rather modifies and interprets pathogenetic ideas of other approaches. The WIKI-D study is the first study (to my knowledge) in which the content of HT was explicitly based on psychodynamic ideas and theories, which makes the demarcation from CBT clearer. On a content level, HT included biographical work, imagination of constructive self-images and positive visions, and activation of resources. CBT, on the other hand, included psychoeducation, activation of wanted behavior, questioning and changing inner beliefs and strengthening interpersonal competencies. Interestingly, Karlsson (2011), who explained the PFC increase in CBT with its role as a cognitive center (as mentioned above), speculates that similar mechanisms could account for activity changes in the PFC that were found in psychodynamic therapies. From a therapeutic point of view, I would expect psychodynamic therapies to affect emotional processing, and cognitive processes to be in turn influenced by these effects. In our case this means that in the HT condition patients underwent hypnosis/hypnotic trance and "emotional work" which led to changes in DMN and STS activity. This again could have influenced the cognitive control center, associated with the PFC, which is so closely connected to the DMN and areas involved in emotional processing. These thoughts are highly hypothetical and future research is needed to clarify the connections and hierarchy of HT-induced cerebral changes.

6.3 Behavioral Effects

Calling to mind Hypothesis 4 regarding behavioral measures, we ought to make a distinction: We collected data related to the specific paradigms during the neurophysiological measurements – reaction times and error rates. And we also collected data about depressive symptoms, namely symptom severity and trait rumination, which – to simplify – we consider behavioral data (even though symptoms include emotional and physical components). Indeed, we did not find any therapy effects on the data directly related to the paradigms, that is reaction times or error rates. Therefore, the cerebral changes induced by therapy did not influence performance during the study tasks. Possibly, the tasks we used (ESP and gait paradigm) were too specific and unrelated to daily life to be affected by therapy. This could also explain why we did not find any emotion-specific FC or cerebral activity during the gait paradigm (Haipt et al., 2022) and ESP (Haipt, Geiger, et al., 2023), respectively. Another possible explanation for the lack of effects is the existence of at least one moderating or mediating factor (or more) that could have influenced the association between therapy-related cerebral changes and performance during these specific tasks. Another reason could be that both paradigms, the ESP and gait paradigm, have not yet been validated for the specific sample used in our studies: depressed German patients. The wording of the ESP had been adopted from another German study that focused on attentional biases, but did not explicitly use an ESP (Rinck & Becker, 2005). The gait paradigm was adopted from a study on emotional processing that did not include a clinical sample (Schneider et al., 2014). In both cases, this change of study design could have affected the outcome. Since the paradigms were used as means to an end, that is to elicit certain brain activity, we did not further examine this lack of effects nor did we explore additional explanations. More research and specific analyses are needed to get to the root of the missing effects on the paradigm-related behavioral data.

The second set of behavioral data contains symptom related outcomes. We did find an effect of therapy on self-reported symptom severity (symptoms significantly decreased) independent of sample size. This result is in line with the outcome of the WIKI-D study, in which the outcome measure was a clinician-administered questionnaire (Fuhr et al., 2021)[6]. In all three analyses, the effect was independent of intervention group. In sum, patients benefited from therapy, regardless of the type of intervention. Interestingly, symptom severity did neither predict nor correlate with our results on a neurophysiological level, neither for both groups nor for HT only. The lack of association between symptom reduction and neurophysiological data could imply that the connection between the effects of therapy on the brain, on the one hand, and symptoms, on the other hand, is indirect. Moderating and/or mediating factors could be of importance here. An interesting candidate for a mediating and/or

[6] 152 patients were included in the study intended to treat and randomized; 134 patients returned to post assessment.

moderating factor is trait rumination, which we included in one study (Haipt et al., 2022). It showed to be of predictive value for the activity change in the STS in the HT group and thereby played a moderating role on the effect of HT on STS activity. Additional analysis showed a positive correlation between this trait rumination and self-reported symptom severity. Possibly, besides its moderating role, trait rumination is also a mediating factor, between symptom severity and cerebral activity change induced by therapy. On a content level, the direct influence of trait rumination on STS activity change and positive correlation to self-reported symptom severity, while the latter did not predict cerebral data, could mean the following: As described in the introduction, rumination is a key symptom in depression and might mirror depression-associated malfunctioning of the DMN on a behavioral level (Berman et al., 2011; Rosenbaum et al., 2017). We suggest that patients who ruminate more also suffer from depression more severely, with all its consequences, including more impaired emotional processing (Haipt et al., 2022). The increase of STS activity in this patient group might reflect a normalization of emotional processing on a neurophysiological level through HT. Patients who were not as impaired – showing less symptom severity and less rumination – were possibly still able to compensate some of the impairments, namely emotional processing. Thanks to HT, they did not have to compensate anymore, so their STS activity decreased. On a theoretical level this makes much sense: the questionnaire on symptom severity we used in our studies (9-item Patient Health Questionnaire Depression Scale (PHQ-9) (Kroenke & Spitzer, 2002)) includes as few as nine questions to cover the whole range of depression symptoms. This range reaches from emotional symptoms like a feeling of worthlessness to cognitive ones like a lack of concentration, as well as physical ones like a disrupted sleep pattern, weight loss/gain, and/or agitation or psychomotoric retardation (American Pschological Association, 2013). Thus, in the PHQ-9 one question reflects one symptom (Kroenke & Spitzer, 2002). Usually, patients participating in a study are flooded with questionnaires; therefore, the PHQ-9 has its advantages as, it is easy, short, and widely accepted. On the other hand, it does not comprise certain domains of depression (emotional, cognitive, physical) in depth, but rather gives a very broad picture. So, possibly, in our case the effect of HT depends on a *certain aspect* of depression, namely rumination, rather than on a general symptom picture. These are all ideas, and the exact roles of symptom severity overall as well as specific symptoms, like rumination, and their connection to therapy-induced cerebral changes need to be further investigated.

Up to this point, I have summarized my results and discussed them in respect to my hypotheses offering possible explanations on a neurophysiological, as well as therapeutic content level. Now, I would like to take my results one step further – and that actually twice – to lead integration to the next level. One objective of my work is to bring two research approaches together, namely intrinsic research and experimental psychopathology, that seemingly focus on completely different things. In intrinsic research the subject of investigation is hypnosis/hypnotic trance itself while experimental psychopathology examines the effects of hypnosis/hypnotic trance on specific somatic or psychological disorders (Oakley & Halligan, 2009). My goal is to discuss my results under the spotlight of each approach to finally find common grounds. Therefore, in the following I will present a biopsychosocial model (Jensen et al., 2015) as part of intrinsic research and integrate my findings into it. Then, I will come back to experimental psychopathology and explore the implications of my findings for the effects of HT on depression.

6.4 The biopsychosocial model of hypnotic response

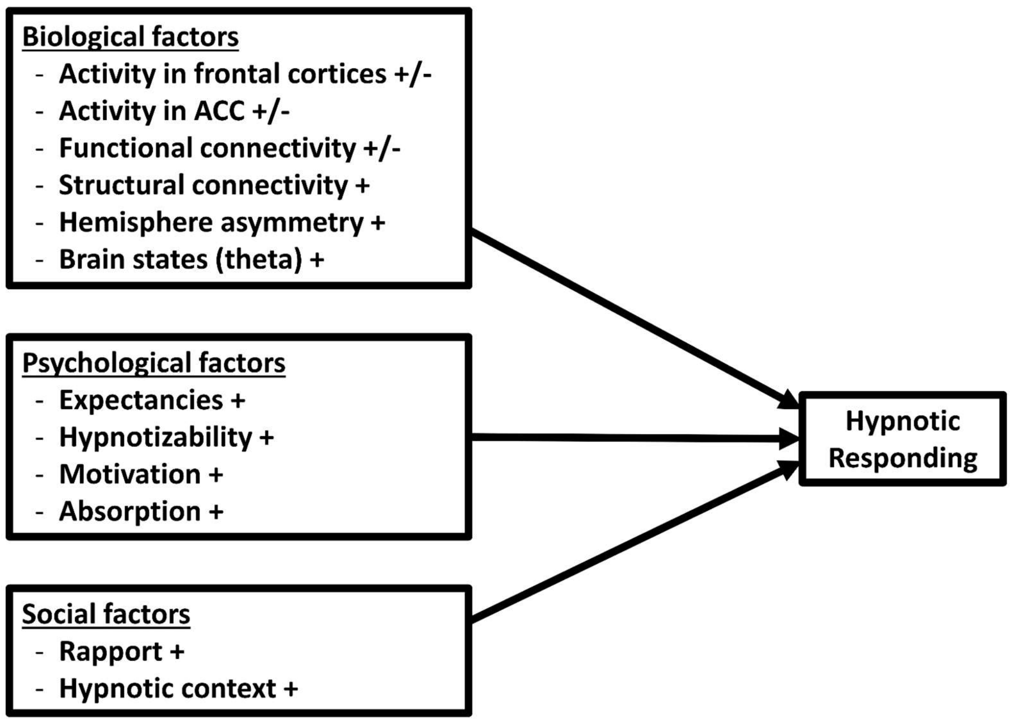
To summarize current understanding about the mechanisms of hypnosis/hypnotic trance Jensen and colleagues (2015) developed an extensive biopsychosocial model. In their review on factors contributing to hypnotic responding[7] they identified three categories: biological, psychological, and social factors (Figure 2). On the psychological and social level, the authors list factors that all add positively to the hypnotic response, meaning that the more the factor exists the stronger is the hypnotic response (in the Figure indicated by "+"). In the biological domain the factors represent various cerebral features, namely activity (in prefrontal areas and the ACC), functional and structural connectivity, EEG (theta) activity, and lateralization (hemispheric asymmetry). Only for the latter three features, studies show a clear positive association with hypnotic response; the other factors have shown positive and negative associations (in the Figure indicated by "+/-"). Yet, it remains unclear, if the biological factors simply reflect hypnotic response or if they causally influence the hypnotic response – a classical correlation – causality problem. The authors propose

[7] By „hypnotic responding“ the authors refer to an individual's behavior in response to a specific hypnotic suggestion or set of suggestions rather than a person's trait (Jensen et al., 2015). I will continue to refer to this as "hypnosis/hypnotic trance".

that factors for which they found positive *and* negative associations with hypnotic response (e.g., prefrontal activity) might rather reflect a response to a specific hypnotic suggestion than a hypnotic response in general. Or, in other words, they suggest a causality of hypnosis/hypnotic trance *onto* the “+/-“-factor rather than the other way around. Factors for which the authors found only a one-way directed association (like structural connectivity) might affect hypnotic responding causally, meaning for example, that increased structural connectivity increases to hypnotic responding in turn. However, it remains unclear, which factor plays a moderating or mediating role – a lack of mediation and moderation analyses does not allow further conclusions.

Figure 2

Biopsychosocial Model by Jensen et al. (2015)



Note. The model contains the findings of reviewed research on biological, psychological, and social factors that contribute to hypnotic responding. “+” indicates a mostly positive and consistent association between the factor and hypnotic responding. “+/-“ indicates both positive and negative associations between the factor and hypnotic responding. The arrows in the graph do not indicate causality. This Figure is taken from the original work (Jensen et al., 2015).

So, when there are so many factors to consider and their roles and their interactions are unclear, why do we need the model at all? Jensen and colleagues (2015) claim that a more comprehensive model – like theirs – can explain more than a restrictive one, which takes one domain (e.g., biological) into account. This explanation seems tautological on one hand, but on the other hand it reflects the complexity of the concept "hypnosis/hypnotic trance". Further, the authors claim that their model makes it unnecessary to prove the mere existence of the listed factors in future research, since they included factors that are already scientifically supported sufficiently. They rather suggest an investigation of the causality or correlation of the factors, an examination of the moderating influence of these factors, and the identification of additional factors – which I will all attempt further on. To that list, I would like to add mediation analyses and possible interactions between the factors. Specifically, the interactions among one domain would be interesting to investigate – like the connection between prefrontal activity and FC – but also the interactions between the domains seem fascinating. For example: Does expectancy (psychological factor) correlate with a biological factor (like FC) in highly suggestible individuals? The main goal of this research would be the refinement of a comprehensive model to further understand the nature of hypnosis and trance – intrinsic research at its best.

6.5 Intrinsic aspect: Integration of my findings into the biopsychosocial model

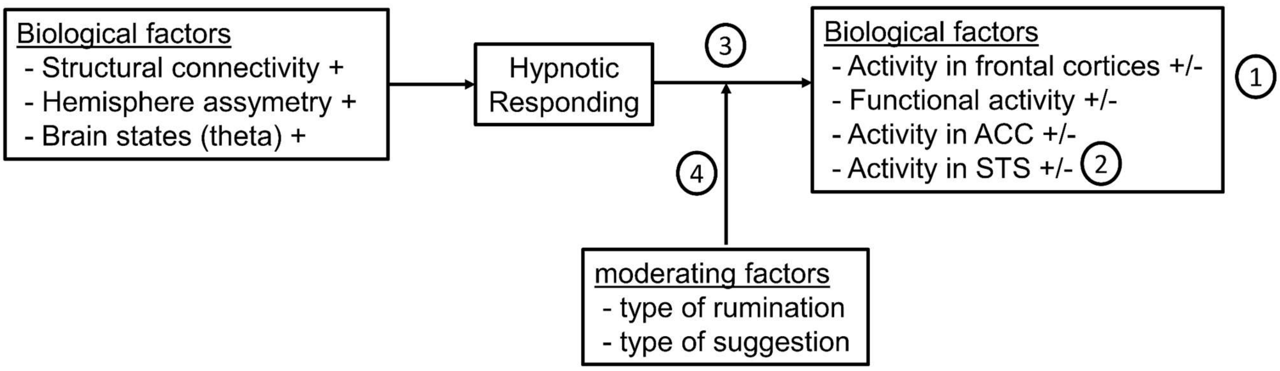
How do the results of our studies fit into all of this? First, it is important to note that we did not measure our patients during hypnosis/hypnotic trance, instead we measured them during different paradigms eliciting activity in cerebral regions we hypothesized to be connected to hypnosis/hypnotic trance. We aimed to investigate how these regions changed over a longer period of time in which hypnotic trance was practiced regularly in a therapeutic context. We found a HT-specific effect for an increasing interhemispheric connection (FC) during resting state, a decrease in prefrontal activity, and changed activity in a temporal region (STS). These findings have four implications for the model (Figure 3)[8]: 1) confirmation of including the PFC and FC into the model; 2) addition of temporal structure (STS) to model; 3) strong hint towards direction of causality (hypnotic responding affecting PFC activity, FC, and STS), and 4) rumination as moderating factor on the causal connection of hypnotic responding onto cerebral response. Let me elaborate each of these

[8] On the base of the model by Jensen et al. (2015) I included my results into the model to develop it further.

implications: First, our results fit into the model of Jensen et al. (2015), confirming an association between hypnosis/hypnotic trance and the PFC and FC. Since PFC activity decreased over time only in the HT group and the therapy groups did not differ in PFC activity before therapy, I can conclude that the practice of hypnosis/hypnotic trance over the therapy period causally affected PFC activity, namely that the practice decreased PFC activity. The findings on FC are not quite as straightforward. Even though we did find an increase of an interhemispheric DMN FC specifically in the HT group, there was also a decrease in DMN FC (in the SAC) found in both therapy groups. Thus, this FC decrease seems to be independent from the type of therapy but might rather reflect a general response to therapy (or simply a correlate of symptom amelioration). It is difficult to draw a conclusion about the effect of hypnosis/hypnotic trance on FC in general. Statements about FC "in general" seem too broad considering the vast complexity of the brain and its connections. Rather, it is important to specify the cerebral regions used to calculate the FC (an inter-hemispheric DMN connection might show very different results than a DMN connection within the SAC). Nevertheless, our findings hint towards an effect of hypnosis/hypnotic trance on this specific, interhemispheric, type of DMN FC.

Figure 3

Biopsychosocial Model 2.0 – Development of biological domain



Note. Advance of the biological domain of the model by Jensen et al. (2015). Since my results included only biological factors, I limited this graph to these. New implications for the model based on my findings are labelled with a circled number.

[9] Due to the low spatial resolution of fNIRS we do not distinguish between the STS and superior temporal gyrus whose lateral part is often referred to as STS region (Takahashi et al., 2010).

Vander Wyk et al., 2009) and understanding others' mental states (Ciaramidaro et al., 2007; Fletcher et al., 1995; Gallagher et al., 2000; Saxe & Kanwisher, 2003; Saxe & Powell, 2006). It does not seem surprising that this area is found to be one of the regions most consistently involved in depression (Fitzgerald et al., 2008), reaching from decreased activation (Canli et al., 2004; Fitzgerald et al., 2008) and aberrant connectivity (Cullen et al., 2009) to grey matter volume reduction (Shah, Glabus, Goodwin, & Ebmeier, 2002; Takahashi et al., 2010). This region became of interest to us because the HT applied in this study included a great deal of work with the patients' emotions: the patients were instructed to identify themselves with their own strengths, positive experiences and memories, and a former or later self, that had not yet suffered or had overcome depression. Negative memories were reframed. Considering this content, we hypothesized the STS to be affected by HT that is comprised of a regular hypnosis/hypnotic trance practice focusing on emotions. Looking at our data (Haipt et al., 2022), this hypothesis does indeed seem supported. Following this train of thought, the connection of the STS to hypnosis/hypnotic trance might be very specific to the type of suggestion that is given, in our case therapy-specific suggestions of which a great amount involved emotional content. It is possible that the STS is not connected to hypnosis/hypnotic trance anymore when other suggestions without emotional content are given. In this work's case I would like to add the STS to the biological domain. However, I want to call to mind that it might not be a region affected by hypnosis/hypnotic trance per se, but might be specific to therapeutic interventions, especially emotional work. Since in the WIKI-D study HT focused on emotional work, the involvement of the STS can be explained. However, it might also be involved in other therapeutic interventions, outside of HT, focusing on emotions or might not be involved, if hypnosis/hypnotic trance was practiced without emotional content.

Thirdly, one of the most interesting implications of our findings – at least in my view – is that they indeed suggest that hypnosis/hypnotic trance *changes* PFC and STS activity, as well as FC (instead of just correlating with it). In the discussion of their model the authors carefully suggest such a causal connection between hypnotic responding (cause) and PFC activity as well as FC. Now, we can provide support for this suggestion with the results from our repeated-measure study. Since the PFC activity, interhemispheric FC and STS activity did not differ between the therapy groups at baseline, but it showed a change in the HT group after therapy, the change can be attributed to the therapeutic intervention, namely HT. Since HT included hypnosis/hypnotic trance as the most important feature defining HT (in relation to CBT), I want to go as far as stating that this result can inform us about the effects of hypnosis/hypnotic trance on the brain more broadly. The patients in the HT group practiced hypnosis/hypnotic trance regularly over 16 to 20 weeks and therefore it seems plausible to say this practice causally affected the PFC and STS activity, as well as FC. However, further corroboration and replication of this result is necessary to allow firm conclusions on the effects of hypnosis generally.

Fourthly, in one of our three analyses (Haipt et al., 2022) we included rumination as moderating factor and found differing directions of STS activity change depending on the amount of rumination (as a reminder: the more the patients ruminated the more the activity in the STS increased over therapy time, the less the patients ruminated the more it decreased). This result shows that the regular practice of hypnosis/hypnotic trance in HT affects the brain differently for different types of people – rumination being the corner stone. This effect occurred while self-reported symptoms were reduced in the HT group overall (as shown in our paper on the DMN (Haipt, Rosenbaum, et al., 2023) and ESP (Haipt, Geiger, et al., 2023)). So, while patients profited from HT (and therefore hypnosis/hypnotic trance) overall, the mechanisms of hypnosis/hypnotic trance might depend on other (moderating) factors, like differences between individuals. In our case rumination was included into the analysis, but it is plausible there are more moderating factors. For example, hypnotizability comes to mind (Jensen et al., 2015) and in future research this variable should be included into analyses. Jensen et al. name the type of suggestion as one moderating factor. Mainly, the suggestions vary greatly among the reviewed studies and probably affect the areas that are examined. A protocol designed to study hand paralysis (Cojan, Waber, Schwartz, et al., 2009) will very plausibly elicit different neural activity than a protocol to study analgesia (Rainville et al., 1999). The list of possible moderating factors can be extended by internal factors like belief in hypnosis or imagery skills in general or – going into a different direction - disorder related factors like symptom severity or frustration over the disease. In two of our studies, we included the change of symptom severity into our analyses and did not find a direct connection to the neurophysiological data. Still, it is plausible to think it could affect the response to hypnosis/hypnotic trance and should be investigated further (and I will get into it in the next chapter). Not to forget the external factors (besides type of suggestion) like the relationship to the hypnotist (or therapist in the clinical field). Even the setting in which the hypnosis/hypnotic trance is practiced (at home, via tape, alone or with others etc.) could be a plausible moderating factor. I agree with Jensen and colleagues: much more future research is needed to identify moderating factors to better understand the complexity of hypnosis/hypnotic trance.

6.6 Subtypes of depression and the role of the DMN

Now, let's go back to the experimental psychopathology and to the question, what happens to the *depressed* brain and underlying neurocognitive processes when we apply HT and what can we learn from it about depression? In order to develop my arguments, I will take a detour to depression research – and I promise I will return to experimental psychopathology and the integration of our results.

When I did my research on depression, I increasingly noticed a general problem in the investigation and treatment of depression: Different domains of symptoms (e.g., cognitive, emotional, or physical symptoms) can be impaired in depressed individuals and the severity of their impairment can differ between individuals. For example, as recently reviewed some studies show a two symptom-based depressed subtypes: a melancholic one and a non-melancholic one. The melancholic subtype showed higher symptom scores and showed more impairments in the psychomotoric domain, mood, early morning awakening, and nonreactivity, but weight loss and loss of energy was not affected by this categorization (Beijers, Wardenaar, van Loo, & Schoevers, 2019). In another study three clinically relevant subtypes were identified varying between symptom domains (the subtypes were severely depressed, cognitive-emotional, and psychosomatic) (Carragher, Adamson, Bunting, & McCann, 2009). However, a distinction between these subtypes is rarely considered in the design of intervention studies. Subtypes are usually neither considered as predicting variable nor as different outcome variables. Further, the disorder is very heterogenous in its onset, course of symptoms, response to treatment, presence and/or type of comorbidity, and compatibility of symptoms with diagnostic criteria (Chahal, Gotlib, & Guyer, 2020).

These findings are reason enough to take a closer look at this subtype idea: As early as 50 years ago, Gottesman and Shields suggested "endophenotypes" as *internal* phenotypes based on neurobiological differences not obvious and external features (Gottesman & Shields, 1973). Even though, their early work was related to the investigation of schizophrenia, their concept can be adapted for other mental disorders (Gottesman & Gould, 2003) and has been done so for e.g. Attention Deficit Hyperactivity Disorder (Crosbie, Pérusse, Barr, & Schachar, 2008), Obsessive Compulsive Disorder (Riesel, 2019), mood disorders (Merikangas et al., 2002), and specifically depression (Goldstein & Klein, 2014)[10]. Following this idea but excluding the question of heritability, the body of research on biotypes of depression has grown enormously over the past years. Promising candidates are cerebral baseline activation, neural response patterns (Drysdale et al., 2017; Hamilton et al., 2012), and large-scale brain networks (Williams, 2017). It seems that besides the DMN, CEN, and SN (which were already explored above), the reward network, affective limbic network, and attention network, all seem to play a role in the pathological working of the depressed brain[11] (Williams, 2017). On behavioral level, these biotypes show differing symptoms (Williams, 2017). Reviewing this idea for depressed adolescents, the authors found that at rest these networks show FC abnormalities within themselves, as well as in their FC between each other (Chahal et al., 2020). The authors suggest that the influence of each of these networks varies among individuals and leads to different biotypes of depressed patients[12]. Further, biomarkers have been shown to predict therapy response (Fonseka, MacQueen, & Kennedy, 2017; Fu, Steiner, & Costafreda, 2013). Chahal et al. predict the future of medical treatment lying in *precision medicine*, meaning the tailoring of treatments according to a certain biotype. They propose, research should aim at assigning a certain treatment (antidepressant medication, psychotherapy, electroconvulsive therapy, transcranial magnetic stimulation, and other forms of treatment) to a certain biotype (Figure 4).

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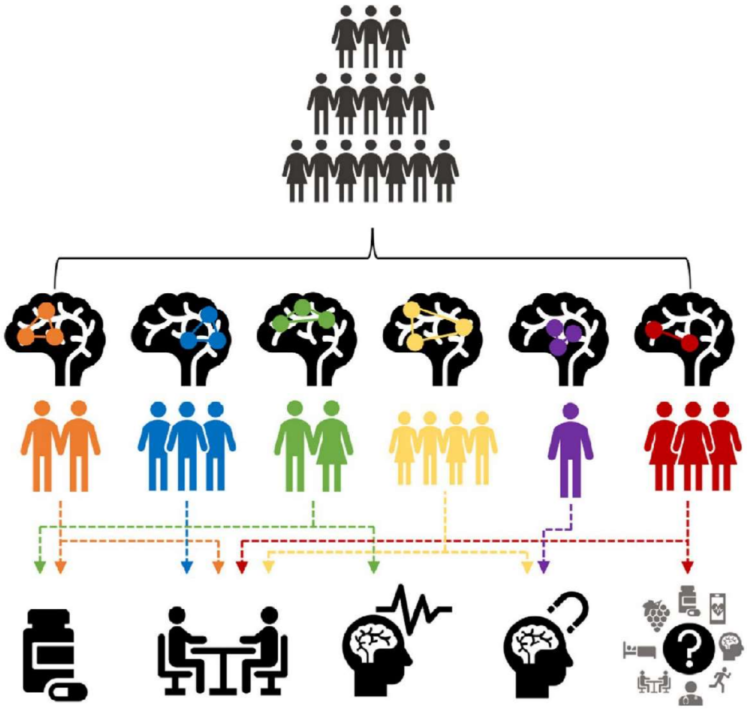
[10] To make things complicated, there seems to be some confusion about the usage of the terms “endophenotype”, “biomarkers” and “intermediate phenotype”. Some researchers use the terms synonymously, others do not. Luckily, Lenzenweger (2013) sheds light on the differences between the terms: *Heritability* seems to be the crucial factor differentiating endophenotype (which implies heritability) and biomarkers (which does not). “Biotypes” are subtypes based on biomarkers (Williams, 2017). “Intermediate phenotype” is not defined as clearly and has been used with various meanings.
[11] In her review the author included studies on resting state as well as task-related FC (Williams, 2017).
[12] Confusingly, in the original work, the authors use the term “brain-symptom phenotype” or “neurophenotype”. For the sake of consistency, I will refer to the concept as biotype.

Figure 4

Depression biotypes and precision medicine for depressed patients



Note. According to and taken from Chahal et al. (2020) a specific biotype (based on the predominance of a certain core network during resting state) determines the optimal treatment for that group of patients. The assignment of a specific therapy to a biotype is not prescribed by the authors, but rather serves illustrative purposes.

In the same year another group of authors offered an additional explanation to the wide range of symptoms and heterogeneity of depression: the DMN seems to be overly connected to other cerebral core networks which account for the many depression symptoms that are not directly associated with the DMN (like movement, memory, reward, or perception) (Scalabrini et al., 2020). I find these two approaches both very interesting and they seem to complement each other. Both approaches include the DMN and other core networks and see the pathology of depression in the malfunctioning of intra- as well as inter-connections of these networks. The difference between these approaches is the hierarchy of networks: While Williams (2017) and Chahal et al. (2020) propose the derivation of biotypes based on the prominence of *one* aberrant network (or at least they do not comment on hierarchy whatsoever), Scalabrini et al. (2020) suggest the DMN to be a *node* network which is abnormally connected to the other networks. What if they were both right? Could we combine the node network idea and the biotype idea? And what would our findings on HT add to this idea?

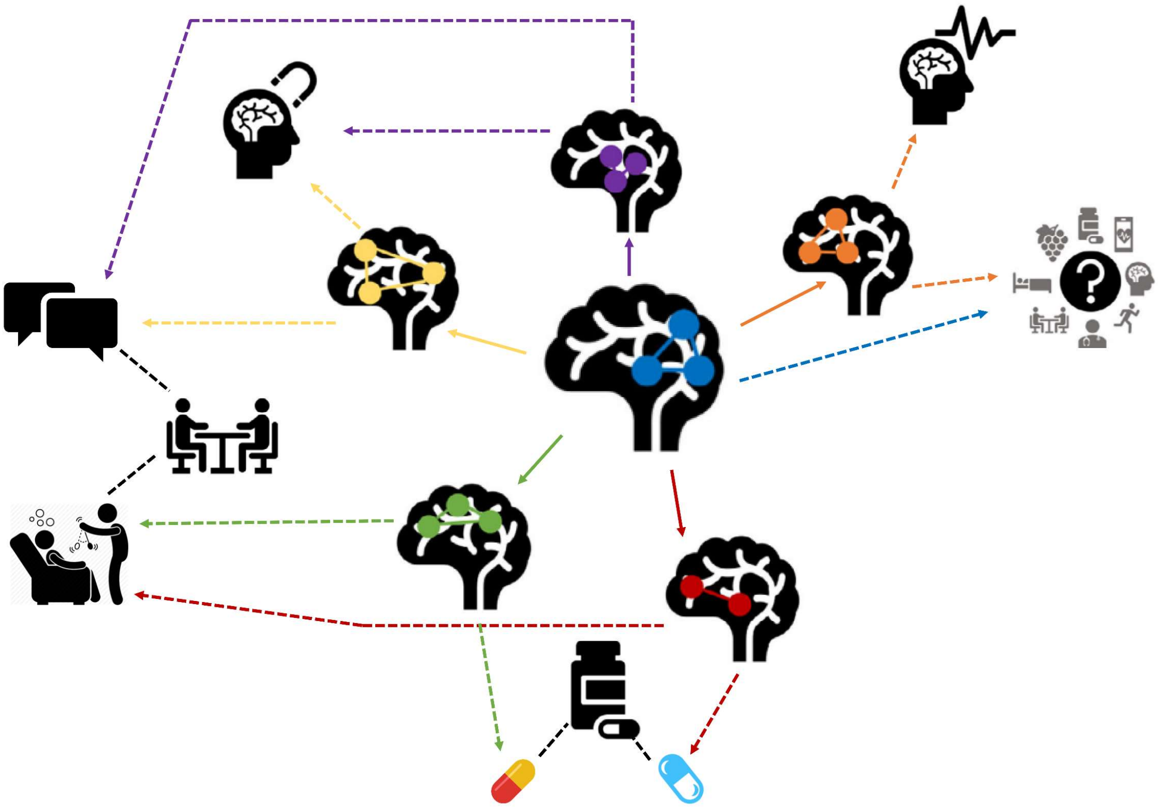
I would like to propose a new model and it is portrayed in Figure 5. I'll call it the "Network Interaction Based Biotype Model" or short NIBB. It portrays a meta network, in which the DMN (brain with blue bubbles)[13] is the central node of a network consisting of other core networks: the attention network (yellow bubbles), SN (green bubbles), the CEN (red bubbles), the affective limbic network (orange bubbles), and the reward network (purple bubbles). All of these have been shown to be involved in depression (Williams, 2017). In the NIBB, the DMN shows abnormalities within itself as well as in the connection to the other core networks (portrayed by solid arrows in Figure 5), following the ideas of Scalabrini et al. 2020. Each type of malfunctioning (hypo- or hyper-connection within itself or to another core network) defines a different biotype of depression (following the idea of Williams (2017) and Chahal et al. (2020)). Further, each of these biotypes responds better to another therapy (or set of therapies), as has been shown in different studies on adolescents and adults[14] (portrayed by dashed arrows in Figure 5). I do not suggest a certain biotype calls for a certain therapy, may it be medication or psychotherapy or any other. Much more research is needed to make this kind of recommendation. The categories Chahal et al. chose for some treatments (like psychotherapy or medication) seem too broad, since they vary greatly in their content or mechanisms of functioning. CBT consists of different methods than other psychotherapies like interpersonal therapy, psychodynamic psychotherapy (Fu, Fan, & Davatzikos, 2019) or HT. Yet, the connection between a biotype and the response to *different* psychotherapies or their underlying mechanisms has not been investigated to my knowledge (the predictive value of biomarkers for the response to psychotherapy has only been researched for CBT (Fu et al., 2013)). Even though different psychotherapies are based on heterogeneous mechanisms, they yield similar efficacies (Fu et al., 2019; Fuhr et al., 2021), but seem to still affect the brain differently. At least when we are comparing CBT to HT, as I am showing in this work. For the sake of keeping things as simple as

[13] I chose the same color assignment to core network as the authors I am referring to (Chahal et al., 2020; Williams, 2017).

[14] For example, the FC between the amygdala and the CEN or SN predicted the response to CBT in adolescents (Straub et al., 2017), medication response was predicted by the FC between the attention network, CEN, and amygdala (Cullen et al., 2016; Klimes-Dougan et al., 2018), and biotypes differed in their response to transcranial magnetic stimulation (Drysdale et al., 2017).

Figure 5

The Network Interaction Based Biotype Model (NIBB)



Note. The DMN (blue) is the node of a meta network in which it is aberrantly connected to itself and other core networks (solid arrows): the attention network (yellow), SN (green), CEN (red), affective
limbic network (orange), and reward network (purple). Depending on which network the DMN is hyper- or hypo-connected to a different biotype of depression is defined. Each biotype calls for another optimal treatment or set of treatments (dashed arrows). The treatment options “psychotherapy” and “medication” are split up further into CBT (speech bubbles) and HT (hypnotist and hypnotized person) and different kinds of antidepressant medication (pills of different colors), respectively.

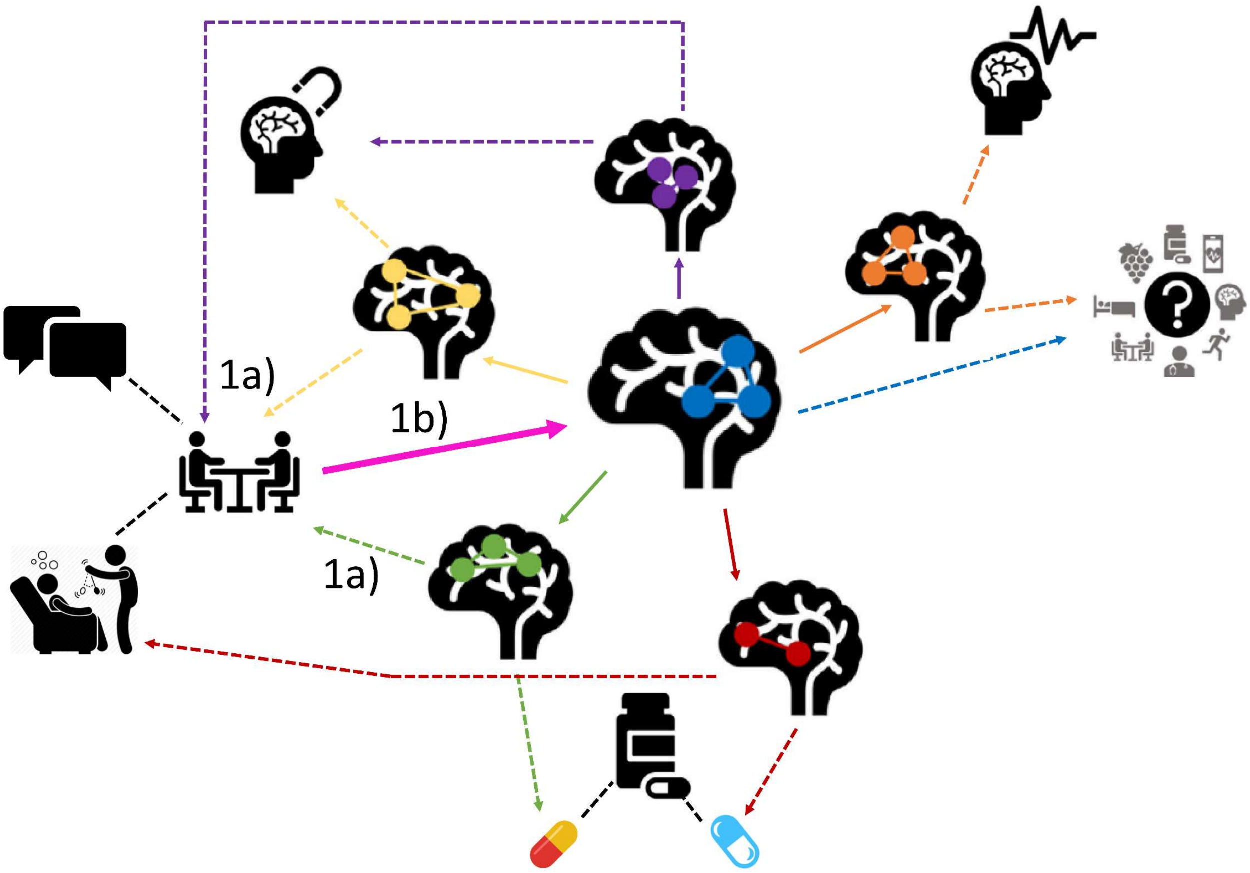
possible, I split the NIBB domain “psychotherapy” into two categories (CBT and HT), but it could be complemented by interpersonal or psychodynamic therapy in the future. Since the same argument extends to the field of medication, the model depicts a division here as well. (Some patients respond to tricyclic antidepressants while others respond better to selective serotonin-reuptake inhibitors (Anderson, 2000) – as one example). I am well aware of the venture the NIBB holds, and I am far from offering enough supportive data for this model. I rather consider the NIBB a next milestone in getting closer to identifying biotypes on the long journey of precision healthcare for depressed patients. With my data I can point into the direction of this next milestone but cannot claim to have reached it. Before we start digging deeper into our data and integrating them into the NIBB, let's look at some critics of the biotype idea for depression. A general problem in psychiatrics is that the disorders are not separate and do neither have clear boundaries between one another nor to normality (Wium-Andersen, Vinberg, Kessing, & McIntyre, 2016). So, many symptoms that are associated with depression, like anhedonia, suicidality, and cognitive dysfunction can also occur in other disorders. If a certain biotype of depression goes along with specific symptoms (e.g. anhedonia) and these symptoms (as well as their underlying neuro-correlate) are also specific to another disorder (e.g. schizophrenia) – what does this biotype make specific to depression? This overlap of symptoms and aberrant involvement of core networks in many psychiatric disorders (Menon, 2011) complicates the identification of specific biotypes in specific disorders. Further, the reliability of neuroimaging methods in precision healthcare can be called into question. For example, one group of authors has shown surprisingly low reliability of two important treatment biomarkers in mood and anxiety disorders when measured with fMRI (Nord, Gray, Charpentier, Robinson, & Roiser, 2017). Much more research is needed to rebut these weak points of biotype models in psychiatry. For now, let's keep these critical points in mind, when looking closer at the NIBB in the following.

6.7 Experimental psychopathology aspect: Implications for depression

Firstly, we learned that through therapy (HT and CBT equally) FC in the SAC, a midline DMN structure, decreased. In line with previous research (Anand et al., 2005; Greicius et al., 2007; Grimm et al., 2009; Sheline et al., 2009) and the idea of Scalabrini et al. (2020) our result could mirror a normalization of DMN functioning through psychotherapy. For the NIBB it could mean that 1a) a wide range of patients, and thus various biotypes, profit from psychotherapy in some way (Figure 6 – multiple dashed arrows lead to psychotherapy). This idea is supported by Fuhr et al. (2021) as well as our findings on the patients' symptom reduction (with patients overall profiting from the therapy equally in both groups). The explanation for this could be that 1b): They profit because psychotherapy affects the node of the meta network itself – namely the DMN.

Figure 6

The first implications of our findings

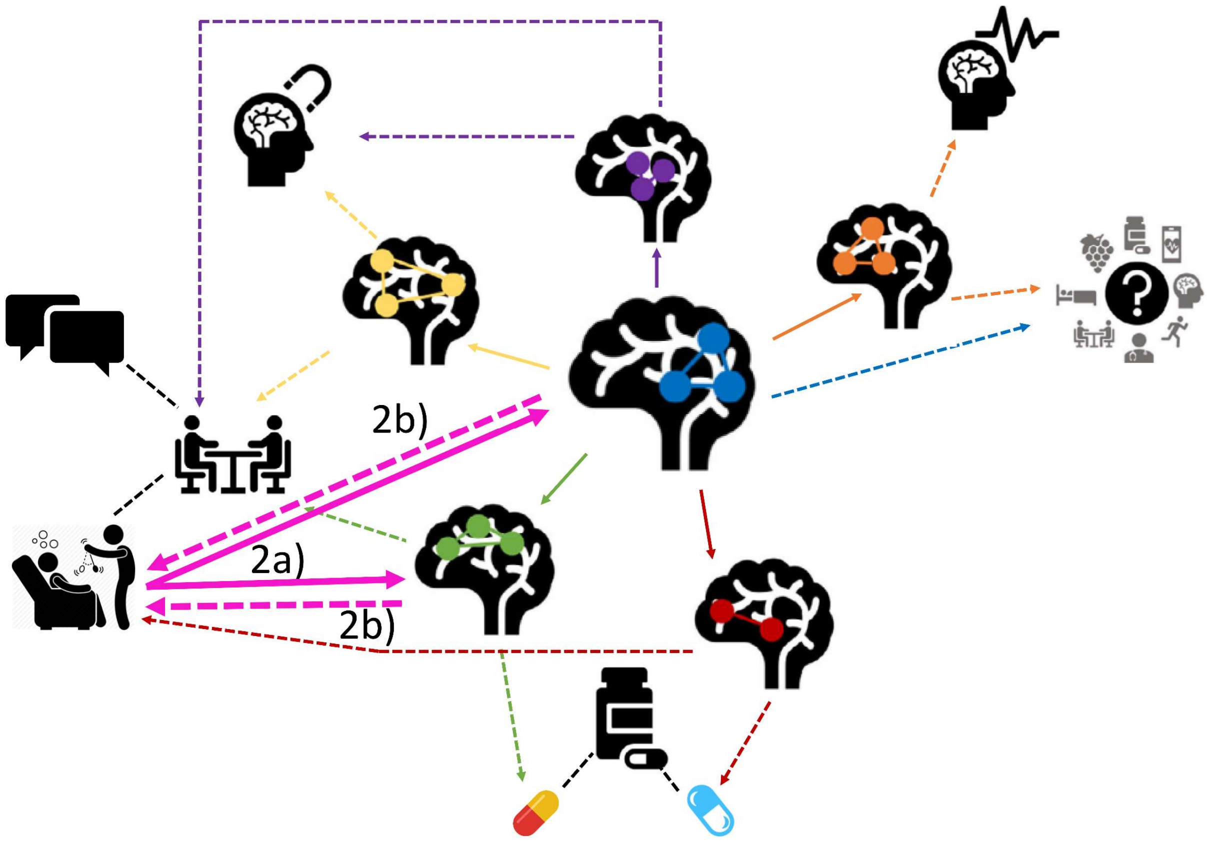


Note. Label 1a) indicates that a wide range of patients, ergo various biotypes, profit from psychotherapy (multiple dashed arrows lead to psychotherapy) and 1b) because psychotherapy directly affects the node of this meta network (the DMN).

Secondly, we learned that an inter-hemispheric DMN connection, STS as well as PFC activity changed only in the HT group. This gives us a very important first conclusion about HT in depression: it works. HT changes neurophysiological processes, and it does so specifically, because we did not find the same changes for CBT. This also means that a mere time effect as explanation can be dismissed – or otherwise the effect would have appeared in the CBT group as well. In the NIBB this gives us a feedback loop (marked with solid pink arrows and "2a)" in Figure 7): Our data suggests that HT specifically affects a DMN component and cerebral areas which might be more important to some biotypes than others[15]. This argument leads to the conclusion that in general, HT can and should be considered a possible treatment option for depressed patients and that HT could be indicated as *precise* treatment for a specific biotype or various specific biotypes (indicated by dashed pink arrows and "2b)" in Figure 7).

Figure 7

The second implications of our findings



Note. Our results on a DMN component, the PFC and STS being affected by HT give us a hint that specific biotypes (hypothetically e.g. the DMN biotype (blue) and others (green)) respond to HT by showing cerebral changes through psychotherapy (indicated by solid pink arrows and "2a)"). This could lead to the conclusion that (a) specific biotype(s) call for HT as precise treatment (indicated by dashed pink arrows and "2b").

[15] The biotype (green) in Figure 7 involved in the feedback loop with HT (pink arrows) was only chosen for illustration purposes and does not imply this *specific* biotype to be affected.

At this point let me repeat, that I did not predict response to therapy or symptom reduction in any of my analyses, so the conclusions I am offering here are of hypothetical nature. In the future the NIBB should be tested by predicting therapy response through neurophysiological data on the FC of the involved core networks.

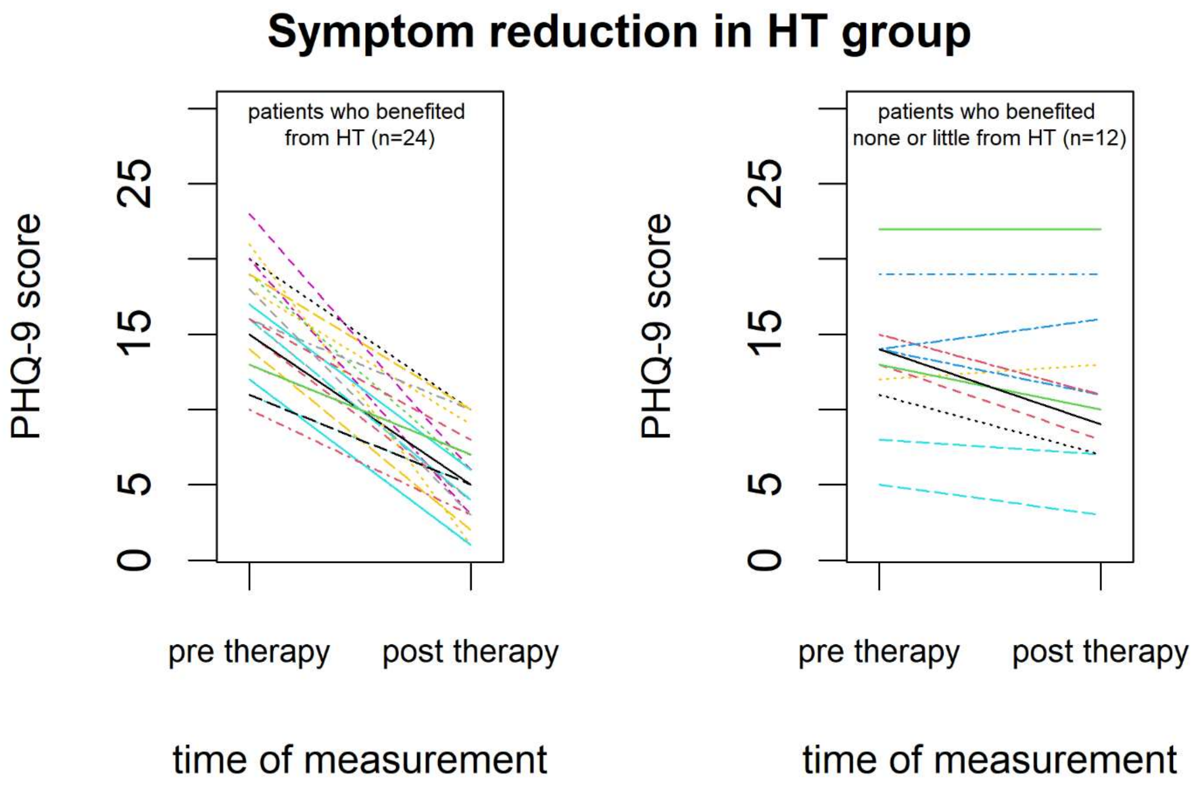
I want to strengthen my last argument on the indication of HT as precise therapy for (a) specific biotype(s) and took another closer look at my data. Even though the HT patients profited from therapy overall, not all of them did so in the same way. As analyzed and reported in our paper on the DMN (Haipt, Rosenbaum, et al., 2023), the mean of self-reported symptoms was significantly decreased after therapy in the HT group[16], but the standard deviation (which was very large to start with) increased. This finding implies that the range of self-reported symptoms was quite large from the beginning and increased over time: Some patients seem to have profited a lot from HT, while others did not. Figure 8 depicts the self-reported symptoms before and after the intervention of the patients in the HT group.

For illustrative purposes only, I divided these patients into two groups: The first group reported a symptom reduction bigger than a standard deviation of the group-level symptom change in the HT group (*SD* = 5.31). The second group included patients that reported no symptom reduction or a symptom reduction that was less than this standard deviation and thus benefited not at all or only a little from HT. Possibly, patients benefited differently from HT because they belong to different depression biotypes. Since the PFC, the STS and the DMN inter-hemispherically were affected by HT, biotypes for which these regions and this specific DMN connection are relevant might have responded better to HT than biotypes based on the malfunctioning of networks in which these regions are not as involved. We need much more research, e.g., stratified randomized controlled trials, to explore this idea, but in the future a differentiation of biotypes should be included in the data analysis of differential therapy response.

[16] $t(35) = 8.63$, $p < .001$, *M*(PHQ-9 pre therapy) = 14.89, *SD*(PHQ-9 pre therapy) = 3.99, *M*(PHQ-9 post therapy) = 7.25, *SD*(PHQ-9 post therapy) = 4.80

Figure 8

Self-reported symptoms before and after therapy in the HT group



Note. Each line represents an individual symptom change. Patients whose symptom change is portrayed on the left showed symptom reduction greater than the overall standard deviation (*SD* = 5.31) for this patient group; patients on the right did not show symptom reduction at all or smaller than the SD. Multiple lines plotted in the left graph overlap, so there are less than 24 lines.

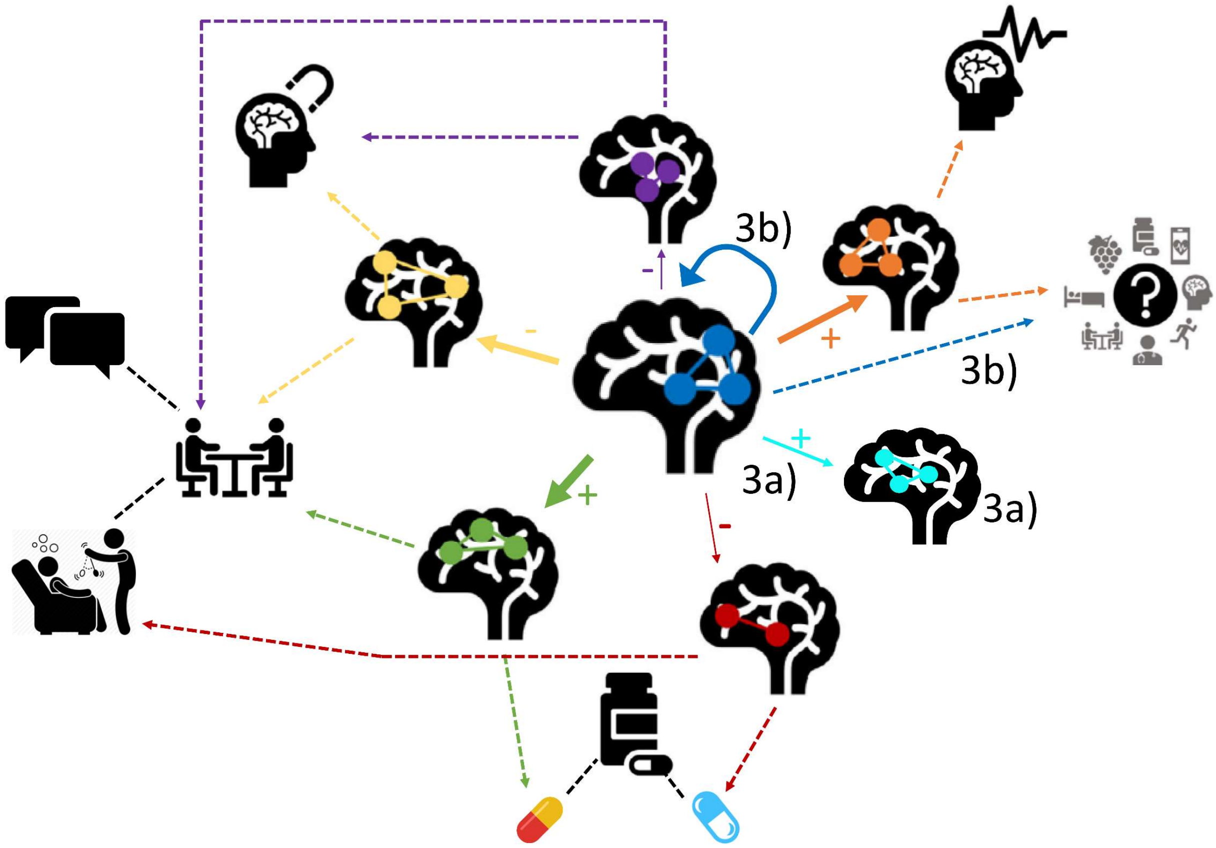
Now, I want to get back to the implications for the NIBB. Thirdly, we demonstrated that rumination is a determining factor for the change of STS activity (Haipt et al., 2022). The less the patients ruminated, the more their STS activity decreased, and the more they ruminated, the more it increased. This finding means not all patients showed the same STS-specific impairments and the effect of therapy on these impairments also varied between patients. Rumination correlated positively with self-reported symptom severity. As mentioned in the discussion of our results above, the STS has been associated with depression (Fitzgerald et al., 2008), but it has not been included as a part of a depression-specific core network by Chahal et al. (2020) and Williams (2017) whose reviews focus on resting state FC rather than emotional processing. If, indeed, the STS were part of an emotional network that is affected by depression, the question arises, whether this network might be task-specific or active during resting state and in what way it might determine a specific biotype. This should be investigated in the future.

From this, I deduce two things for the NIBB: Firstly, it supports the idea that the STS, possibly as part of a network, could be another core region whose malfunctioning determines a specific depression biotype (portrayed with “3a)” and in light blue in Figure 9). In this case it could be a biotype specifically showing impairments in emotional processing. This biotype could be connected to rumination on symptom level and thus the DMN on neurophysiological level (portrayed with “3a)” and light blue arrow in Figure 9). How this biotype would look like on a symptom level could go in different directions: An “emotional” biotype of depression could be a person who feels highly guilty, worthless, sad, and hopeless while at the same time this person ruminates a lot, ergo thinks a lot about his/her short-comings and problems. On the other hand, the “emotional” biotype could be a person featuring a *lack* of emotions (feeling empty), not being able to assess emotions in others etc., while ruminating a lot and always “over-thinking” things rather than feeling them. Both ideas can be supported by the findings that depression goes along with reduced STS activity (Fitzgerald et al., 2008) and this activity increased through therapy in high ruminators (Haipt et al., 2022). What this change of STS activity looks like on a symptom level and how it is connected to rumination and the DMN remains unclear and should be examined in the future.

Secondly, as rumination has been suggested to be the behavioral reflection of depression-specific DMN malfunctioning (Berman et al., 2011; Rosenbaum et al., 2017), it could serve as an indicator for the degree of malfunctioning of the DMN as a main node in the NIBB (displayed by “3b)” and blue arrow pointing back at the DMN in Figure 9). Possibly, it is not enough to categorize patients into biotypes based on the dominance of a certain core network to assign them specific therapies. Maybe it is necessary to look at the *degree* of malfunctioning of the affected network, especially when it concerns the DMN. Indeed, specific DMN components associated with rumination have been shown to be a risk factor for the lack of therapy response (Teismann, Willutzki, Michalak, & Schulte, 2008) and the recurrency of depression (Marchetti, Koster, Sonuga-Barke, & De Raedt, 2012; Michalak, Hölz, & Teismann, 2011). The degree of DMN malfunctioning could determine the extent of hypo- or hyperconnections to other networks (marked with “+” and “-“ and varying arrow widths in Figure 9) and possibly the number of altered connections to other networks. This again could have consequences on the success of therapy and on the way therapies work (indicated by “3b)” and blue dashed arrow in Figure 9).

Figure 9

The third implications of our findings



Note. 3a) The STS activation change might indicate the involvement of another network in depression, which is emotion-specific, and this could portray another biotype (light blue). 3b) The degree of DMN within-FC malfunctioning could represent an own biotype and the extent (width of arrows) and direction of malfunctioning (hyperconnection “+” and hypoconnection “-“) could be of importance for the assignment of optimal treatment.

So far on the theory. Now, how could an implementation of a biotype-treatment model like the NIBB look like in practice? Let me give an example: A patient, let’s call her Jane, might show decreased amygdala volume which goes along with problems in emotional perception (Hamilton, Siemer, & Gotlib, 2008). On a neurophysiological level she might show impairments in the affective limbic network (Williams, 2017) and in the NIBB she would categorize as “affective limbic biotype” (orange in Figure 9). On a symptom level, let’s assume for the example, her social life is impaired, she feels depressed and lost pleasure in activities. Her doctor has recently read a review on biomarkers as predictors for treatment outcome (Fonseka et al., 2017) and sends her to stimulation therapy, like transcranial magnetic stimulation. Indeed, Jane responds to therapy and soon she feels better. Another patient, John, might report depressive symptoms, including impaired emotional processing and a lack of concentration due to mind-wandering, while at the same time showing little rumination. On neurophysiological level he might show altered STS activity (Takahashi et al., 2010), aberrantly increased FC in the DMN (Rosenbaum et al., 2017), and no abnormal connections to other core networks. In the NIBB he would categorize as “DMN biotype” (dark blue in Figure 9). His doctor, who is also well read (Michalak et al., 2011), recommends him a specific psychotherapy, and soon John’s symptoms improve and he stays without relapse. Or John lives in a future in which HT has proven itself to be an adequate treatment for the “DMN biotype”. He would undergo HT and benefit from it. On a neurophysiological level this success would be mirrored by decreased STS activity, as shown in low ruminators after HT (Haipt et al., 2022). These examples are thought to portray how precision medicine could work in the future.

Unfortunately, we are not there yet and much more research is needed. The idea of biotypes for depression based on FC (in this case during resting state) is a first start but requires further exploration: other networks, e.g. emotional networks and task-relevant networks[17], should be investigated and considered as possible biotype candidates, the extent and direction of malfunctioning between the DMN and other networks needs to be further investigated and the behavioral measures or symptoms differing between the biotypes should be identified. Also, criteria which separate biotypes of depression from other psychiatric disorders, need to be determined (as discussed introductorily). As shown above, HT helped depressed patients and it affected the brain – a great first start. But from here, it should be examined which

[17] It has been shown that elderly people did not only have depression-specific alterations in FC during resting state but also during tasks (Rosenbaum et al., 2016).

person was affected in what way and how this is connected to improvement. Further, neuroimaging methods need to be further developed to make them more reliable.

6.8 Bringing the approaches together

As could be read on the previous pages, a lot can be learned from our study results. We can look through a theoretical lens of hypnosis research and focus on hypnosis/hypnotic trance as special, altered, state (intrinsic research). Since the patients of our study practiced hypnosis/hypnotic trance repeatedly over several months during HT, we gained information of long-term effects of hypnosis/hypnotic trance on the brain. This intrinsic approach guides our view inwardly, to the roots of hypnosis/hypnotic trance itself. Glancing through a medical lens we can take the same results and learn from them about depression and its treatment (experimental psychopathology). Thus, experimental research guides our view to a disorder, and we use hypnosis/trance, in this work specifically HT, as a specific angle to look from. Now, one question remains: How do these approaches connect? To find the answer, it is necessary to look at the purpose they serve.

Conducting intrinsic research on hypnosis/hypnotic trance helps us understand the state of hypnosis/hypnotic trance more thoroughly. Hypnosis/hypnotic trance has been compared previously to other, altered, states of mind like conversion disorder or schizophrenic phenomena (Halligan & Oakley, 2013). So, learning about hypnosis/hypnotic trance as a specific state could also mean learning about these disorders. This, again, could help us develop treatments for these disorders and reduce suffering in patients. On the other hand, getting to the roots of hypnosis/hypnotic trance could help us find a state, that is beneficial or healing itself. From therapeutic experience I can report that a hypnotic trance alone can relieve and relax people – not only patients suffering from symptoms, but anyone who is open to the experience.

At the same time, experimental psychopathology offers the advantage of looking at a certain disorder from many different angles to gain a multi-faceted view of it. In our case we looked at depression with the perspective of *how* therapy affected the brain, especially HT, to learn about the underlying mechanisms of depression. The goal is to get closer to the roots of depression to ultimately find optimal treatments. As described above, due to its heterogeneity it has been suggested to categorize depressed patients into subtypes, for example based on neurophysiological differences (biotypes), and match treatment options to these biotypes. The critical question, though, is: How can we know which treatments fits which biotype? An empirical approach (bottom-up process) consisting of several randomized controlled trials would be ideal: Patients would be randomly assigned to a certain therapy, while their biotype would be determined with neurophysiological measurement and behavioral assessment. The therapeutic success (or lack thereof) would be the outcome variable and help in turn inform about the biotype-treatment match. If results were satisfactory and biotype categories really would predict treatment response, further validating would be needed. This could include studies in which some patients were assigned treatment according to their biotype and then compared to randomly assigned patients. This approach sounds nice in theory, but the sample sizes would have to be immense, which would cost a lot of money and time. Here, we chose a different approach – a top-down process – through which we looked at the effect of a certain therapy and learned about its underlying processes. Data analysis suggested that patients are affected differently by a certain therapy and this in turn gives us tentative clues about possible biotypes of depression[18]. To sum up this argument, this kind of experimental psychopathology, as part of instrumental research, makes medicine more precise.

From close-up the intrinsic and instrumental approach glance into two different directions but looking at the bigger picture, they both serve the same purpose: They give us clues about how therapy can work and for whom – in the end, scientists conducting either kind of research try to reduce suffering in others. Hypnosis/hypnotic trance has been demonstrated to be effective, but it has not been understood satisfactorily. Both approaches, intrinsic and instrumental, help us to get a deeper grasp of the phenomenon “hypnosis/hypnotic trance” and ultimately promote its acknowledgement to make it accessible to more patients who suffer from psychiatric conditions.

6.9 Limitations and Future Research

When developing the idea of including neurophysiological measurements in the WIKI-D study, I was confronted with a substantial gap in literature. Still, we took the leap and developed hypotheses and a study design that would allow us to explore the cerebral effects of HT compared to CBT. However, the exploratory nature

[18] Since this is a big leap in interpreting our results, much more research is needed in this field.

of our study might also be one of its biggest limitations – much groundwork is needed to be done to further substantiate our findings. This reaches from validating the paradigms we used for a clinical, German speaking, sample, defining more or other cerebral regions of interest, finding factors distinguishing HT from CBT on a content level and identifying co-variates (moderating or mediating factors) that possibly play an important role in the effects of therapy on the brain (some suggestions for moderating/mediating factors can be found in the psychological and social domain of hypnotic response in the biopsychosocial model by Jensen et al. (2015)). Another advantage of our study is that we gathered a lot of data for alternative analyses which could be conducted with small financial effort. For example: Due to the low penetration depth of fNIRS, data from subcortical areas could not be collected. However, we did indeed measure a subsample of 24 patients with fMRI[19], so the raw data for subcortical examination exists. In addition to the fNIRS measurements, we also collected data with an EEG placed on the midline of the head, reaching from frontal to parietal positions. EEG has a higher temporal resolution than fNIRS and fMRI. Therefore, it would be possible to explore processes that are more time sensitive and associated with subcortical structures like the ACC.

Many questions arise around the psychiatric field: 1) Are our results specific to depressive patients? This question could be answered with comparing our results to the data of a healthy control group, which we do indeed have. In addition to our patient sample, we tested 38 healthy individuals with fNIRS and EEG on all three paradigms. Since we did not assume a change of their cerebral activity, we measured them once. A comparison to this group could show how depressed patients are different than healthy controls before therapy in respect to the biotype idea. Further, moderating/mediating factor candidates (like rumination or suggestibility) could be investigated in the relation to depression. 2) Are the effects we found specific to HT for depression, or can they be found in the treatment of other disorders as well? A whole new study with similar paradigms, measurement methods, and same sample size would be necessary to conduct accompanying a therapy study. 3) Does the type of medication and the recurrence of depressive episode predict the effects we found? As mentioned above, medication treatment of depressed patients is associated with decreased DMN FC, as is symptom severity in

[19] These 24 patients underwent fNIRS and fMRI measurements with all three paradigms, before and after therapy.

recurrently depressed people (Yan et al., 2019). Again, here we do have the data: In the WIKI-D study the amount of previous depressive episodes as well as the type of medication was recorded, so the factor could be easily included into further analyses. This last argument also extents to including suggestibility as a factor, since this variable was assessed in all patients included in the WIKI-D study (we did not test the healthy controls for suggestibility). In my opinion, the identification of biotypes is the most promising aspect of future research to promote precision medicine. Also, it would be of great interest and use to assess patients repeatedly over the course of a therapy and possibly even during therapy sessions. Since measurement methods become more practicable, this could be possible in the future. As an example, portable NIRS devices have now been introduced and such devices could be used for in-session measurements.

6.10 Conclusion

When I first encountered psychotherapy, I soon learned about HT and experienced hypnosis/hypnotic trance myself. It got me interested in this specific state of consciousness and I wondered how it is different from other therapies, especially well-established ones like CBT. After researching this question, I faced a huge gap of literature and after reviewing the little there was, I had more questions than answers. This motivated me to take on the scientific adventure of conducting this project. My goal was to explore hypnosis/hypnotic trance beyond swinging pendula and spinning swirls. I wanted to critically examine its mechanisms and learn how it works, especially compared to a commonly used therapy, like CBT. And I wanted to do this with the standards of modern science.

This work is one of a kind, because it is the first time a study this large, supplemental to a therapy study, has been conducted: We included 86 patients of which 75 returned to the second measurement, all of them completed a therapy of at least 16 out of 20 sessions. Not only one therapy group (HT) was investigated, but CBT as well; additionally, we measured 38 healthy individuals. We used three different paradigms, and three different measurement methods (fNIRS, fMRT and EEG). Only a subset of this huge data set has been analyzed so far. But even this fraction of analysis has presented us with interesting and partly unexpected results. We found HT-specific changes in the DMN, the temporal lobe and the PFC, while we did not find specific effects for CBT. An overall therapy effect was observed in one DMN component. These findings have multiple implications on a neurophysiological level and assumptions about their connection to the content of each therapy were made. Further, I used our results to further understand hypnotic phenomena when hypnosis/trance is practiced regularly, and linked them to depression and its treatment with HT. All of this brings us one step closer to helping more people suffering from this disorder, with more precise and ultimately better treatment. Many questions remain unanswered and with my research I created even more. Still, I hope at the end this work opens a new chapter in the investigation of HT on a neurophysiological level and is the first steppingstone to much more research to come.

7. Bibliography

Alladin. (2006). Cognitive hypnotherapy for treating depression. In *The clinical use of hypnosis with cognitive behavior therapy: A practitioner's casebook* (pp. 139–187).

Alladin, A., & Alibhai, A. (2007). Cognitive hypnotherapy for depression: An empirical investigation. *International Journal of Clinical and Experimental Hypnosis*, *55*(2), 147–166. https://doi.org/10.1080/00207140601177897

American Pschological Association. (n.d.). Hypnosis. Retrieved February 17, 2023, from https://dictionary.apa.org/hypnosis

American Pschological Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington: American Psychological Association.

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., … Lowe, M. J. (2005). Activity and connectivity of brain mood regulating circuit in depression: A functional magnetic resonance study. *Biological Psychiatry*, *57*(10), 1079–1088. https://doi.org/10.1016/j.biopsych.2005.02.021

Anderson, I. M. (2000). Selective serotonin reuptake inhibitors versus tricyclic antidepressants: A meta-analysis of efficacy and tolerability. *Journal of Affective Disorders*, *58*(1), 19–36. https://doi.org/10.1016/S0165-0327(99)00092-0

Anderson, I. M., Shippen, C., Juhasz, G., Chase, D., Thomas, E., Downey, D., … Deakin, J. F. W. (2011). State-dependent alteration in face emotion recognition in depression. *The British Journal of Psychiatry*, *198*(4), 302–308. https://doi.org/10.1192/bjp.bp.110.078139

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-Anatomic Fractionation of the Brain's Default Network. *Neuron*, *65*(4), 550–562. https://doi.org/10.1016/j.neuron.2010.02.005

Barabasz, M. (2007). Efficacy of hypnotherapy in the treatment of eating disorders. *International Journal of Clinical and Experimental Hypnosis*, *55*(3), 318–335. https://doi.org/10.1080/00207140701338688

Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive Therapy for Depression*. New York: Guilford.

Beijers, L., Wardenaar, K. J., van Loo, H. M., & Schoevers, R. A. (2019). Data-driven biological subtypes of depression: systematic review of biological approaches to depression subtyping. *Molecular Psychiatry*, *24*(6), 888–900. https://doi.org/10.1038/s41380-019-0385-5

Berman, M. G., Peltier, S., Nee, D. E., Kross, E., Deldin, P. J., & Jonides, J. (2011). Depression, rumination and the default network. *Social Cognitive and Affective Neuroscience*, *6*(5), 548–555. https://doi.org/10.1093/scan/nsq080

Brass, M., Schmitt, R. M., Spengler, S., & Gergely, G. (2007). Investigating Action Understanding: Inferential Processes versus Action Simulation. *Current Biology*, *17*(24), 2117–2121. https://doi.org/10.1016/j.cub.2007.11.057

Canli, T., Sivers, H., Thomason, M. E., Whitfield-Gabrieli, S., Gabrieli, J. D. E., & Gotlib, I. H. (2004). Brain activation to emotional words in depressed vs healthy subjects. *NeuroReport*, *15*(17), 2585–2588. https://doi.org/10.1097/00001756-

200412030-00005

Carballedo, A., Scheuerecker, J., Meisenzahl, E., Schoepf, V., Bokde, A., Möller, H., … Frodl, T. (2011). Functional connectivity of emotional processing in depression. *Journal of Affective Disorders*, *134*, 272–279. https://doi.org/10.1016/j.jad.2011.06.021

Carragher, N., Adamson, G., Bunting, B., & McCann, S. (2009). Subtypes of depression in a nationally representative sample. *Journal of Affective Disorders*, *113*(1–2), 88–99. https://doi.org/10.1016/j.jad.2008.05.015

Chahal, R., Gotlib, I. H., & Guyer, A. E. (2020). Research Review: Brain network connectivity and the heterogeneity of depression in adolescence – a precision mental health perspective. *The Journal of Child Psychology and Psychiatry*, *61*(12), 1282–1298. https://doi.org/10.1111/jcpp.13250

Ciaramidaro, A., Adenzato, M., Enrici, I., Erk, S., Pia, L., Bara, B. G., & Walter, H. (2007). The intentional network: How the brain reads varieties of intentions. *Neuropsychologia*, *45*(13), 3105–3113. https://doi.org/10.1016/j.neuropsychologia.2007.05.011

Cojan, Y., Waber, L., Carruzzo, A., & Vuilleumier, P. (2009). Motor inhibition in hysterical conversion paralysis. *NeuroImage*, *47*(3), 1026–1037. https://doi.org/10.1016/j.neuroimage.2009.05.023

Cojan, Y., Waber, L., Schwartz, S., Rossier, L., Forster, A., & Vuilleumier, P. (2009). The brain under self-control: modulation of inhibitory and monitoring cortical networks during hypnotic paralysis. *Neuron*, *62*(6), 862–875. https://doi.org/10.1016/j.neuron.2009.05.021

Connolly, C. G., Wu, J., Ho, T. C., Hoeft, F., Wolkowitz, O., Eisendrath, S., … Yang, T. T. (2013). Resting-State Functional Connectivity of Subgenual Anterior Cingulate Cortex in Depressed Adolescents. *Biological Psychiatry*, *74*(12), 898–907. https://doi.org/10.1016/j.biopsych.2013.05.036.Resting-State

Crosbie, J., Pérusse, D., Barr, C. L., & Schachar, R. J. (2008). Validating psychiatric endophenotypes: Inhibitory control and attention deficit hyperactivity disorder. *Neuroscience and Biobehavioral Reviews*, *32*(1), 40–55. https://doi.org/10.1016/j.neubiorev.2007.05.002

Cullen, K. R., Gee, D. G., Klimes-Dougan, B., Gabbay, V., Hulvershorn, L., Mueller, B. A., … Milham, M. P. (2009). A preliminary study of functional connectivity in comorbid adolescent depression. *Neuroscience Letters*, *460*(3), 227–231. https://doi.org/10.1016/j.neulet.2009.05.022

Cullen, K. R., Klimes-Dougan, B., Vu, D. P., Westlund Schreiner, M., Mueller, B. A., Eberly, L. E., … Lim, K. O. (2016). Neural Correlates of Antidepressant Treatment Response in Adolescents with Major Depressive Disorder. *Journal of Child and Adolescent Psychopharmacology*, *26*(8), 705–712. https://doi.org/10.1089/cap.2015.0232

Dalili, M. N., Penton-Voak, I. S., Harmer, C. J., & Munafò, M. R. (2015). Meta-analysis of emotion recognition deficits in major depressive disorder. *Psychological Medicine2*, *45*(6), 1135–1144. https://doi.org/10.1017/S0033291714002591

Deeley, Q., Oakley, D., Toone, B., Giampietro, V., Brammer, M. J., Williams, S. C. R., & Halligan, P. W. (2012). Modulating the default mode network using hypnosis. *The International Journal of Clinical and Experimental Hypnosis*, *60*(2), 206–228. https://doi.org/10.1080/00207144.2012.648070

Deen, B., Koldewyn, K., Kanwisher, N., & Saxe, R. (2015). Functional organization of social perception and cognition in the superior temporal sulcus. *Cerebral Cortex*, *25*(11), 4596–4609. https://doi.org/10.1093/cercor/bhv111

Derbyshire, S. W. G., Whalley, M. G., Stenger, V. A., & Oakley, D. A. (2004). Cerebral activation during hypnotically induced and imagined pain. *NeuroImage*, *23*(1), 392–401. https://doi.org/10.1016/j.neuroimage.2004.04.033

DeRubeis, R. J., Siegle, G. J., & Hollon, S. D. (2008). Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. *Nature Reviews. Neuroscience*, *9*(10), 788–796. https://doi.org/10.1038/nrn2345

Dienes, Z., & Hutton, S. (2012). Understanding hypnosis metacognitively: RTMS applied to left DLPFC increases hypnotic suggestibility. *Cortex*, *49*(2), 386–392. https://doi.org/10.1016/j.cortex.2012.07.009

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. *Brain Structure and Function*, *213*(1–2), 93–118. https://doi.org/10.1007/s00429-008-0189-x

Dryman, M. T., & Heimberg, R. G. (2018). Emotion regulation in social anxiety and depression: a systematic review of expressive suppression and cognitive reappraisal. *Clinical Psychology Review*, *65*, 17–42. https://doi.org/10.1016/j.cpr.2018.07.004

Drysdale, A. T., Grosenick, L., Downar, J., Dunlop, K., Mansouri, F., Meng, Y., … Liston, C. (2017). Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nature Medicine*, *23*(1), 28–38. https://doi.org/10.1038/nm.4246

Egner, T., Jamieson, G., & Gruzelier, J. (2005). Hypnosis decouples cognitive control from conflict monitoring processes of the frontal lobe. *NeuroImage*, *27*(4), 969–978. https://doi.org/10.1016/j.neuroimage.2005.05.002

Elliott, R., Zahn, R., Deakin, J. F. W., & Anderson, I. M. (2011). Affective cognition and its disruption in mood disorders. *Neuropsychopharmacology*, *36*(1), 153–182. https://doi.org/10.1038/npp.2010.77

Fitzgerald, P. B., Laird, A. R., Maller, J., & Daskalakis, Z. J. (2008). A Meta-Analytic Study of Changes in Brain Activation in Depression. *Human Brain Mapping*, *29*(6), 683–695. https://doi.org/10.1002/hbm.20426.A

Flammer, E., & Alladin, A. (2007). The efficacy of hypnotherapy in the treatment of psychosomatic disorders: Meta-analytical evidence. *International Journal of Clinical and Experimental Hypnosis*, *55*(3), 251–274. https://doi.org/10.1080/00207140701338696

Fletcher, P. C., Happe, F., Frith, U., Baker, S. C., Dolan, R. J., Frackowiak, R. S. J., & Frith, C. D. (1995). Other minds in the brain: a functional imaging study of “theory of mind” in story comprehension. *Cognition*, *57*(2), 109–128.

https://doi.org/10.1016/0010-0277(95)00692-R

Fonseka, T. M., MacQueen, G. M., & Kennedy, S. H. (2017). Neuroimaging biomarkers as predictors of treatment outcome in Major Depressive Disorder. *Journal of Affective Disorders*, *233*, 21–35. https://doi.org/10.1016/j.jad.2017.10.049

Franklin, G., Carson, A., & Welch, K. (2016). Cognitive behavioural therapy for depression: systematic review of imaging studies. *Acta Neuropsychiatrica*, *28*(2), 61–74. https://doi.org/10.1017/neu.2015.41

Fu, C. H. Y., Fan, Y., & Davatzikos, C. (2019). Addressing heterogeneity (and homogeneity) in treatment mechanisms in depression and the potential to develop diagnostic and predictive biomarkers. *NeuroImage: Clinical*, *24*, 1–7. https://doi.org/10.1016/j.nicl.2019.101997

Fu, C. H. Y., Steiner, H., & Costafreda, S. G. (2013). Predictive neural biomarkers of clinical response in depression: A meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. *Neurobiology of Disease*, *52*, 75–83. https://doi.org/10.1016/j.nbd.2012.05.008

Fuhr, K., Meisner, C., Broch, A., Cyrny, B., Hinkel, J., Jaberg, J., … Batra, A. (2021). Efficacy of hypnotherapy compared to cognitive behavioral therapy for mild to moderate depression - Results of a randomized controlled rater-blind clinical trial. *Journal of Affective Disorders*, *286*, 166–173. https://doi.org/10.1016/j.jad.2021.02.069

Fuhr, K., Schweizer, C., Meisner, C., & Batra, A. (2017). Efficacy of hypnotherapy compared to cognitive-behavioural therapy for mild-to-moderate depression: Study protocol of a randomised-controlled rater-blind trial (WIKI-D). *BMJ Open*, *7*(11), 1–10. https://doi.org/10.1136/bmjopen-2017-016978

Gallagher, H. L., Happé, F., Brunswick, N., Fletcher, P. C., Frith, U., & Frith, C. D. (2000). Spatial selectivity in the temporoparietal junction, inferior frontal sulcus, and inferior parietal lobule. *Neuropsychologia*, *38*(1), 11–21. https://doi.org/10.1167/15.13.15

Goldstein, B. L., & Klein, D. N. (2014). A review of selected candidate endophenotypes for depression. *Clinical Psychology Review*, *34*(5), 417–427. https://doi.org/10.1016/j.cpr.2014.06.003

Gotlib, I. H., Krasnoperova, E., Neubauer Yue, D., & Joormann, J. (2004). Attentional Biases for Negative Interpersonal Stimuli in Clinical Depression. *Journal of Abnormal Psychology*, *113*(1), 127–135. https://doi.org/10.1037/0021-843X.113.1.127

Gottesman, I. I., & Gould, T. D. (2003). The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. *American Journal of Psychiatry*, *160*, 636–645. https://doi.org/https://doi.org/10.1176/appi.ajp.160.4.636

Gottesman, I. I., & Shields, J. (1973). Genetic theorizing and schizophrenia. *The British Journal of Psychiatry*, *122*(566), 15–30. https://doi.org/10.1192/bjp.122.1.15

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., … Schatzberg, A. F. (2007). Resting-State Functional Connectivity in Major

Depression: Abnormally Increased Contributions from Subgenual Cingulate Cortex and Thalamus. *Biological Psychiatry*, *62*(5), 429–437. https://doi.org/10.1016/j.biopsych.2006.09.020

Greicius, M. D., Kiviniemi, V., Tervonen, O., Vainionpa, V., Alahuhta, S., Reiss, A., & Menon, V. (2008). Persistent Default-Mode Network Connectivity During Light Sedation. *Human Brain Mapping*, *29*(7), 839–847. https://doi.org/10.1002/hbm.20537

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences*, *100*(1), 253–258. https://doi.org/https://doi.org/10.1073/pnas.0135058100

Grimm, S., Boesiger, P., Beck, J., Schuepbach, D., Bermpohl, F., Walter, M., … Northoff, G. (2009). Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects. *Neuropsychopharmacology*, *34*(4), 932–943. https://doi.org/10.1038/npp.2008.81

Gruzelier, J. H. (1998). A working model of the neurophysiology of hypnosis. *Contemporary Hypnosis*, *15*(1), 3–21. https://doi.org/https://doi.org/10.1002/ch.112

Guo, W., Liu, F., Zhang, J., Zhang, Z., Yu, L., Liu, J., … Xiao, C. (2014). Abnormal default-mode network homogeneity in first-episode, drug-naive major depressive disorder. *PLoS ONE*, *9*(3), 1–7. https://doi.org/10.1371/journal.pone.0091102

Haipt, A., Geiger, N., Schunk, S., Fuhr, K., Batra, A., & Ehlis, A.-C. (2023). *How psychotherapy changes the depressed brain: activity in the left prefrontal cortex reduced after Hypnotherapy but not Cognitive Behavioral Therapy*. Tübingen.

Haipt, A., Rosenbaum, D., Fuhr, K., Batra, A., & Ehlis, A.-C. (2023). *Differential Effects of Hypnotherapy and Cognitive Behavioral Therapy on the Default Mode Network of Depressed Patients*. Tübingen.

Haipt, A., Rosenbaum, D., Fuhr, K., Giese, M., Batra, A., & Ehlis, A.-C. (2022). The effects of hypnotherapy compared to cognitive behavioral therapy in depression: a NIRS-study using an emotional gait paradigm. *European Archives of Psychiatry and Clinical Neuroscience*, *272*(4), 729–739. https://doi.org/10.1007/s00406-021-01348-7

Halligan, P. W., & Oakley, D. A. (2013). Hypnosis and cognitive neuroscience: Bridging the gap. *Cortex*, *49*(2), 359–364. https://doi.org/10.1016/j.cortex.2012.12.002

Halsband, U., & Wolf, T. G. (2015). Functional changes in brain activity after hypnosis in patients with dental phobia. *Journal of Physiology*, *109*(4–6), 131–142. https://doi.org/10.1016/j.jphysparis.2016.10.001

Halsband, U., & Wolf, T. G. (2021). Current neuroscientific research database findings of brain activity changes after hypnosis. *American Journal of Clinical Hypnosis*, *63*(4), 372–388. https://doi.org/10.1080/00029157.2020.1863185

Hamilton, J. P., Etkin, A., Furman, D. J., Lemus, M. G., Johnson, R. F., & Gotlib, I. H. (2012). Functional neuroimaging of major depressive disorder: A meta-analysis and new integration of baseline activation and neural response data. *American Journal of Psychiatry*, *169*(7), 693–703. https://doi.org/10.1176/appi.ajp.2012.11071105

Hamilton, J. P., Siemer, M., & Gotlib, I. H. (2008). Amygdala volume in major depressive disorder: A meta-analysis of magnetic resonance imaging studies. *Molecular Psychiatry*, *13*(11), 993–1000. https://doi.org/10.1038/mp.2008.57

Hammond, D. C. (2013). A Review of the History of Hypnosis Through the Late 19th Century. *American Journal of Clinical Hypnosis*, *56*(2), 174–191. https://doi.org/10.1080/00029157.2013.826172

Häuser, W., Marschall, U., Layer, P., & Grobe, T. (2019). The prevalence, comorbidity, management and costs of irritable bowel syndrome—an observational study using routine health insurance data. *Deutsches Arzteblatt International*, *116*(27–28), 463–470. https://doi.org/10.3238/arztebl.2019.0463

Horovitz, S. G., Braun, A. R., Carr, W. S., Picchioni, D., Balkin, T. J., Fukunaga, M., & Duyn, J. H. (2009). Decoupling of the brain's default mode network during deep sleep. *Proceedings of the National Academy of Sciences*, *106*(27), 11376–11381. https://doi.org/10.1073/PNAS.0901435106

Jensen, M. P., Adachi, T., Tomé-Pires, C., Lee, J., Osman, Z. J., & Miró, J. (2015). Mechanisms of hypnosis: Toward the development of a biopsychosocial model. *International Journal of Clinical and Experimental Hypnosis*, *63*(1), 34–75. https://doi.org/10.1080/00207144.2014.961875

Jiang, H., White, M. P., Greicius, M. D., Waelde, L. C., & Spiegel, D. (2017). Brain activity and functional connectivity associated with hypnosis. *Cerebral Cortex*, *27*(8), 4083–4093. https://doi.org/10.1093/cercor/bhw220

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. *JAMA Psychiatry*, *72*(6), 603–611. https://doi.org/10.1001/jamapsychiatry.2015.0071

Karlsson, H. (2011). How Psychotherapy Changes the Brain. *Psychiatric Times*, *28*(8), 1–5. https://doi.org/10.0.3.249/S0033291709991607

Kerestes, R., Ladouceur, C. D., Meda, S., Nathan, P. J., Blumberg, H. P., Maloney, K., … Phillips, M. L. (2012). Abnormal prefrontal activity subserving attentional control of emotion in remitted depressed patients during a working memory task with emotional distracters. *Psychological Medicine*, *42*, 29–40. https://doi.org/10.1017/S0033291711001097

Klimes-Dougan, B., Westlund Schreiner, M., Thai, M., Gunlicks-Stoessel, M., Reigstad, K., & Cullen, K. R. (2018). Neural and neuroendocrine predictors of pharmacological treatment response in adolescents with depression: A preliminary study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *81*, 194–202. https://doi.org/10.1016/j.pnpbp.2017.10.015

Kroenke, K., & Spitzer, R. L. (2002). The PHQ-9: A new depression diagnostic and severity measure. *Psychiatric Annals*, *32*, 509–521. https://doi.org/10.3928/0048-5713-20020901-06

Lawrence, N. S., Williams, A. M., Surguladze, S., Giampietro, V., Brammer, M. J., Andrew, C., … Phillips, M. L. (2004). Subcortical and Ventral Prefrontal Cortical Neural Responses to Facial Expressions Distinguish Patients with Bipolar Disorder and Major Depression. *Biological Psychiatry*, *55*, 578–587. https://doi.org/10.1016/j.biopsych.2003.11.017

Lee, H. H., Choi, Y. Y., & Choi, M. G. (2014). The efficacy of hypnotherapy in the treatment of irritable bowel syndrome: A systematic review and meta-analysis. *Journal of Neurogastroenterology and Motility*, *20*(2), 152–162. https://doi.org/10.5056/jnm.2014.20.2.152

Leichsenring, F., & Steinert, C. (2017). Is Cognitive Behavioral Therapy the Gold Standard for Psychotherapy ? The Need for Plurality in Treatment and Research. *Jama*, *318*(14), 1323–1324. https://doi.org/10.1001/jama.2017.13737

Lenzenweger, M. F. (2013). Endophenotype, intermediate phenotype, biomarker: Definitions, concept comparisons, clarifications. *Depression and Anxiety*, *30*(3), 185–189. https://doi.org/10.1002/da.22042

Lowén, M. B. O., Mayer, E. a., Sjöberg, M., Tillisch, K., Naliboff, B., Labus, J., … Walter, S. a. (2013). Effect of hypnotherapy and educational intervention on brain response to visceral stimulus in the irritable bowel syndrome. *Alimentary Pharmacology and Therapeutics*, *37*(12), 1184–1197. https://doi.org/10.1111/apt.12319

Lueken, U., & Hahn, T. (2016). Functional neuroimaging of psychotherapeutic processes in anxiety and depression: from mechanisms to predictions. *Current Opinion in Psychiatry*, *29*(1), 25–31. https://doi.org/10.1097/YCO.0000000000000218

Marchetti, I., Koster, E. H. W., Sonuga-Barke, E. J., & De Raedt, R. (2012). The Default Mode Network and recurrent depression: A neurobiological model of cognitive risk factors. *Neuropsychology Review*, *22*(3), 229–251. https://doi.org/10.1007/s11065-012-9199-9

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science*, *315*(5810), 393–395. https://doi.org/10.1126/science.1131295

Mazzoni, G., Venneri, A., McGeown, W. J., & Kirsch, I. (2013). Neuroimaging Resolution of the Altered State Hypothesis. *Cortex*, *49*(2), 400–410. https://doi.org/https://doi.org/10.1016/j.cortex.2012.08.005

McGeown, W. J., Mazzoni, G., Venneri, A., & Kirsch, I. (2009). Hypnotic induction decreases anterior default mode activity. *Consciousness and Cognition*, *18*(4), 848–855. https://doi.org/10.1016/j.concog.2009.09.001

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in Cognitive Sciences*, *15*(10), 483–506. https://doi.org/10.1016/j.tics.2011.08.003

Merikangas, K. R., Chakravarti, A., Moldin, S. O., Araj, H., Blangero, J., Burmeister, M., … Takahashi, J. S. (2002). Future of genetics of mood disorders research. *Biological Psychiatry*, *52*(6), 457–477. https://doi.org/10.1016/S0006-3223(02)01471-3

Michalak, J., Hölz, A., & Teismann, T. (2011). Rumination as a predictor of relapse in mindfulness-based cognitive therapy for depression. *Psychology and Psychotherapy: Theory, Research and Practice*, *84*(2), 230–236. https://doi.org/10.1348/147608310X520166

Milling, L. S., Valentine, K. E., McCarley, H. S., & LoStimolo, L. M. (2018). A Meta-Analysis of Hypnotic Interventions for Depression Symptoms: High Hopes for Hypnosis? *American Journal of Clinical Hypnosis*, *61*(3), 227–243. https://doi.org/10.1080/00029157.2018.1489777

Nolen-Hoeksema, S. (1991). Responses to depression and their effects on the duration of depressive episodes. *Journal of Abnormal Psychology*, *100*(4), 569–582. https://doi.org/10.1037/0021-843X.100.4.569

Nord, C. L., Gray, A., Charpentier, C. J., Robinson, O. J., & Roiser, J. P. (2017). Unreliability of putative fMRI biomarkers during emotional face processing. *NeuroImage*, *156*, 119–127. https://doi.org/10.1016/j.neuroimage.2017.05.024

O'Toole, S. K., Solomon, S. L., & Bergdahl, S. A. (2016). A Meta-Analysis of Hypnotherapeutic Techniques in the Treatment of PTSD Symptoms. *Journal of Traumatic Stress*, *29*(1), 97–100. https://doi.org/10.1002/jts.22077

Oakley, D. A., Walsh, E., Mehta, M. A., Halligan, P. W., & Deeley, Q. (2021). Direct verbal suggestibility: Measurement and significance. *Consciousness and Cognition*, *89*, 1–20. https://doi.org/10.1016/j.concog.2020.103036

Oakley, D., & Halligan, P. (2009). Hypnotic suggestion and cognitive neuroscience. *Trends in Cognitive Sciences*, *13*(6), 264–270. https://doi.org/10.1016/j.tics.2009.03.004

Oosterink, F. M. D., De Jongh, A., & Hoogstraten, J. (2009). Prevalence of dental fear and phobia relative to other fear and phobia subtypes. *European Journal of Oral Sciences*, *117*(2), 135–143. https://doi.org/10.1111/j.1600-0722.2008.00602.x

Patel, G. H., Sestieri, C., & Corbetta, M. (2019). The evolution of the temporoparietal junction and posterior superior temporal sulcus. *Cortex*, *118*, 38–50. https://doi.org/10.1016/j.cortex.2019.01.026

Patil, A. V., Safaie, J., Moghaddam, H. A., Wallois, F., & Grebe, R. (2011). Experimental investigation of NIRS spatial sensitivity. *Biomedical Optics Express*, *2*(6), 1478–1493. https://doi.org/10.1364/boe.2.001478

Pelphrey, K. A., Singerman, J. D., Allison, T., & McCarthy, G. (2003). Brain activation evoked by perception of gaze shifts: The influence of context. *Neuropsychologia*, *41*(2), 156–170. https://doi.org/10.1016/S0028-3932(02)00146-X

Pelphrey, K., Morris, J., & McCarthy, G. (2004). Grasping the Intentions of Others: The Perceived Intentionality of an Action Influences Activity in the Superior Temporal Sulcus during Social Perception. *Journal of Cognitive Neuroscience*, *16*(10), 1706–1716. https://doi.org/10.1162/0898929042947900

Peter, B. (2000). Hypnotische Selbstkontrolle. Die wirksame Psychotherapie des Teufelsbanners Johann Joseph Gaßner um 1775. *Hypnose Und Kognition*, *17*(1 + 2), 19–34.

Price, J. L., & Drevets, W. C. (2010). Neurocircuitry of Mood Disorders. *Neuropsychopharmacology*, *35*, 192–216. https://doi.org/10.1038/npp.2009.104

PsychThG, W. B. P. nach § 11. (2006). Gutachten zur wissenschaftlichen Anerkennung der Hypnotherapie. *Psychotherapeutenjournal*, *2*, 164–167.

Pyka, M., Burgmer, M., Lenzen, T., Pioch, R., Dannlowski, U., Pfleiderer, B., … Konrad, C. (2011). Brain correlates of hypnotic paralysis—a resting-state fMRI study. *NeuroImage*, *56*(4), 2173–2182. https://doi.org/10.1016/j.neuroimage.2011.03.078

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*(2), 676–682. https://doi.org/https://doi.org/10.1073/pnas.98.2.676

Rainville, P., Hofbauer, R. K., Bushnell, M. C., Duncan, G. H., & Price, D. D. (2002). Hypnosis modulates activity in brain structures involved in the regulation of consciousness. *Journal of Cognitive Neuroscience*, *14*(6), 887–901. https://doi.org/10.1162/089892902760191117

Rainville, P., Hofbauer, R. K., Paus, T., Duncan, G. H., Bushnell, M. C., & Price, D. D. (1999). Cerebral Mechanisms of Hypnotic Induction. *Journal of Cognitive Neuroscience*, *11*(1), 110–125. https://doi.org/10.1162/089892999563175

Revenstorf, D., & Peter, B. (2009). *Hypnose in Psychotherapie, Psychosomatik und Medizin*. Heidelberg: Springer.

Riesel, A. (2019). The erring brain: Error-related negativity as an endophenotype for OCD—A review and meta-analysis. *Psychophysiology*, *56*(4), 1–22. https://doi.org/10.1111/psyp.13348

Rinck, M., & Becker, E. S. (2005). A comparison of attentional biases and memory biases in women with social phobia and major depression. *Journal of Abnormal Psychology*, *114*(1), 62–74. https://doi.org/10.1037/0021-843X.114.1.62

Rosenbaum, D., Hagen, K., Deppermann, S., Kroczek, A. M., Haeussinger, F. B., Heinzel, S., … Ehlis, A. C. (2016). State-dependent altered connectivity in late-life depression: A functional near-infrared spectroscopy study. *Neurobiology of Aging*, *39*, 57–68. https://doi.org/10.1016/j.neurobiolaging.2015.11.022

Rosenbaum, D., Haipt, A., Fuhr, K., Haeussinger, F. B., Metzger, F. G., Nuerk, H. C., … Ehlis, A. C. (2017). Aberrant functional connectivity in depression as an index of state and trait rumination. *Scientific Reports*, *7*(1), 1–12. https://doi.org/10.1038/s41598-017-02277-z

Rotaru, T. S., & Rusu, A. (2016). A Meta-Analysis for the Efficacy of Hypnotherapy in Alleviating PTSD Symptoms. *International Journal of Clinical and Experimental Hypnosis*, *64*(1), 116–136. https://doi.org/10.1080/00207144.2015.1099406

Saxe, R., & Kanwisher, N. (2003). People thinking about thinking people: The role of the temporo-parietal junction in “theory of mind.” *NeuroImage*, *19*(4), 1835–1842. https://doi.org/10.4324/9780203496190

Saxe, R., & Powell, L. J. (2006). It’s the Thought That Counts. *Psychological Science*, *17*(8), 692–699. https://doi.org/10.1111/J.1467-9280.2006.01768.X

Scalabrini, A., Vai, B., Poletti, S., Damiani, S., Mucci, C., Colombo, C., … Northoff, G. (2020). All roads lead to the default-mode network—global source of DMN abnormalities in major depressive disorder. *Neuropsychopharmacology*, *45*(12), 2058–2069. https://doi.org/10.1038/s41386-020-0785-x

Schneider, S., Christensen, A., Häußinger, F. B., Fallgatter, A. J., Giese, M. A., & Ehlis, A. C. (2014). Show me how you walk and I tell you how you feel - A functional near-infrared spectroscopy study on emotion perception based on human gait. *NeuroImage*, *85*, 380–390. https://doi.org/10.1016/j.neuroimage.2013.07.078

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., … Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*, *27*(9), 2349–2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Shah, P. J., Glabus, M. F., Goodwin, G. M., & Ebmeier, K. P. (2002). Chronic, treatment-resistant depression and right fronto-striatal atrophy. *British Journal of Psychiatry*, *180*(5), 434–440. https://doi.org/10.1192/bjp.180.5.434

Sheline, Y. I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., … Raichle, M. E. (2009). The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(6), 1942–1947. https://doi.org/10.1073/pnas.0812686106

Shih, M., Yang, Y. H., & Koo, M. (2009). A Meta-analysis of hypnosis in the treatment of depressive symptoms: A brief communication. *International Journal of Clinical and Experimental Hypnosis*, *57*(4), 431–442. https://doi.org/10.1080/00207140903099039

Sonuga-Barke, E. J., & Castellanos, F. X. (2007). Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. *Neuroscience & Biobehavioral Reviews*, *31*(7), 977–986.

Spiegel, D., & Moore, R. (1997). Imagery and hypnosis in the treatment of cancer patients. *Oncology-Huntington*, *11*(8), 1179–1188.

Straub, J., Metzger, C. D., Plener, P. L., Koelch, M. G., Groen, G., & Abler, B. (2017). Successful group psychotherapy of depression in adolescents alters fronto-limbic resting-state connectivity. *Journal of Affective Disorders*, *209*, 135–139. https://doi.org/10.1016/j.jad.2016.11.024

Surguladze, S. A., Senior, C., Young, A. W., Brébion, G., Travis, M. J., & Phillips, M. L. (2004). Recognition Accuracy and Response Bias to Happy and Sad Facial Expressions in Patients with Major Depression. *Neuropsychology*, *18*(2), 212–218. https://doi.org/10.1037/0894-4105.18.2.212

Suslow, T., Dannlowski, U., Lalee-mentzel, J., Donges, U., Arolt, V., & Kersting, A. (2004). Spatial processing of facial emotion in patients with unipolar depression : a longitudinal study. *Journal of Affective Disorders*, *83*(1), 59–63. https://doi.org/10.1016/j.jad.2004.03.003

Takahashi, T., Yücel, M., Lorenzetti, V., Walterfang, M., Kawasaki, Y., Whittle, S., … Allen, N. B. (2010). An MRI study of the superior temporal subregions in patients with current and past major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *34*(1), 98–103. https://doi.org/10.1016/j.pnpbp.2009.10.005

Teismann, T., Willutzki, U., Michalak, J., & Schulte, D. (2008). Bedeutung von Rumination und Ablenkung für den Therapieerfolg depressiver Patienten. *Verhaltenstherapie*, *18*(4), 215–222. https://doi.org/10.1159/000165687

Thom, J., Kuhnert, R., Born, S., & Hapke, U. (2017). 12-Monats-Prävalenz der selberichteten ärtzlich diagnostizierten Depression in Deutschland. *Journal of Health Monitoring*, *2*(3), 72–80. https://doi.org/10.17886/RKI-GBE-2017-057

Treatment Target: Depression. (2022). Society of Clinical Psychology. Retrieved April 10, 2023, from https://div12.org/diagnosis/depression/

Valentine, K. E., Milling, L. S., Clark, L. J., & Moriarty, C. L. (2019). The Efficacy of Hypnosis as a Treatment for Anxiety: A Meta-Analysis. *International Journal of Clinical and Experimental Hypnosis*, *67*(3), 336–363. https://doi.org/https://doi.org/10.1080/00207144.2019.1613863

Vander Wyk, B. C., Hudac, C. M., Carter, E. J., Sobel, D. M., & Pelphrey, K. A. (2009). Action Understanding in the Superior Temporal Sulcus Region. *Psychological Science*, *20*(6), 771–777. https://doi.org/http://doi.org/10.1111/j.1467-9280.2009.02359.x

Vanhaudenhuyse, A, Laureys, S., & Faymonville, M. (2014). Neurophysiology of hypnosis. *Clinical Neurophysiology*, *44*(4), 343–353. https://doi.org/10.1016/j.neucli.2013.09.006

Vanhaudenhuyse, Audrey, Noirhomme, Q., Tshibanda, L. J., Bruno, M.-A., Boveroux, P., Schnakers, C., … Boly, M. (2010). Default network connectivity refelcts the level of consciousness in non-communicative brain-damaged patients. *Brain: A Journal of Neurology*, *133*(1), 161–171. https://doi.org/10.1093/brain/awp313

Whorwell, P. J. (2011). IBS: Hypnotherapy—a wasted resource? *Nature Reviews Gastroenterology & Hepatology*, *9*(1), 12–13. https://doi.org/10.1038/nrgastro.2011.235

Wilhelm-Goessling, C., Schweizer, C., Dürr, C., Fuhr, K., & Revenstorf, D. (2020). *Hypnotherapie bei Depressionen: Ein Manual für Psychotherapeuten*. (A. Batra & F. Hohagen, Eds.) (1st ed.). Stuttgart: Kohlhammer Verlag.

Williams, L. M. (2017). Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. *Depression and Anxiety*, *34*(1), 9–24. https://doi.org/10.1002/da.22556

Windholz, G. (1996). Hypnosis and inhibition as viewed by Heidenhain and Pavlov. *Integrative Physiological and Behavioral Science*, *31*(2), 155–162. https://doi.org/10.1007/BF02699787

Wium-Andersen, I. K., Vinberg, M., Kessing, L. V., & McIntyre, R. S. (2016). Personalized medicine in psychiatry. *Nordic Journal of Psychiatry*, *71*(1), 12–19. https://doi.org/10.1080/08039488.2016.1216163

Yan, C.-G., Chen, X., Li, L., Castellanos, F. X., Bai, T.-J., Bo, Q.-J., … Zang, Y.-F.

(2019). Reduced default mode network functional connectvity in patients with recurrent major depressive disorder. *Proceedings of the National Academy of Sciences*, *116*(18), 9078–9083.

Zhu, X., Wang, X., Xiao, J., Liao, J., Zhong, M., Wang, W., & Yao, S. (2012). Evidence of a Dissociation Pattern in Resting-State Default Mode Network Connectivity in First-Episode, Treatment-Naive Major Depression Patients. *Biological Psychiatry*, *71*(7), 611–617. https://doi.org/10.1016/j.biopsych.2011.10.035

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