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Effects and Mechanisms of Cognitive Control Training Combined with Transcranial Direct Current Stimulation in Subjective Cognitive Decline.

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Abbreviations

AD	Alzheimer’s disease
ANOVA	Analysis of variance
BDNF	Brain-derived neurotrophic factor
CC	Cognitive control
CDT	Clock-drawing test
CERAD-NAB	CERAD (Consortium to Establish a Registry for Alzheimer's Disease) Neuropsychology Assessment Battery
COMT	Catechol-O-methyltransferase
dlPFC	Dorsolateral prefrontal cortex
EHI	Edinburgh Handedness Inventory
GABA	Gamma-aminobutyric acid
GDS	Geriatric Depression Scale
IADL	Instrumental activities of daily living
LTD / LTP	Long-term depression / Long-term potentiation
M.I.N.I.	Mini-international Neuropsychiatric Interview
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
NIBS	Non-invasive brain stimulation
NMDA	N-methyl-D-aspartate
PANAS	Positive and Negative Affect Schedule
PASAT	Paced Auditory Serial Addition Task
SCD	Subjective cognitive decline
SCD-I	Subjective Cognitive Decline Initiative
SRQ	State Rumination Questionnaire
STAI	State-Trait Anxiety Inventory
STP	Self-Report on Task Performance
SWLS	Satisfaction With Life Scale
tDCS	Transcranial direct current stimulation
TMT A&B	Trail Making Test Parts A and B
v-2-back	Verbal 2-back task
WLT	Word-List Learning Test

1. Introduction

"I have lost myself, so to say." (Auguste Deter)

Memory is a fundamental facet of cognitive and social functioning. Recalling the past and contextualizing new experiences allows us to better navigate present and future, and form robust models of ourselves and our environments (Atkinson and Shiffrin, 1968).

Older age is inherently associated with a decline in memory and other aspects of cognitive performance. Various structural and functional alterations, including genetic predisposition, neuro- and psychophysiological mechanisms (e.g. slowed processing speed, decreased distraction control), may account for these changes (Cabeza et al., 2018). In view of current global demographic developments such as population aging, rising life expectancy and growing prevalence of dementia, efforts aimed at moderating cognitive decline are becoming increasingly relevant.

1.1. Subjective Cognitive Decline (SCD)

A growing number of elderly people seek medical help due to perceived cognitive changes that extend beyond that expected as part of normal aging. By formal testing, mild cognitive impairment (MCI) or dementia might be diagnosed, but in some individuals, examination can fail to reveal objective evidence of decline. The term subjective cognitive decline (SCD) has been recently coined to describe this condition, „*characterized by a self-perceived deterioration of cognitive abilities in the absence of objective deficits or depression (Jessen et al., 2014a)*" (Stoynova et al., 2019). Prevalence of SCD in healthy older adults is currently estimated at around 25% (Röhr et al., 2020) and associated with an overall increased mortality rate (Luck et al., 2015).

Multiple longitudinal studies have found that SCD represents a significant risk factor for the development of dementia, specifically Alzheimer's disease (AD) (Jessen et al., 2014b; Pike et al., 2022; Slot et al., 2019; X. T. Wang et al., 2021). Concomitant memory concerns show particular predictive value in this regard (Jessen et al., 2014b; van Harten et al., 2018). Compared to those without SCD, individuals with self-perceived memory deficits and related worries are twice as likely to develop dementia (Mitchell et al., 2014), while subjects with SCD but no associated worries do not experience higher conversion rates to AD (Wolfsgruber et al., 2016). In neurobiological terms, this notion is supported by studies revealing a quantitative association between typical AD biomarkers (amyloid β, tau protein) and the extent of subjective cognitive complaints (Amariglio et al., 2018; Miebach et al., 2019; Verfaillie et al., 2019; Wen et al., 2022). Furthermore, some neuroimaging studies show that individuals with SCD and related worries may experience similar brain volumetric changes to those found in early AD stages (Parker et al., 2022; Scheef et al., 2012).

Beside the strain of concerns, SCD substantially reduces quality of life and mental wellbeing (Mol et al., 2009; Pusswald et al., 2015; Roehr et al., 2017). Specifically, SCD is associated with less health-oriented life-style (Wei et al., 2019) and lower social participation (Rotenberg et al., 2020), which in turn may further impair cognitive resilience and healthy aging (Beard et al., 2016).

In summary, SCD is a highly prevalent condition and increasingly considered as a possible first clinical manifestation of AD in many cases (Jessen et al., 2014a). Thus, this condition holds promise for early interventional strategies (Fernández-Blázquez et al., 2016) and attracts growing attention of researchers and clinicians. Studies evaluating the efficacy of therapeutic interventions are still scarce (Smart et al., 2017). Nevertheless, the burden for people with SCD and the possible preventive potential regarding objective cognitive decline suggest the need for strategies to better understand and effectively address this complaint.

1.2. Cognitive Control (CC)

Cognitive control (CC) is a term used to describe the ability to align thoughts and actions with internal goals while processing information and stimuli in the most effective and value-congruent way (Miller, 2000; Niendam et al., 2012). There are many components involved in these complex processes. In particular, selective attention allocation plays an important role in planning, prioritizing and reaching a desired outcome (Mackie et al., 2013; Posner and Petersen, 1990). However, distracting stimuli and stress may impair performance and amplify rumination

(Gross and John, 2003). CC enables the discrimination between goal-relevant and disruptive stimuli and helps augmenting the former as well as ignoring the latter (Egner and Hirsch, 2005; Koechlin et al., 2003). For that purpose, the regulation of emotional appraisal and reaction is essential (Ochsner and Gross, 2005; Pessoa, 2008) and is facilitated among others by neglecting negative affect, disengagement from no longer relevant input and retention of non-task-based memories (Anderson and Green, 2001; Roiser et al., 2012). Through managing interfering events, emotions and thoughts, CC keeps one's actions aligned with personal goals but also allows for flexibility in behavior and cognition in the face of changing external conditions (Diamond, 2013; Goschke, 2003). Furthermore, CC is involved in the storage and manipulation of goal-related information while performing a task, thus contributing to a functional working memory, executive control and what can be described as intelligent behavior (Gazzaley et al., 2004; Miller, 2000).

1.2.1. The Role of the Dorsolateral Prefrontal Cortex (dlPFC)

The prefrontal cortex, one of the longest maturing and distinguishing brain regions in hominids (Semendeferi et al., 1997), is considered a major hub of CC (Coutlee and Huettel, 2012; Egner and Hirsch, 2005). More precisely, numerous neuroimaging studies have identified a key involvement of the dorsolateral prefrontal cortex (dlPFC) in executive control (Calkins et al., 2015), emotion regulation (Ochsner and Gross, 2005; Vanderhasselt et al., 2013), working memory (Barbey et al., 2013; Brunoni and Vanderhasselt, 2014) and decision-making processes (McGuire and Botvinick, 2010).

There is a particularly significant link between the dlPFC and the limbic system, a subcortical brain structure responsible for primary emotional processing and response (Roy et al., 2009; Siegle et al., 2007b). Although emphasis is often put on the top-down modulating role of the dlPFC over the amygdala (Ochsner et al., 2002; Phan et al., 2005), the interaction can be bidirectional. Dolcos and McCarthy showed that, when participants are presented with distractive negative stimuli, their memory performance decreases (Dolcos and McCarthy, 2006). Furthermore, activation in the amygdala is elevated, while the dlPFC shows reduced activity. Similarly, positive stimuli have been observed to increase prefrontal activity and task performance (Herrington et al., 2005).

Despite the scientific consensus on the importance of dlPFC in CC, the underlying intricate processes are not yet understood in detail (Duverne and Koechlin, 2017).

1.2.2. Deficient Cognitive Control in Psychiatric Disorders and SCD

The clinical significance of CC becomes evident when considering that, if impaired, it underlies numerous psychiatric conditions (Goschke, 2014; McTeague et al., 2017). Deficits in attention allocation, emotion regulation and working memory are linked to internalizing disorders such as anxiety (Hirsch and Mathews, 2012; Shi et al., 2019), depression (Grahek et al., 2018; Joormann and D'Avanzato, 2010) and posttraumatic stress disorder (Aupperle et al., 2012). As first postulated by Beck, biased information processing is fundamental to the occurrence and maintenance of depressive symptoms (Beck, 1967): Excessive emphasis is put on negative emotion and experiences, while attentional disengagement and removal from memory is significantly delayed (Beck, 2008). Elevated rumination and worry play a crucial role in anxiety disorders as well (McEvoy et al., 2013). The increased occupation with negative information, also termed negativity bias, is indicative of a deficient CC and impairs neuronal capacity for goal-oriented behavior (Fales et al., 2008). Of note, negativity bias is correlated with an increased frequency of stressful events (Snyder and Hankin, 2016). Higher levels of stress in turn further deplete neural resources through attention allocation to possible threats and thus weaken CC abilities (Koster et al., 2011), implying a complex reciprocal cause and effect (Van den Bergh et al., 2020). Imaging studies support the concept of reduced regulation via CC over emotion in depression by revealing increased activation of the amygdala and contrasting decreased activation of the dlPFC in this patient population (Groenewold et al., 2013; Siegle et al., 2007b). Furthermore, people with lesions of the dlPFC experience subsequent depressive symptoms at a significantly higher rate (Koenigs and Grafman, 2009).

Our cognitive capacities can not only be hampered in the context of disease, but also naturally decline with increasing age (Cabeza and Dennis, 2013). Although structural and functional changes of CC functions accompany healthy aging and are subject to variation (Raz et al., 2005), pathological deterioration may occur. A correlation for instance has been observed between impaired CC and an accelerated depletion of cognitive reserve in dementia (Dodich et al., 2017; Sendi et al., 2021).

Psychological models indicate that distractive thoughts, worries about failure in cognitive challenges and compensation strategies like cognitive reappraisal draw heavily on executive resources and impair performance (Eysenck et al., 2007). As described above, worries about perceived cognitive decline are a central characteristic of SCD. This *“increased occupation with concerns about memory impairment is linked with deficient cognitive control (CC), negatively biased self-related cognitive processes, and reduced efficiency of executive functioning (Plewnia et al., 2015b; [Stogmann et al., 2016]). Consistently, [neurophysiological findings suggest that] a major hub of the CC network, […] [the dlPFC,] shows compensatory activation in this condition (Erk et al., 2011).”* (Stoynova et al., 2019). Recently, Lu et al. found significant volumetric reduction, cortical thinning and decreased gyrification of the left dlPFC in SCD to MCI converters compared to healthy older adults (Hanna Lu et al., 2021), thus further highlighting the importance and interventional potential of this brain region in SCD.

“It is therefore conceivable that a consolidation of CC [through strengthening of the dlPFC] may reduce the burden of concerns and potentially represent a perspective to support resilience against memory decline.” (Stoynova et al., 2019).

1.2.3. Cognitive Control Training (PASAT)

Cognitive control training has proven to be an effective and accessible tool in the activation and strengthening of the dlPFC (Segrave et al., 2014; Siegle et al., 2007a). It is usually implemented through computerized repetitive tasks, which activate specific brain regions and potentially improve related cognitive functions such as emotion regulation or executive functioning.

A commonly used procedure is the adaptive Paced Auditory Serial Addition Task (PASAT) (Gronwall, 1977). Participants are continuously presented with auditory stimuli in the form of digits which they have to add up. Visual feedback on the correctness of the answer is given immediately, serving as a distractive stimulus provoking negative affect and thoughts. The presentation speed adapts according to individual performance, rendering the task slightly stressful and frustrating (Lejuez et al., 2003). The PASAT engages working memory, executive control, attention direction and adaptation abilities (Gonzalez et al., 2006) and has been shown to specifically activate the dlPFC (Brunoni and Vanderhasselt, 2014; Lazeron et al., 2003; Plewnia et al., 2015a).

When compared to healthy controls, baseline performance in the PASAT is poorer in individuals with deficient cognitive control, such as depressed patients (Jones et al., 2010). However, repetitive CC training with PASAT has been shown to strengthen executive control and emotion regulation by reducing rumination (Hoorelbeke et al., 2015; Vanderhasselt et al., 2015) and thus improve cognitive functioning overall (Siegle et al., 2007a). Especially when the task is adapted to the subjects' performance speed, it effectively mitigates depressive symptoms (Koster et al., 2017).

Of note, recent studies have revealed that the performance gains and benefits from CC training are greatest in older adults (Nguyen et al., 2019). Considering the naturally occurring decline in CC with aging (Braver et al., 2009), as well as the heighten deficits in those with SCD due to straining memory concerns (Elfgren et al., 2010), the PASAT holds promise to beneficially influence cognitive functioning or augment other possible therapeutic interventions for this condition.

1.3. Transcranial Direct Current Stimulation (tDCS)

In recent years there has been growing research interest in non-invasive brain stimulation (NIBS) as a tool for enhancement and modification of cognitive abilities (Duecker et al., 2014). In general, it is used to attune neuronal excitability and plasticity through methods such as transcranial magnetic stimulation and transcranial direct current stimulation (tDCS) (Ziemann et al., 2008). Although often applied to healthy subjects in research context, NIBS also shows promising potential as a complementary or alternative treatment for some neuropsychiatric diseases (Begemann et al., 2020).

1.3.1. Principles of Operation

TDCS is a safe and easily implementable intervention which temporarily modulates cortical activity (Nitsche et al., 2008). It operates by sending weak electrical currents through the scalp from an anodal to a cathodal electrode, thus changing the membrane potentials of neurons and the likelihood of occurrence of action potentials in the targeted area without tDCS generating action potentials itself (Nitsche and Paulus, 2000; Stagg and Nitsche, 2011). Anodal stimulation, by and large, is considered to induce neuronal hypopolarisation and enhance cortical excitability, while cathodal stimulation precipitates hyperpolarisation and reduces excitability (Brunoni et al., 2012; Nitsche and Paulus, 2000).

However, it is important to note, that some studies have shown reverse effects with anodal tDCS hampering excitability (Monte-Silva et al., 2010) and cathodal stimulation resulting in depolarization (Batsikadze et al., 2013). This may be explained by the spatial orientation of neurons in relation to the electrical current flow direction, since stimulation has different effects on the soma and the dendrite of the cell (Rahman et al., 2013). Membrane potentials of neurons close to the surface and those in deeper areas were observed to be influenced in opposite ways by tDCS (Creutzfeldt et al., 1962; Datta et al., 2008). Furthermore, a current directed perpendicularly to the neuron is more likely to have fluctuating effects as opposed to a current vector aligned with the neuron's orientation (Kabakov et al., 2012; Rahman et al., 2013).

Other hypothesized mechanisms of action of tDCS include changes in the network connectivity of the brain (Hunter et al., 2013) as well as alterations in hemodynamics of the stimulated region with anodal stimulation improving and cathodal stimulation reducing blood vessel perfusion (Nord et al., 2013; Stagg et al., 2013). Moreover, molecular findings indicate a complex interaction between tDCS and neurotransmitters. Anodal stimulation has been shown to decrease the levels of gamma-aminobutyric acid (GABA), a transmitter with primarily inhibitory action at receptors, and increase glutamate concentrations, a major excitatory neurotransmitter, whereas cathodal stimulation elicits inverse effects (Stagg et al., 2009). Further studies suggest that the character and extent of tDCS-induced outcomes depend on transmitter concentrations, such as dopamine (Plewnia et al., 2013) and GABA (S. Kim et al., 2014), and in addition seem to be facilitated by N-methyl-D-aspartate (NMDA) receptors (Nitsche et al., 2012).

Electrical stimulation has been applied since the very early stages of human civilization (Priori, 2003) and valuable insights have been gained from scientific research especially in the past century (Paulus and Opitz, 2013), however the exact underlying mechanisms of tDCS are yet to be fully comprehended.

1.3.2. Stimulation Parameters

In order to conduct tDCS stimulation, a direct current stimulator and a pair of electrodes are needed. In study settings, the size of the electrodes usually range between 25 – 35cm^2 and stimulation is administered for 20 – 25min with an intensity of 0,5 – 2mA (Brunoni et al., 2012; Nitsche et al., 2008). The electrodes are most commonly covered in little plate-shaped sponges, which were previously immersed in saline solution, in order to minimize skin resistance, since it significantly affects stimulation quality (Parazzini et al., 2014). Notably, the electrical current density is reduced by 50 percent during the passage of the head skin, skull and meninges (Rush and Driscoll, 1968).

If anodal stimulation is intended, the anode is placed over the targeted area and the cathode – over the reference site, while in cathodal stimulation the exact opposite positioning is required. As mentioned above, neuronal orientation relative to the current direction can influence tDCS outcomes. Accordingly, positioning both electrodes on the scalp may lead to opposing or interfering stimulation effects (Bikson et al., 2010; Nitsche et al., 2008). This can be prevented via extracephalic placement of the reference electrode, however the risk of suboptimal current distribution is then increased (DaSilva et al., 2011).

TDCS is particularly well-suited for research purposes since it can be reliably placebo-controlled: In sham conditions, the current is only applied for a few seconds, which leads to sensations identical to those in verum conditions, thus efficiently blinding participants without inducing stimulation effects (Gandiga et al., 2006).

Importantly, stimulation parameters differ greatly among different studies, resulting in varying results and impeded comparability (Berryhill and Martin, 2018; Krause and Kadosh, 2014). The efficacy of tDCS is for example influenced by current intensity and stimulation duration (Paulus, 2004), however the relationship often seems to be non-linear (Batsikadze et al., 2013; Nitsche and Paulus, 2000; Weller et al., 2020). The size of the stimulated area as well as whether the stimulation is concurrent with a performed task also play an important role (Benwell et al., 2015). Additional modifying factors for the after-effects of tDCS can be baseline neural excitability (Brunoni et al., 2012; Silvanto et al., 2008), medication (Woods et al., 2016), anatomical variations (J. H. Kim et al., 2014), gender (Chaieb et al., 2008), age (Saldanha et al., 2020) and nicotine intake (Thirugnanasambandam et al., 2011). It is therefore necessary to take into account possible moderating characteristics when designing a tDCS study and analysing its results (Horvath et al., 2014). To increase its interventional potential, the knowledge on optimal stimulation parameters and inter-individual response differences needs to be further expanded (Chase et al., 2020).

1.3.3. Safety and Adverse Effects

Following current guidelines (Antal et al., 2017), tDCS is a safe, well-tolerated form of neuromodulation (Brunoni et al., 2011). The most frequently observed side effects include tingling and itching sensations at the electrode site, which increase with higher intensities and fade away quickly after stimulation is ended (Fertonani et al., 2015). In rare cases, fatigue, headache, or nausea are reported, albeit transient. Administration of tDCS over consecutive days with lower intensities does not increase the risk of adverse events (Bikson et al., 2016a).

Although cognitive processes can be biased by tDCS, to date, no pathological neural alterations or lasting impairing cognitive changes have been observed (Iyer et al., 2005). In animal models, tDCS-induced brain lesions were detected only when stimulation intensities were amplified a hundredfold compared to those used on humans (Liebetanz et al., 2009; Nitsche et al., 2008).

1.3.4. Effects on Cognitive Control and dlPFC

In numerous previous experiments, tDCS has proven to ameliorate cognitive functioning in various ways (Kronberg et al., 2017; Wiegand et al., 2019). In particular, when applied to the dlPFC, it strengthens CC by enhancing executive functions (Hongliang Lu et al., 2021) and planning ability (Dockery et al., 2009), ameliorating emotion regulation and frustration tolerance (Feeser et al., 2014; Plewnia et al., 2015a), improving working memory (Hill et al., 2016; Ruf et al., 2017; Trumbo et al., 2016) and supporting multitasking capacity (Nelson et al., 2016). Anodal tDCS to the left dlPFC significantly reduces distractibility by negative information and feedback and can facilitate neuroplasticity and learning, presumably via support of prefrontal inhibitory control of threat-related limbic activation (Plewnia et al., 2015b) but also through augmentation of memory functions (Zwissler et al., 2014).

These promising effects are attained not only in healthy subjects (Miniussi et al., 2013), but also in patients suffering from neurological (Flöel, 2014) or psychiatric disorders (Kuo et al., 2014). Especially depressive symptoms appear to be significantly mitigated through anodal tDCS over the left dlPFC, since it moderates a possible source for this disease, namely negativity bias (Brunoni et al., 2014; Wolkenstein and Plewnia, 2013). This notion is supported by multiple studies, which show superiority of anodal tDCS to placebo (Kekic et al., 2016; Meron et al., 2015; Shiozawa et al., 2014) and, in some cases, similar impact when compared with pharmacotherapy (Brunoni et al., 2016). In contrast, cathodal stimulation has been shown to promote depression-like cognitive patterns even in the healthy (Wolkenstein et al., 2014). As a result, anodal tDCS to the left dlPFC is already being utilized in many countries as an off-label treatment option (Bikson et al., 2016b; Lefaucheur et al., 2017). Although in some studies the positive effects were shown to last for up to several months (Razza et al., 2021), long-term follow-ups are still scarce.

1.3.5. Use in Physiological and Pathological Aging

Naturally, tDCS and its potential impact on cognitive abilities have also gained scientific attention in the field of geriatric psychiatry. Recent works indicate that elderly subjects as well as patients with MCI and AD might benefit from focal modulation of brain activity by NIBS techniques (Gonsalvez et al., 2017; Siegert et al., 2021). Accordingly, comprehensive efforts are made to harness the neuroplasticity-enhancing effects of tDCS for tackling dementia- or age-related cognitive decline (Andrade et al., 2018; Woods et al., 2018).

Favorable results have already been yielded particularly in the state of MCI after anodal stimulation mainly to the left dlPFC, reflected in amelioration of domains such as processing speed, episodic verbal memory, planning ability, delayed recall, selective attention tasks and even cerebral glucose metabolism (Cruz Gonzalez et al., 2018; Murugaraja et al., 2017; Prehn and Flöel, 2015; Yun et al., 2016). Multisession anodal tDCS has also been observed to improve cognitive functions in AD like recognition memory (Ferrucci et al., 2008; Khedr et al., 2014) and affect pathological AD-related electroencephalogram activity (Marceglia et al., 2016). Of note, most studies in dementia research employ an electrical current intensity of 2 mA, as it induces significant cognitive changes more reliably than lower strengths (Lefaucheur, 2016; T. Wang et al., 2021).

As suggested by meta-analyses, stimulation after-effects are generally stronger in the presence of AD compared to MCI or physiological aging (Chu et al., 2021; Hsu et al., 2015; Inagawa et al., 2019). Nevertheless, the benefits of tDCS when applied to healthy older adults shouldn’t be disregarded, since this approach may possibly strengthen memory functions and slow down cognitive deterioration (Antonenko et al., 2018; Goldthorpe et al., 2020). As of yet, relatively few experiments have investigated the effects of tDCS on subjects with SCD, with some demonstrating positive modulation of memory processes in this condition as well (Manenti et al., 2017; Vaqué-Alcázar et al., 2021).

Despite all these promising results, evidence is still inconsistent due to the small number of studies with predominantly disparate and small samples as well as various outcome measures (Horne et al., 2021; Murugaraja et al., 2017; Nilsson et al., 2017). Robust randomized controlled trials would therefore be essential to examine the short- and long-term effects of tDCS on aging brains (Habich et al., 2020; Prehn and Flöel, 2015).

1.3.6. Combining tDCS with CC Training

As tDCS does not produce neuronal activity itself but merely modulates cortical excitability (Nitsche and Paulus, 2000), it has been shown that it specifically enhances already activated brain regions (Bikson and Rahman, 2013; Polanía et al., 2018). Consequently, stimulation outcomes strongly depend on its timing of administration in relation to undergoing cognitive processes (Martin et al., 2014; Weller et al., 2020). In support of this notion, research indicates that 'online' tDCS concurrent with the execution of a cognitive training task generates better training gains as compared to 'offline' tDCS applied right before task performance (Ohn et al., 2008; Segrave et al., 2014; Vicario et al., 2019). By way of example, when conducting the PASAT, the left dlPFC is activated in order to maintain focus despite distracting negative feedback and frustration. Administering tDCS over this brain area during the task further enhances the involved CC functions, which is then manifested in an overall better performance (Plewnia et al., 2015b; Wiegand et al., 2019).

Notably, similar observations have been made in elderly subjects with online stimulation facilitating more pronounced effects on cognition and memory than offline application (Hsu et al., 2015; Huo et al., 2018).

1.4. Study Aim and Hypothesis

As described above, *"we have previously shown that the enhancement of PFC activity by transcranial direct current stimulation (tDCS) can support CC reflected in reduced distractibility by negative information and feedback (Plewnia et al., 2015a). Moreover, neuronal reorganization and learning can be facilitated by concurrent excitability enhancing tDCS (Ruf et al., 2017). Based on this evidence a targeted intervention combining the neuroplasticity-enhancing effects of tDCS and CC circuit retraining holds promise to reduce the negatively biased self-perception of cognitive performance in SCD.*

We tested this notion in a randomized, single-blind, sham-controlled proof-of-principle study by applying 2mA active or sham tDCS with the anode over the left PFC and the cathode at the contralateral deltoid muscle during 12 sessions of CC training in participants with SCD. We hypothesized that this tDCS-enhanced

CC training will reduce the amount of concerns regarding memory impairment.“ (Stoynova et al., 2019). Secondary objectives were to test the efficacy of this intervention on performance outcomes in PASAT and transfer tasks, on quality of life and on rumination and anxiety levels.

Noteworthy, this rationale has not yet been applied to SCD, hence this study initially investigated the effects of CC training combined with tDCS in this condition and aimed to provide effect-size estimates for larger clinical studies.

2. Materials and Methods

2.1. Participants

This study was performed according to the research criteria proposed by the Subjective Cognitive Decline Initiative (SCD-I) Working Group (Jessen et al., 2014a).

Healthy subjects above the age of 60 years, who were experiencing memory related concerns, were recruited via radio and newspaper announcements. An initial telephone interview was conducted to assess basic eligibility criteria (see Table 1). If these were met, the volunteers were invited to a more thorough screening session comprising of various tests and questionnaires (see 2.2.). *“Exclusion criteria were age <60 years, left-handedness, objective cognitive impairment (CERAD-Plus neuropsychological battery >1.5 standard deviations below adjusted normal performance), current depression (Geriatric Depression Scale Score > 5) or other neurologic or psychiatric disorders (assessed by the Mini-International Neuropsychiatric Interview) (Jessen et al., 2014a).”* (Stoynova et al., 2019). The eligibility criteria are shown in detail in Table 2.

Table 1. Telephone interview assessing basic eligibility criteria before subjects were invited for a thorough screening session.

Question	Answer required for inclusion
Are you right-handed?	Yes
Do you feel like your memory has been declining in the past few months?	Yes
Does this worry you?	Yes
Have your relatives and friends also noticed a decline in your memory and are worrying about it?	No
Have you been diagnosed with dementia by a physician?	No

Do you have any diagnosed neurological or psychiatric disorders?	No
Have you had a depressive episode in the past few months?	No

Table 2. Eligibility criteria.

Inclusion criteria	**Exclusion criteria**
Age > 60 years	Age < 60 years
Right-handedness	Left-handedness
Subjective feeling of memory decline	Objective cognitive impairment (CERAD-NAB-Plus > 1.5 SD below adjusted normal performance)
Concerns about memory decline	Current depression (GDS > 5)
	Current active substance dependence or abuse
	Other psychiatric disorders (assessed by M.I.N.I.)
	Neurological disorders
	Epileptic seizures in the clinical history
	Metallic objects in the head region
	Legal guardianship

Abbreviations: CERAD-NAB (Consortium to Establish a Registry for Alzheimer's Disease - neuropsychological assessment battery), GDS (Geriatric Depression Scale), M.I.N.I. (Mini-international Neuropsychiatric Interview).

In total, 43 subjects were screened, of which 33 completed all training sessions. Two of them had to be excluded due to protocol violations and one due to development of cancer-related depression. In addition, the CERAD-Plus results of four subjects indicated presence of objective cognitive impairment (MCI), as assessed by an experienced psychiatrist, which lead to their exclusion as well. Overall, 26 participants were included in the statistical analysis.

The study was conducted in compliance with the Declaration of Helsinki as assessed by the Ethics Committee of the Medical Faculty of the University of Tuebingen (Nr. 158/2017BO2) and registered at Clinical-Trials.gov (Identifier: NCT03236454). After providing each participant with detailed information about the study, written informed consent was obtained. All subjects received financial compensation for their participation.

2.2. Study Design

In this randomized, sham-controlled study all participants underwent the same experimental protocol, but only half of them (n = 14) received anodal tDCS, whereas the other half (n = 12) received sham stimulation. The experiment consisted of a screening session, a pre-session, 12 training sessions, a post-session and a follow-up 3 months after completed training (see Figure 1).

During *screening* a series of neuropsychological and psychometric tests were conducted which examined the eligibility criteria (see Table 3). In particular, the CERAD-Plus, a widely used neuropsychological assessment battery proposed by the American ‘Consortium to Establish a Registry for Alzheimer’s Disease’ (Morris et al., 1989), was applied to screen the participants for objective cognitive impairment.

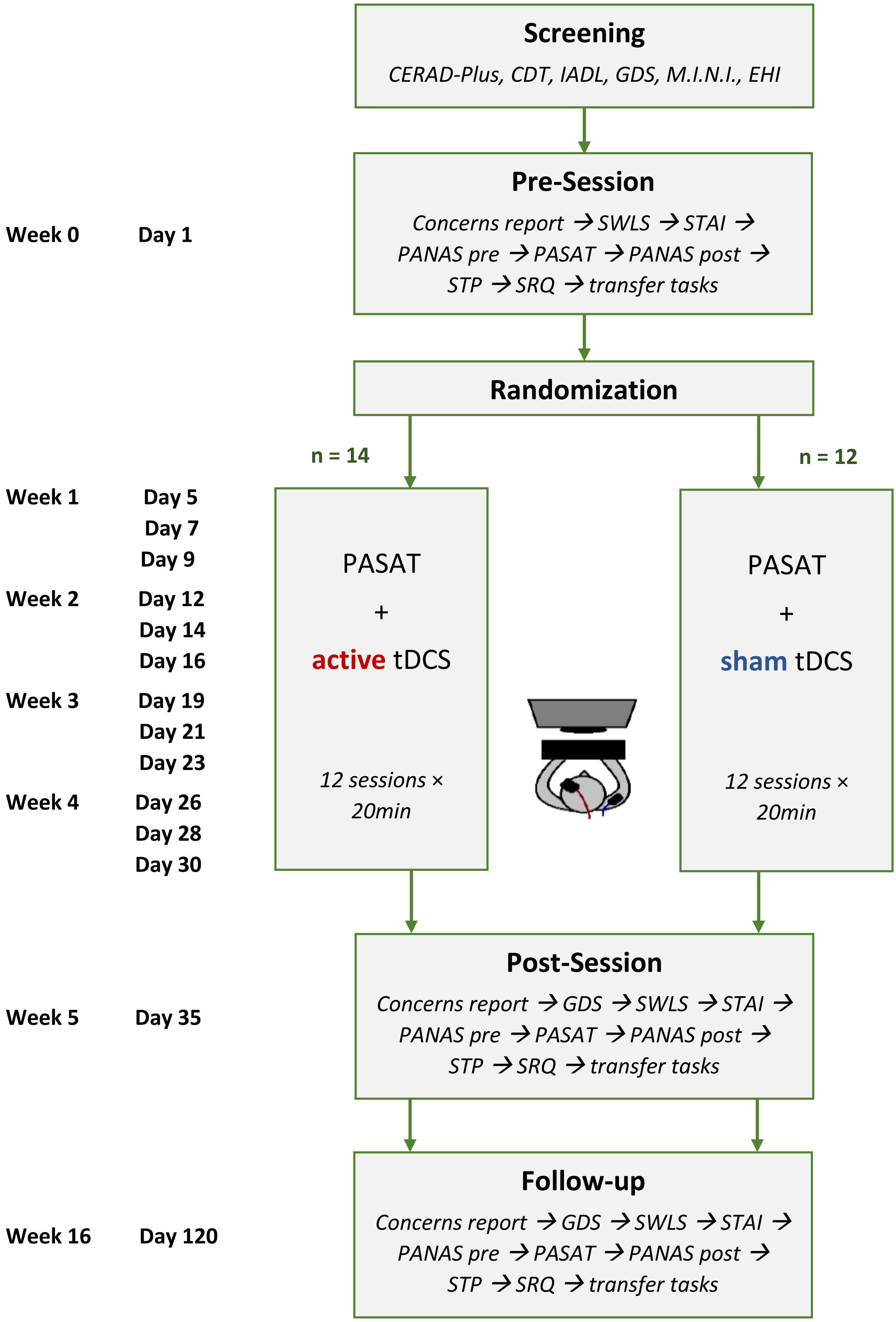

Figure 1. Study timeline. For detailed explanation of the abbreviated tests, see Table 3.

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Within the following *pre-session* subjects stated the onset as well as the amount of their memory concerns by means of a 10-point Likert-Scale (1 = minimal concerns and 10 = maximum of concerns). Health related quality of life was measured by the Satisfaction With Life Scale (SWLS), trait and state anxiety – through the State-Trait Anxiety Inventory (STAI). A baseline assessment of the training (PASAT) and transfer tasks (Verbal 2-back Task, Trail Making Test Parts A and B, Word-List Learning Test) was conducted. Furthermore, participants filled in the Positive and Negative Affect Schedule (PANAS) before and after the PASAT, by which mood changes through the test were measured. In addition, self-report on task performance (STP) and state rumination regarding the PASAT were assessed via questionnaires (see Table 3).

Table 3. Neuropsychological and psychometric tests used in this study. Indicated in parentheses below each test is the session in which it was administered. Evaluated German translation versions were used for all questionnaires.

Test	**Explanation of the test**
CERAD-NAB-Plus *(screening)*	The CERAD-NAB is a widely used neuropsychological assessment battery proposed by the American ‘Consortium to Establish a Registry for Alzheimer’s Disease’, which can detect even mild cognitive decline associated with AD (Morris et al., 1989). The battery consists of five subtests assessing different cognitive abilities: *Verbal Fluency; Modified Boston Naming Test; Mini-Mental State Examination; Word List Test; Constructional Praxis Test.* These five tests are administered in eight steps and eleven scores are calculated (including *Word List Intrusions, Word List Savings in %* and *Constructional Praxis Savings in %).* The CERAD-NAB-Plus consists of three additional subtests assessing executive functioning and mental speed: *Trail Making Test A and B; Phonemic Fluency (S-Words)* (Schmid et al., 2014). The final evaluation is implemented in a custom Excel application, whereby demographically adjusted z-scores (age, sex and years of education) are calculated and compared to a standard normal distribution (Berres et al., 2000).

	In this study we included participants who performed better than -1.5 standard deviations (SD) below the adjusted normal performance on the CERAD-NAB-Plus. The assessment was supervised by an experienced geriatric psychiatrist. Since the test was not embedded in a comprehensive AD diagnostic procedure, participants were not informed about their results.
CDT *(screening)*	The clock-drawing test (CDT) is a commonly used rapid screening tool that can detect executive cognitive dysfunction in the beginning stages of AD with high sensitivity and specificity (Shulman et al., 1986). The participants are asked to draw a clock with all its numbers as well as its hands pointing at the time ’10 past 11’. According to the Shulman system, the drawings are rated from 1 to 6, with 1 representing a perfect clock (healthy subject) and 6 – a complete misrepresentation of a clock (highest level of impairment). (Shulman et al., 1986). Only subjects with scores less than or equal to 3 were included in this study.
IADL *(screening)*	The self-report questionnaire ‘instrumental activities of daily living’ (IADL) assesses functional capacity via 8 complex skills (Lawton and Brody, 1969) and can be used as an effective additional screening for MCI and AD. (Lindbergh et al., 2016) From a total of 24 points, at least 22 for female and 18 for male participants were required in this study.
GDS *(screening, post, follow-up)*	The Geriatric Depression Scale (GDS) is a 30-item questionnaire specifically developed to assess depression in older adults (Yesavage et al., 1982). Scores above 5 points indicate presence of depression and lead to exclusion from this study.
M.I.N.I. *(screening)*	The Mini-International Neuropsychiatric Interview (M.I.N.I.) is a short, structured diagnostic interview assessing psychiatric disorders as defined by the DSM-IV and ICD-10 and is especially well suited for research purposes (Sheehan et al., 1998). Presence of any psychiatric disorder was an exclusion criteria in this study.
EHI *(screening)*	The Edinburgh Handedness Inventory (EHI) yields a quantitative evaluation of handedness (Oldfield, 1971). Subjects indicate their preferences regarding using their left or right hand in 10 daily activities (e.g., brushing teeth), after which a laterality index is calculated. For this study, values above +70 were considered right-handed.
SWLS *(pre, post, follow-up)*	The Satisfaction With Life Scale (SWLS) addresses global satisfaction with one’s life without emphasizing on specific life domains such as relationships or physical health (Pavot and Diener, 1993). Subjects answer the following 5 questions on a 7-point Likert scale:

	1. In most ways my life is close to my ideal. *2. The conditions of my life are excellent.* *3. I am satisfied with my life.* *4. So far, I have gotten the important things I want in life.* *5. If I could live my life over, I would change almost nothing.* Scores range between 5 and 35 points, a higher score indicating a higher life satisfaction.
STAI *(pre, post, follow-up)*	The State-Trait Anxiety Inventory (STAI) is a self-report questionnaire, which consists of 20 items assessing state anxiety (current anxiety) and 20 items assessing trait anxiety (general feelings of anxiety) (Spielberger, 1983). The questions are answered on a 4-point Likert scale. Higher scores indicate higher levels of anxiety.
PANAS *(pre, post, follow-up)*	The Positive and Negative Affect Schedule (PANAS) consists of 20 adjectives describing positive or negative affects (Crawford and Henry, 2004). Subjects are asked to rate how much each adjective represents their current emotional state on a 5-point Likert-scale. By administering this questionnaire immediately before (*PANAS 1*) and after (*PANAS 2*) the PASAT, we measured possible mood changes caused by the test.
STP *(pre, post, follow-up)*	The Self-Report on Task Performance is a 5-item questionnaire assessing the following domains on a 7-point Likert scale: general satisfaction with task performance, self-appraisal in comparison to other participants, frustration and anger levels evoked by the task (reverse scored), as well as concentration intensity during the task (Weller, 2016). The STP was administered after the PASAT and PANAS 2 at pre-, post- and follow-up session. Higher scores indicate a more positive self-evaluation.
SRQ *(pre, post, follow-up)*	The State Rumination Questionnaire (SRQ) consists of 10 items on a 5-point Likert scale measuring current amount of rumination in response to a specified preceding task (LeMoult et al., 2013). Subsequent to filling out the STP questionnaire, participants were asked to remain sitting quietly for another 5 minutes. After this rumination phase, the SRQ was handed out at pre-, post- and follow-up session. Higher scores indicate higher levels of rumination.

After pre-session the subjects were randomly assigned to one of the two study arms.

The *training sessions* started 4 days after the pre-testing and were administered over a period of 4 consecutive weeks (3 training sessions per week). In each session, 3 different participants took part in the training simultaneously. *"The PASAT was performed completely parallel to sham or active tDCS. […] Due to the use of multichannel tDCS, the operator was not blinded. During training and the self-rating of concerns, interaction with the experimenter was limited to a minimum. To test blinding efficacy after tDCS-enhanced training, the participants guessed if they received active or sham stimulation"* (Stoynova et al., 2019) after the last training session and rated possible adverse effects on a custom 5-point Likert-Scale. Furthermore, they stated whether they perceived improvement in PASAT performance due to possible stimulation.

A *post-session* and a *follow-up*, both identical to the pre-session, were conducted 4 days and 3 months after completed training, respectively.

Of note, tDCS was applied only during the 12 training sessions. Information regarding group allocation was given to the subjects only after they completed the whole experiment (including follow-up).

2.3. Transcranial Direct Current Stimulation

"A multichannel DC-Stimulator (NeuroConn GmbH, Germany) was used to apply 2mA tDCS via a pair of rubber electrodes (5 x 7 cm, 35cm^2)" (Stoynova et al., 2019). Each electrode was coated in adhesive conducting paste (Ten 20 conductive Neurodiagnostic Electrode Paste, Weaver and Company, Aurora, Colorado), whereas the skin below it was cleaned via 70 % ethanol and a peeling gel (Nuprep Skin Prep Gel, Weaver and Company, Aurora, Colorado). "*The anode was placed over the left PFC (F3 according to the 10-20 system) and the cathode on the right deltoid muscle"* (Stoynova et al., 2019) to avoid modulation of other brain regions (Nitsche et al., 2008). The impedance of the electrodes was kept below 15 kΩ.

Duration of the anodal tDCS was 20 minutes with a linear fade-in/fade-out phase of 5 seconds each. In the sham condition, the stimulation was applied for 40 seconds at the beginning, inducing a tingling sensation without any effects in the brain (Gandiga et al., 2006).

2.4. Cognitive Control Training (PASAT)

"CC training was performed with the computerized adaptive Paced Auditory Serial Addition Task (PASAT) (Gronwall, 1977). Subjects heard single digits and were instructed to add each new digit to the preceding one. Concurrent with the new digit, visual feedback was given on correct (green screen) and incorrect or missed (red screen) answers" (Stoynova et al., 2019) (see Figure 2). Participants were asked to resume adding the digits as quickly as possible when they have made a mistake. In order to minimize possible agility bias, the answers had to be typed on an adapted keyboard instead of via a mouse cursor. Tagging of numbers was prevented by participants using only one finger of their right hand (Weller et al., 2020). The inter-stimulus-interval between digit presentations, which was 3s at the start of each session, adapted according to task performance: It decreased by 0.1 second after four consecutive correct answers and increased by 0.1 second after four consecutive incorrect ones. *"By adapting task difficulty to the individual maximum and distractive performance feedback, the PASAT is well-suited for a CC training (Siegle et al., 2007a)"* (Stoynova et al., 2019).

Each PASAT session consisted of one exercise block with 11 supervised rounds, as well as three training blocks of 5 minutes each with unlimited number of rounds and 30s break between blocks. The total number of correct answers from each session, which was moderated by the inter-stimulus-interval between digit presentations, served as a performance indicator. Only results from the training blocks were included in analyses. Stimulation was started one minute before the PASAT and lasted during the complete training session (20 min).

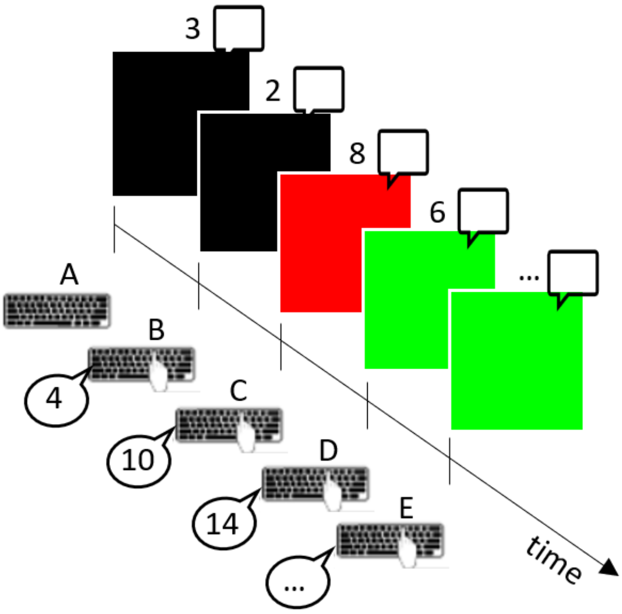


Figure 2. Paced Auditory Serial Addition Task (PASAT) illustration. Participants heard single digit numbers over headphones and were required to add the last to the second to last number (e.g., A+B, B+C, C+D). Concomitant with each new digit, feedback on correct (green screen) and wrong or missed answers (red screen) was given.

2.5. Transfer Tasks

2.5.1. Near-transfer Task (Verbal 2-back Task)

To test whether the training effects transferred to untrained tasks of similar complexity (near-transfer, lateral transfer) (Woodworth and Thorndike, 1901), a verbal 2-back task (v-2-back) which engages working memory and fluid intelligence (Jaeggi et al., 2010; Kirchner, 1958) was carried out at post and follow-up session. Participants were presented with a sequence of random single letters on a computer screen and had to press the space bar when the current letter matched the letter two presentations before (see Figure 3). The task consisted of one exercise block with 22 letters and two training blocks of 6 minutes each with 30s break in between. The outcome measure was calculated by subtracting the false responses (false presses and missed presses) from the standardized hit rate (60 correct presses and 184 correctly omitted presses, 244 correct responses in total) (Haatveit et al., 2010; Stanislaw and Todorov, 1999).

Both the v-2-back task and the PASAT were programmed and implemented in PsychoPy v1.82.02 (Peirce, 2009).

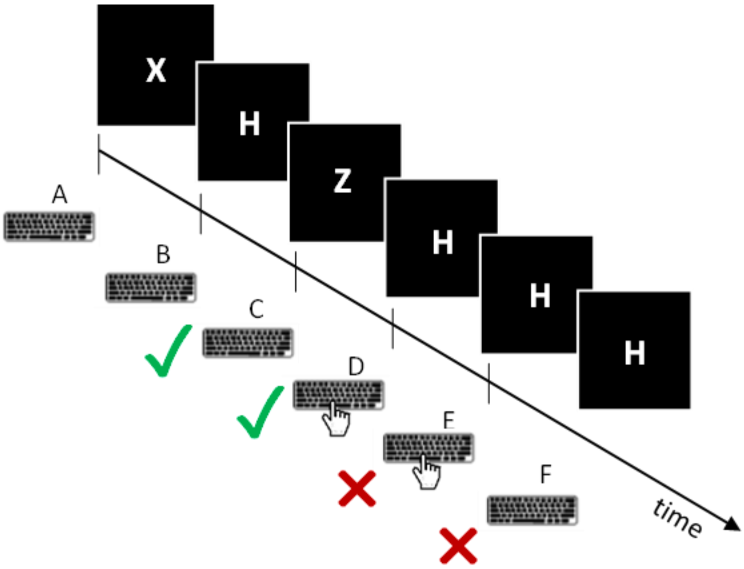


Figure 3. Verbal 2-back task illustration. Single letters are presented on a computer screen. The space bar has to be pressed when the current letter matches the letter two presentations before. C – correctly omitted press; D – correct press; E – false press; F – missed press.

2.5.2. Far-transfer Task (TMT A and B; WLT)

Furthermore, we examined possible far-transfer of learning (vertical transfer) from the trained task to tasks of dissimilar, higher complexity. For this, we used the Trail Making Test Parts A and B (TMT A&B) and the Word-List Learning Test (WLT). The baseline assessment was conducted at screening session, since both tests are part of the CERAD-NAB-Plus.

In the TMT participants are required to draw connecting lines between 25 consecutive circled targets as fast as possible on a sheet of paper without lifting the pen from the paper (R., 1958; Schmid et al., 2014). Part A evaluates cognitive processing speed and asks subjects to connect the numbers from 1 to 25 in ascending order. Part B evaluates executive functioning and includes numbers from 1 to 13 as well as letters from A to L, which have to be connected in alternating ascending order (1-A-2-B-3-C…). Errors are indicated immediately by the administrator and the subject is allowed to correct them during the test. The completion time in seconds serves as a performance indicator for both tests.

The WLT consists of three subparts assessing immediate and delayed memory and the ability to learn new non-associated verbal information: Participants learn 10 words shown on paper for 3 consecutive trials (Word List Memory); these have to be recalled at a later time (Word List Recall) and, finally, recognized among another 10 distractor words (Word List Recognition) (Morris et al., 1989). A different set of new words was compiled for each session (screening, post, follow-up).

The tests were conducted in the following order: WLT Memory, TMT A, TMT B, WLT Recall, WLT Recognition.

2.6. Outcome Measures

The change in amount of memory concerns was assessed as primary outcome measure in this study. Participants were asked to report the amount of their concerns regarding cognitive decline on a self-rate 10-point Likert-Scale (1 = minimal concerns and 10 = maximum of concerns) at the pre-, post- and follow-up sessions (see Figure 4). There was no option of “no concerns”, since only subjects with current memory concerns were included in this study.

Predefined and registered secondary outcome measures were group comparisons (active vs. sham tDCS) regarding changes in PASAT performance, performance in the near and far-transfer tasks (v-2-back, TMTA&B, WLT), as well as scores of PANAS, STAI, SRQ, SWLS, GDS and STP.

For each measure the pre-session outcomes were compared with the post-session and follow-up outcomes respectively.

Wie ausgeprägt sind die Sorgen um Ihr Gedächtnis? (1 gering – 10 sehr stark)

gering	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**sehr stark**

Figure 4. 10-point Likert-Scale assessing amount of memory concerns in German. Translation: How pronounced are your worries about your memory? (1 minor – 10 most intense)

2.7. Statistical Analysis

Statistical analyses were performed via the software programs SPSS Statistics for Microsoft Windows (version 24.0) (IBM Corp., 2016) and R for Windows (version 3.5.0) (R Core Team, 2018) including the package nlme (R Core Team, 2018b).

For all analyses only p-values less than 0.05 were considered statistically significant. The confidence interval was set to 95%. Shapiro-Wilk tests were applied to assess normality assumptions. Equality of variances was examined via Levene tests and sphericity, via Mauchly's test of sphericity. In cases of non-sphericity, Greenhouse-Geisser corrections were applied for $\varepsilon \leq 0.75$ and Huynh-Feldt corrections for $\varepsilon > 0.75$. Effect sizes are reported in the form of partial Eta-squared (η_p^2) for the effects and interactions of the analyses of Variance (ANOVA) and Cohen's d for the t-test comparisons. The performed t-tests were two-tailed.

2.7.1. Sample Characteristics

A chi-square test was used to assess group composition regarding gender. Other demographic data including age, years of education, EHI score, CERAD-NAB-Plus subtests scores, amount of memory concerns before training and duration of memory concerns were analyzed via independent t-tests. Baseline differences in task performance (PASAT and v-2-back) and questionnaires scores (SWLS, SRQ, STAI, GDS and STP) were also assessed through t-tests.

2.7.2. Memory concerns

To investigate the effects of tDCS on the amount of memory concerns, a two-way mixed ANOVA was used with *condition* (active tDCS, sham) as between-subject factor and *time* (pre-session, post-session, follow-up) as within-subject factor. In case of a significant interaction between these factors, post-hoc paired t-tests were applied to analyze the change in amount of memory concerns at post-session as well as follow-up relative to baseline for both groups separately. Between-group comparisons were then used to assess differences at each session.

2.7.3. PASAT performance

"To examine the effects of tDCS on across-session learning of the PASAT, a linear mixed-effect model was fitted with the number of correct responses [n_corr] as dependent variable, session, group, and baseline [n_corr_bs] as fixed effects. Random-intercept and random-slope were entered to account for unsystematic individual differences." (Stoynova et al., 2019). The pre-session performance served as a regression coefficient and the sham group performance as a reference for planned contrasts. This model was thus implemented via the formula: *n_corr ~ group x session + n_corr_bs w*ith *~ 1 + session | subject* for random effects. Compared to a conventional ANOVA-framework, it allows for detailed assessment of training gains by forming learning slopes over the course of all sessions with respect to baseline performance while also accounting for systematic and unsystematic variation (Ruf et al., 2017).

2.7.4. Transfer Tasks, Affective States, Anxiety, Rumination and Other Questionnaires

Following secondary outcome measures were analyzed through repeated measures ANOVAs with *condition* as between-subject factor, *time* (pre-session, post-session, follow-up) as within-subject factor and *condition* x *time* interaction: changes in transfer tasks performance (v-2-back, WLT, TMTA&B), STAI, SRQ, SWLS, GDS and STP scores. In case of significant results, post-hoc paired and independent t-tests were applied.

To evaluate mood changes caused by the PASAT and possible modulation of tDCS, PANAS scores from before and after the task (PANAS 1 and 2) were also assessed via repeated measures ANOVA with main effects *condition* (active tDCS, sham) and *time* (PANAS 1 and PANAS 2), as well as *condition* x *time* interaction. Pre-, post- and follow-up sessions were investigated one by one in regard to these effects. The PANAS scores were divided into positive and negative affects and explored separately.

2.7.5. Correlations

Possible correlations between variables were analyzed with Pearson correlations (r). Spearman correlation coefficients (r_s) were calculated in case of non-normal distribution of the data or nonlinear relationships between variables.

2.7.6. Blinding Efficacy and Adverse Effects

A chi-square test was applied to examine blinding of group allocation. Reported adverse effects of tDCS were assessed item wise via independent t-tests with *condition* as between-subject factor.

3. Results

3.1. Sample Characteristics

In total, 26 subjects (14 anodal, 12 sham) completed all measurements sessions and were included in the statistical analysis. The two study groups were compared regarding their demographic characteristics, baseline performance in the study tasks and scores in the presented questionnaires at pre-session (see Table 4).

Table 4. "Sample characteristics and baseline comparisons between groups.
A. The table shows mean values with standard errors in parentheses [for demographic data, task performance and questionnaires scores].
B. The table shows mean values with standard errors in parentheses for each CERAD-Plus variable for each group." (Stoynova et al., 2019)

A.

Measure	**sham**	**anodal**	**t/χ^2**	**p-value**
Gender (female/male)	8/4	6/8	χ^2 = 1.47	0.225
Age	69.00 (1.78)	68.93 (1.64)	t(24) = 0.030	0.977
Education (years)	14.58 (0.78)	16.18 (0.76)	t(24) = -1.454	0.159
EHI	92.22 (3.58)	85.60 (5.04)	t(24) = 1.038	0.310
Amount of memory concerns	4.92 (0.60)	5.36 (0.53)	t(24) = -0.554	0.585
Duration of memory concerns (years)	3.83 (0.63)	3.25 (0.49)	t(24) = 0.741	0.466
PASAT performance	158.83 (9.52)	170.07 (11.68)	t(24) = -0.729	0.473
v-2-back performance	206.58 (7.63)	208.21 (5.32)	t(24) = -0.179	0.859
STAI trait	32.08 (2.07)	40.64 (1.84)	t(24) = -3.100	0.005
STAI state	34.75 (2.22)	39.79 (2.94)	t(24) = -1.331	0.196
SRQ	24.50 (1.62)	24.57 (1.51)	t(24) = -0.032	0.975
SWLS	28.67 (1.35)	27.14 (1.32)	t(24) = 0.803	0.430
GDS	2.00 (0.33)	2.29 (0.35)	t(24) = -0.586	0.563
STP	19.00 (1.81)	20.86 (0.79)	t(24) = -0.988	0.333

B.

CERAD-Plus Variable	sham	anodal	t-test	p-value
Verbal Fluency	22.50 (1.29)	23.29 (1.76)	t(24) = -0.349	0.730
Boston Naming Test	14.67 (0.19)	14.71 (0.16)	t(24) = -0.192	0.849
Mini-Mental State Examination	29.58 (0.23)	29.14 (0.18)	t(24) = 1.543	0.136
Word List – Total	24.58 (0.75)	23.14 (0.82)	t(24) = 1.279	0.213
Word List – Intrusions	1.42 (0.40)	1.14 (0.31)	t(24) = 0.549	0.588
Word List – Recall	8.25 (0.31)	8.29 (0.27)	t(24) = -0.089	0.930
Word List – Savings	88.50% (2.77%)	89.57% (2.70%)	t(24) = -0.276	0.785
Word List – Recognition	98.75% (0.65%)	99.29% (0.49%)	t(24) = -0.670	0.509
Constructional Praxis	10.50 (0.20)	10.29 (0.24)	t(24) = 0.670	0.509
Constructional Praxis – Recall	11.17 (0.51)	11.71 (0.46)	t(24) = -0.801	0.431
Constructional Praxis – Savings	94.58% (2.16%)	99.21% (2.81%)	t(24) = -1.275	0.215
Phonemic Fluency	15.67 (1.25)	13.14 (1.32)	t(24) = 1.375	0.182
Trail Making Test, Part A	43.92 (5.83)	40.79 (3.73)	t(24) = 0.465	0.646
Trail Making Test, Part B	84.42 (8.01)	119.00 (34.91)	t(24) = -0.898	0.378

The table is reprinted from Stoynova et al. (2019).

The average age of participants was M = 68.96 years (SD = 6.02) and 54% (14 subjects) were female. The mean education duration was M = 15.44 years (SD = 2.85). All participants were right-handed with an average laterality index of M = 88.65 (SD = 16.62) as assessed by the EHI. The amount of memory concerns before training on a 10-point Likert-scale (from 1 = minimal concerns to 10 = maximum of concerns) averaged at M = 5.15 (SD = 1.99). The duration of these concerns prior to the experiment was rated at M = 3.52 years (SD = 1.98) on average. Life satisfaction as assessed by the SWLS (ranging from 5 = extremely unsatisfied to 35 = extremely satisfied) was above average for both groups with M = 27.85 (SD = 4.79).

No significant differences in demographic data, baseline task performance (see Table 4A) and cognitive abilities as assessed by the CERAD-NAB-Plus (see

Table 4B) were found between both groups. From the administered questionnaires only the scores from STAI trait differed significantly between groups (t(24) = -3.100; p = 0.005).

3.2. Effects of tDCS on Memory Concerns

Participants quantified their memory concerns on a 10-point Likert-scale at pre-, post- and follow-up sessions. The change in amount of memory concerns served as a primary outcome measure in this study.

“A mixed two-way ANOVA [see Figure 5] with between-subject factor ‘stimulation condition’ (active tDCS, sham) and within-subject factor ‘time’ (pre-training, post-training, follow-up) demonstrated a significant interaction between these factors with a large effect size (F(1,24) = 10.088, p = 0.004, η_p^2= 0.296). Post-hoc t-tests indicated a reduction of memory concerns after tDCS-enhanced CC training (t(13) = 3.816, p = 0.002, d = 1.02) and after three months follow-up (t(13) = 2.662, p = 0.02, d = 0.7). No change was found with sham stimulation [t(11) = -1.059, p = 0.312, d = 0.31 after training and t(11) = -0.272, p = 0.791, d = 0.08 after follow-up]. Between-group comparisons confirmed that at the pre-session, the amount of memory concerns was not different in both groups (t(24) = -0.554, p = 0.585, d = 0.22), but that tDCS-enhanced CC training resulted in less memory concerns than the similar training with sham stimulation (t(24) = 2.543, p = 0.018, d = 1.0). However, at follow-up this difference was no longer significant (t(24) = 1.350, p = 0.190, d = 0.054) [see Table 5].”(Stoynova et al., 2019).

In addition, at the end of post-session subjects were asked whether they perceived an improvement in their memory through the training sessions. Answers were rated on a 3-point Likert-scale: 0 = no improvement, 1 = slight improvement, 2 = distinct improvement. On average, participants indicated slight to no perceived improvement (M = 0.42, SD = 0.504). A Kruskal-Wallis test found no significant difference between groups ($\chi^2(1) = 0.707$, p = 0.400).

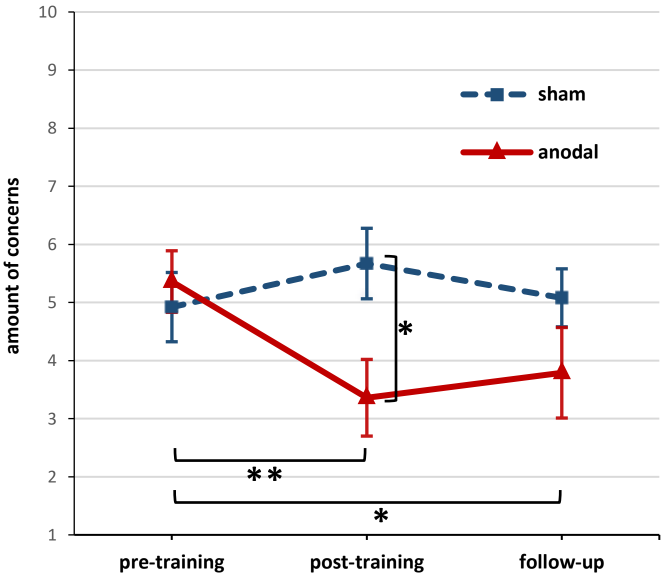


*Figure 5. „Amount of memory concerns before and after tDCS-enhanced cognitive training. ** p < 0.01, * p < 0.05“* (Stoynova et al., 2019). *Standard bars represent standard error of the mean. Anodal tDCS significantly reduces the amount of memory concerns compared to sham treatment.*
The figure is reprinted from Stoynova et al. (2019).

Table 5. "Reported amount of memory concerns. The table shows mean values with standard errors in parentheses for each session and group.” (Stoynova et al., 2019)

Measure	**sham**	**anodal**	**t-test**	**p-value**
Memory concerns at pre-session	4.92 (0.60)	5.36 (0.53)	t(24) = -0.554	0.585
Memory concerns at post-session	5.67 (0.61)	3.36 (0.66)	t(24) = 2.543	0.018
Memory concerns at follow-up	5.08 (0.50)	3.79 (0.78)	t(24) = 1.350	0.190

The table is reprinted from Stoynova et al. (2019).

3.3. Effects of tDCS on PASAT Performance

“[The linear mixed-effect] model showed that PASAT performance was improved by training (t(280) = 7.47, p < 0.0001, SE = 0.869). However, active tDCS did not enhance performance increase compared to sham treatment (t(280) = -0.57, p = 0.569, SE = 1.184).”(Stoynova et al., 2019). The mean numbers of correct trials

for each session are shown in Table 6, as well as in Figure 6 in the shape of learning curves.

Table 6. “PASAT performance. The table shows mean number of correct trials of each group for each session with standard errors in parentheses.” (Stoynova et al., 2019)

Session	**sham**	**anodal**	**t-test**	**p-value**
1 (pre-session)	158.83 (9.52)	170.07 (11.68)	t(24) = -0.729	0.473
2	185.09 (12.64)	195.29 (13.78)	t(23) = -0.531	0.600
3	197.67 (11.03)	206.29 (13.97)	t(24) = -0.473	0.641
4	213.50 (9.31)	214.46 (15.51)	t(24) = -0.052	0.959
5	223.91 (10.11)	225.29 (14.24)	t(23) = -0.075	0.941
6	229.42 (9.58)	237.00 (14.00)	t(23) = -0.432	0.670
7	235.92 (9.23)	240.50 (12.48)	t(24) = -0.287	0.777
8	244.00 (8.45)	247.64 (12.42)	t(24) = -0.234	0.817
9	8.474 (29.36)	253.36 (12.44)	t(24) = -0.237	0.815
10	249.00 (7.99)	253.36 (11.11)	t(24) = -0.309	0.760
11	254.50 (8.01)	264.77 (8.71)	t(24) = -0.864	0.397
12	257.25 (7.89)	259.71 (9.24)	t(23) = -0.199	0.844
13	258.08 (8.53)	259.50 (10.46)	t(24) = -0.103	0.919
14 (post-session)	253.58 (7.74)	255.07 (11.15)	t(24) = -0.106	0.916
15 (follow-up)	249.50 (10.18)	256.08 (11.57)	t(23) = -0.424	0.676

The table is reprinted from Stoynova et al. (2019).

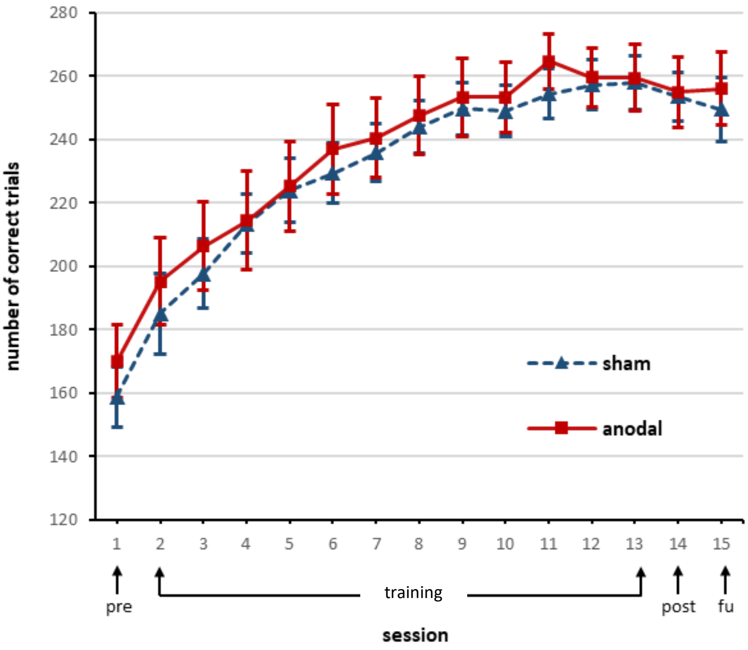


Figure 6. "PASAT performance – the mean number of correct trials of each group is shown for each session; abbreviations: fu, follow-up" (Stoynova et al., 2019). *Standard bars represent standard error of the mean. Performance increased over time with no significant differences between groups.*
The figure is reprinted from Stoynova et al. (2019).

At post-session participants were asked to rate their learning success in the PASAT on an 11-point Likert-scale (from 0 = no learning success to 10 = biggest possible learning success). At large, the perceived learning success was below moderate (M = 3.77, SD = 2.438) with no significant difference between groups (t(24) = -1.006, p = 0.325, d = 0.4).

Furthermore, we inquired whether subjects thought that possible tDCS stimulation had improved their performance in the PASAT. This was assessed via a 5-point Likert-scale (1 = not at all and 5 = extremely). The results indicated low to moderate perceived tDCS-induced performance enhancement (M = 2.04, SD = 1.038). No significant difference between groups was reached in the Kruskal-Wallis test ($\chi^2(1) = 0.747$, p = 0.387).

3.4. Effects of tDCS on Transfer Tasks

3.4.1. Near transfer (v-2-back)

The results of the two-way mixed ANOVA on the v-2-back task showed that there was no significant main effect either of *condition* ($F(1,24) < 0.001$, $p = 0.991$, $\eta_p^2 < 0.001$) or of *time* ($F(2,48) = 1.52$, $p = 0.229$, $\eta_p^2 = 0.6$) on performance outcome overall. Similarly, no significant interaction was found between *condition* x *time* in terms of correct responses ($F(2,48) = 0.355$, $p = 0.703$, $\eta_p^2 = 0.015$). Figure 7 illustrates these results.

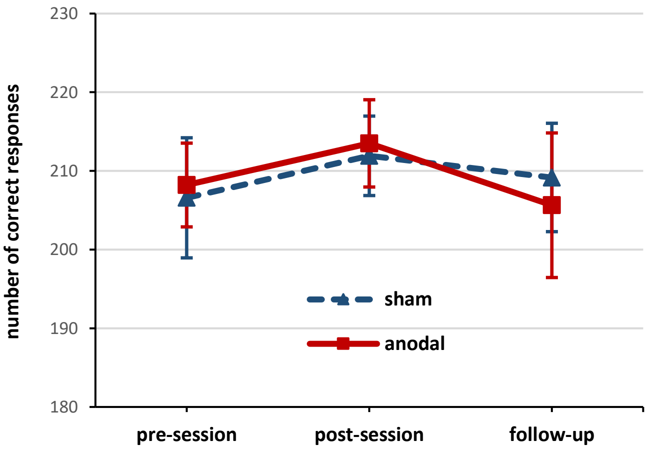


Figure 7. Verbal 2-back task performance – the mean of correct responses (correct presses and correctly omitted presses) of each group is shown for each session. Standard bars represent standard error of the mean. The maximum of possible correct responses was 244. No performance increase or significant differences between groups can be found.

3.4.2. Far transfer (TMT, WLT)

Regarding the results of the TMT A, the two-way mixed ANOVA with Greenhouse-Geisser corrections showed no statistical significance for main effects *condition* ($F(1,24) = 0.376$, $p = 0.545$, $\eta_p^2 = 0.015$), *time* ($F(1.192, 28.612) = 1.022$, $p = 0.335$, $\eta_p^2 = 0.041$), and the interaction *condition* x *time* ($F(1.192, 28.612) = 0.452$, $p = 0.541$, $\eta_p^2 = 0.018$) (see Figure 8A).

The ANOVA of the TMT B also did not reveal statistical significance for any of the main effects: *condition* ($F(1,24) = 0.055$, $p = 0.817$, $\eta_p^2 = 0.002$), *time* ($F(2,48) =$

1.629, p = 0.207, $\eta_p^2 = 0.064$) and *condition* x *time* interaction (F(2,48) = 1.041, p = 0.361, $\eta_p^2 = 0.042$) (see Figure 8B).

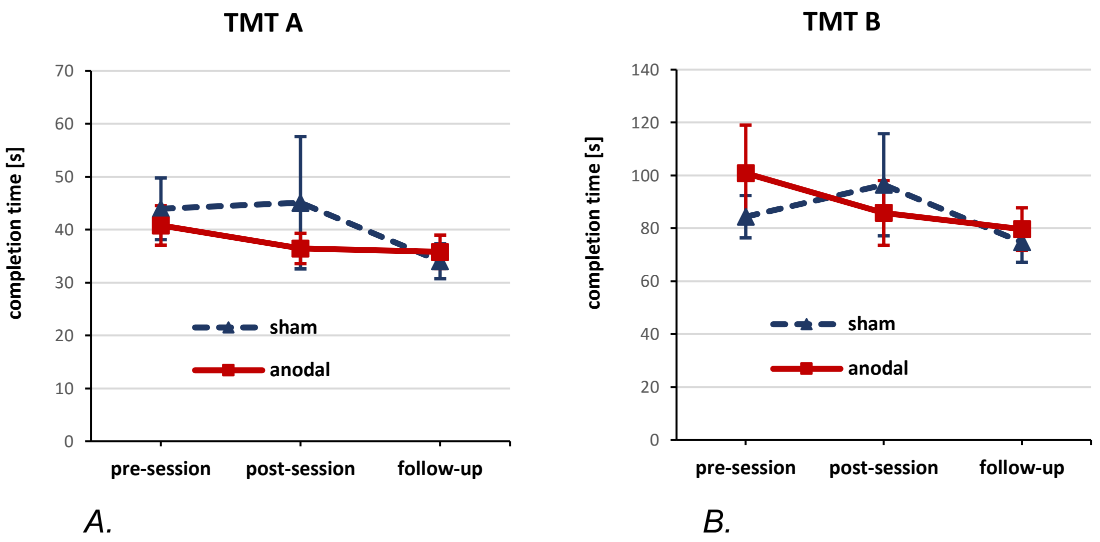
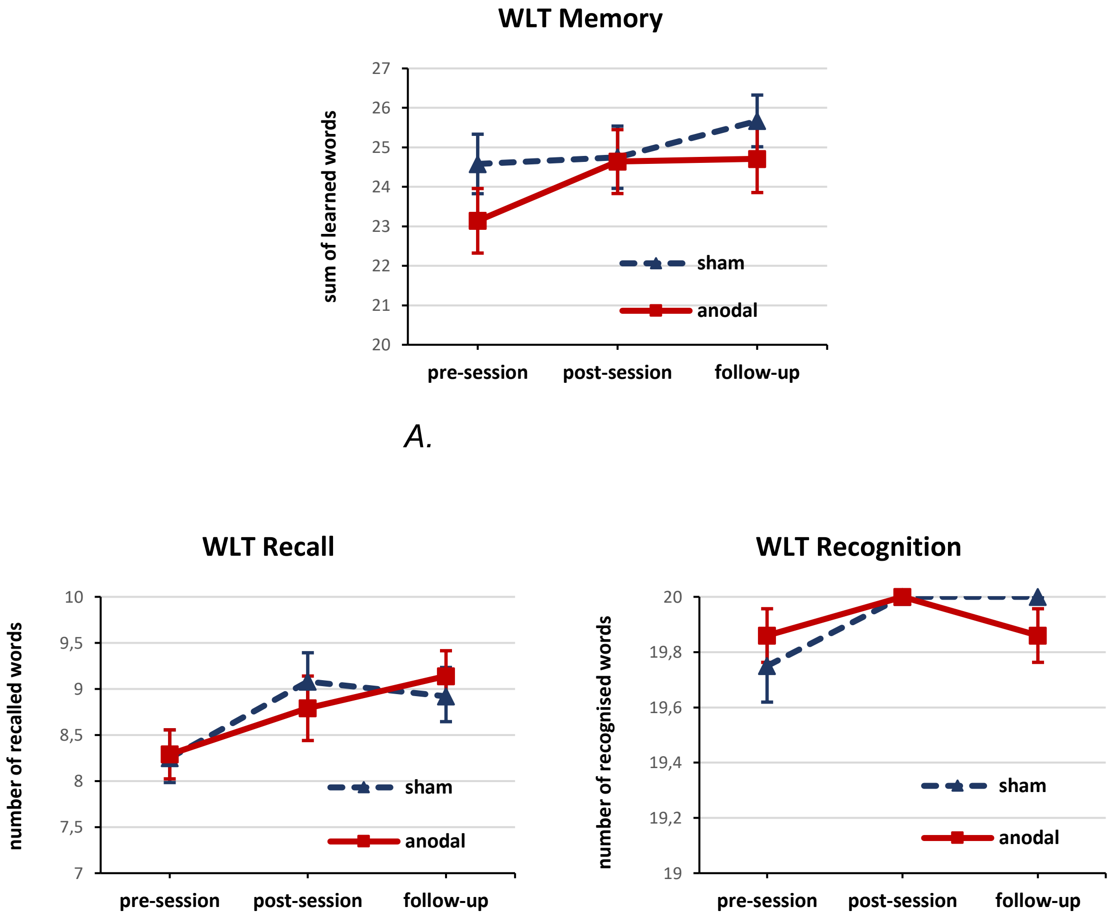


Figure 8. Trail Making Test (TMT) – the mean completion time in seconds of each group is shown for each session. Standard bars represent standard error of the mean. No performance increase or significant differences between groups can be found.
A. Results for Trail Making Test A.
B. Results for Trail Making Test B.

The three subparts of the WLT were analyzed separately and showed similar results in the applied two-way mixed ANOVAs (see Figure 9). Huynh-Feldt corrections are reported for WLT Recognition due to non-sphericity. Main effect *condition* did not reach statistical significance in WLT Memory (F(1,24) = 0.722, p = 0.404, $\eta_p^2 = 0.029$), WLT Recall (F(1,24) = 0.001, p = 0.974, $\eta_p^2 < 0.001$) or WLT Recognition (F(1,24) = 0.028, p = 0.869, $\eta_p^2 = 0.001$). Statistical significance was however found for main effect *time* in WLT Memory (F(2,48) = 3.976, p = 0.025, $\eta_p^2 = 0.142$), WLT Recall (F2,48) = 8.392, p = 0.001, $\eta_p^2 = 0.259$) and WLT Recognition (F(1.792, 43.014) = 3.706, p = 0.037, $\eta_p^2 = 0.134$). There was no statistically significant interaction between *condition* x *time* regarding outcomes in WLT Memory (F(2,48) = 1.005, p = 0.374, $\eta_p^2 = 0.04$), WLT Recall (F(2,48) = 0.856, p = 0.431, $\eta_p^2 = 0.034$) or WLT Recognition (F(1.792, 43.014) = 0.113, p =

0.240, $\eta_p^2 = 0.058$). In summary, these results reveal improvement in the WLT over time but no tDCS-related performance gains.



A.

B.

C.

Figure 9. Word List Learning Test (WLT) – the mean number of words of each group is shown for each session. Standard bars represent standard error of the mean. Performance increased over time with no significant differences between groups.
A. Shown is the sum of words learned after three trials of a 10-word list presentation. The maximum score is 30 words.
B. Shown is the number of correctly recalled words after a delay of approximately 10 minutes. The maximum score is 10 words.
C. Shown is the number of correctly recognized words among 10 other distractor words. The maximum score is 10 words.

3.5. Affective States

Mean PANAS scores for positive and negative affect in the respective sessions are shown in Table 7. The repeated measures ANOVAs showed no statistical significance for main effect *condition* for positive or negative affect in either of the sessions. In contrast, main effect *time* was significant for both affects in all sessions. Positive affect increased in pre- and post-session and decreased at follow-up after the PASAT, while negative affect increased in all sessions after completion of the task. No statistically significant interactions between *condition* x *time* were found for either of the examined sessions. Detailed statistical results are presented in Table 8.

Table 7. PANAS scores. The table shows mean positive and negative affect scores of each group for each session with standard deviations in parentheses. PANAS 1 was administered right before the PASAT, PANAS 2 – immediately after the PASAT. Scores range from 10 = lowest positive/negative mood to 50 = highest positive/negative mood.

		Sham		**anodal**	
Session	**Affect**	**PANAS 1**	**PANAS 2**	**PANAS 1**	**PANAS 2**
Pre	**positive**	21.42 (7.342)	26.42 (5.485)	22.36 (7.652)	27.57 (7.633)
	negative	10.75 (1.545)	21.0 (10.018)	12.43 (4.536)	17.21 (8.368)
Post	**positive**	22.92 (7.204)	26.75 (8.281)	25.36 (9.204)	27.07 (6.944)
	negative	11.25 (1.357)	17.58 (8.051)	11.21 (1.528)	14.64 (8.289)
Follow-up	**positive**	32.33 (6.597)	28.25 (6.771)	31.43 (6.560)	28.07 (6.673)
	negative	11.08 (1.165)	19.00 (6.822)	11.07 (1.940)	15.50 (9.121)

Table 8. Statistical analyses of PANAS. Results of the repeated measures ANOVAs regarding the main effects are shown for both affective states in each session. Main effect "time" represents the period between PANAS 1 to PANAS 2.

Session	Affect	Effect	ANOVA
Pre	**positive**	*Condition*	$F(1,24) = 0.212, p = 0.650, \eta_p^2 = 0.009$
		Time	$F(1,24) = 9.698, p = 0.005, \eta_p^2 = 0.288$
		condition x *time*	$F(1,24) = 0.004, p = 0.948, \eta_p^2 < 0.001$
	negative	*Condition*	$F(1,24) = 0.222, p = 0.642, \eta_p^2 = 0.009$
		Time	$F(1,24) = 23.239, p < 0.001, \eta_p^2 = 0.492$
		condition x *time*	$F(1,24) = 3.069, p = 0.093, \eta_p^2 = 0.113$
Post	**positive**	*Condition*	$F(1,24) = 0.229, p = 0.637, \eta_p^2 = 0.009$
		Time	$F(1,24) = 5.107, p = 0.033, \eta_p^2 = 0.175$
		condition x *time*	$F(1,24) = 0.745, p = 0.397, \eta_p^2 = 0.030$
	negative	*Condition*	$F(1,24) = 0.751, p = 0.395, \eta_p^2 = 0.030$
		Time	$F(1,24) = 9.958, p = 0.004, \eta_p^2 = 0.293$
		condition x *time*	$F(1,24) = 0.882, p = 0.357, \eta_p^2 = 0.035$
Follow-up	**positive**	*Condition*	$F(1,24) = 0.052, p = 0.821, \eta_p^2 = 0.002$
		Time	$F(1,24) = 11.090, p = 0.003, \eta_p^2 = 0.316$
		condition x *time*	$F(1,24) = 0.106, p = 0.748, \eta_p^2 = 0.004$
	negative	*Condition*	$F(1,24) = 0.968, p = 0.335, \eta_p^2 = 0.039$
		Time	$F(1,24) = 17.659, p < 0.001, \eta_p^2 = 0.424$
		condition x *time*	$F(1,24) = 1.410, p = 0.247, \eta_p^2 = 0.055$

3.6. Anxiety

On average, mean STAI scores for both groups in all sessions indicated low to moderate anxiety levels (see Table 9 for detailed report on mean values).

Table 9. STAI scores. The table shows mean total scores from STAI trait and STAI state with standard deviations in parentheses for each session and group.

	Session	**sham**	**anodal**	**t-test**	**p-value**
STAI trait	pre	32.08 (7.17)	40.64 (6.89)	t(24) = -3.100	0.005
	post	33.42 (6.89)	35.86 (6.14)	t(24) = -0.924	0.365
	follow-up	31.83 (5.65)	34.57 (6.16)	t(24) = -1.173	0.252
STAI state	pre	34.75 (7.68)	39.79 (10.99)	t(24) = -1.331	0.196
	post	32.33 (5.35)	32.71 (5.93)	t(24) = -0.171	0.866
	follow-up	32.92 (4.17)	33.93 (5.37)	t(24) = -0.530	0.601

Regarding the STAI trait scores, a repeated measures ANOVA with Huynh-Feldt corrections (see Figure 10A) revealed statistical significance for both main effect *condition* (F(1,24) = 4.419, p = 0.046, η_p^2 = 0.155) and main effect *time* (F(1.757, 42.157) = 3.445, p = 0.047, η_p^2 = 0.126). The interaction between these factors was also significant with a large effect size (F(1.757, 42.157) = 4.093, p = 0.028, η_p^2 = 0,146). As assessed by post-hoc independent t-tests, trait anxiety levels decreased significantly in the anodal group after training (t(13) = 2.436, p = 0.030, d = 0.651) and after follow up (t(13) = 2.757, p = 0.016, d = 0.737), but did not change in the sham treated group (t(11) = -0.813, p = 0.433, d = 0.235 after training and t(11) = 0.162, p = 0.874, d = 0.047 after follow-up). At pre-session trait anxiety scores of the anodal group were significantly higher compared to the sham group (t(24) = -3.10, p = 0.005, d = 1.220), thus accounting for the lack of significant differences between groups at post-session (t(24) = -0.924, p = 0.365, d = 0.363) and follow-up (t(24) = -1.173, p = 0.252, d = 0.461).

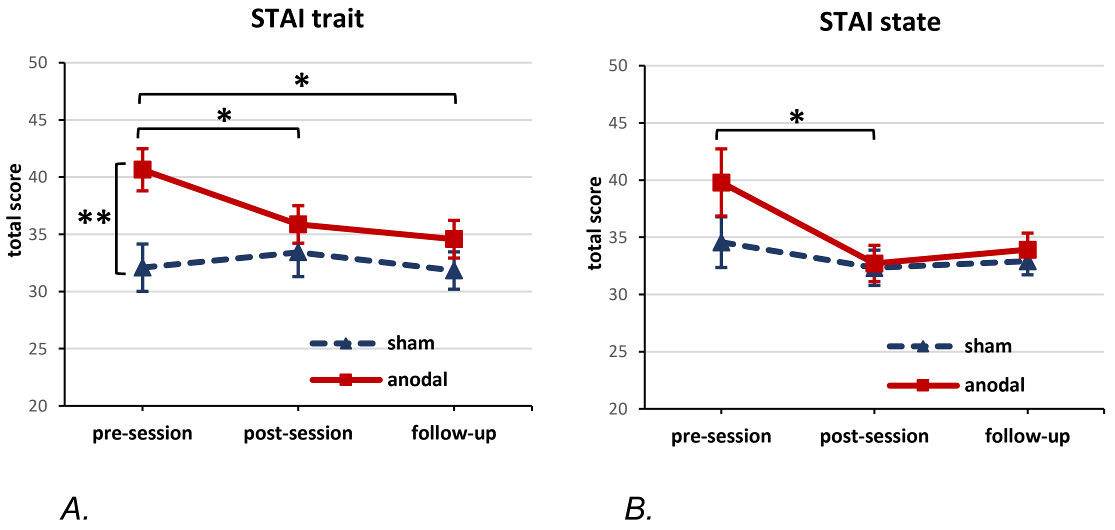


*Figure 10. State-Trait Anxiety Inventory (STAI) – the mean total scores of each group are shown for each session. Standard bars represent standard error of the mean. Possible scores range from 20 = lowest anxiety levels to 80 = highest anxiety levels. ** p < 0.01, * p < 0.05*
A. Results from the STAI trait. Anxiety levels decreased significantly over time only in the group which received anodal tDCS.
B. Results from the STAI state. Anxiety levels decreased over time with no significant differences between groups.

The ANOVA of the STAI state scores with a Greenhouse-Geisser correction (see Figure 10B) showed statistical significance only for main effect *time* (F(1.489, 35.732) = 4.736, p = 0.023, $\eta_p^2 = 0.165$) signifying a slight to moderate reduction in state anxiety levels in both groups. No statistical significance was observed for either main effect *condition* (F(1,24) = 1.129, p = 0.299, $\eta_p^2 = 0.045$) or *condition* x *time* interaction (F(1.489, 35.732) = 1.189, p = 0.304, $\eta_p^2 = 0.047$).

3.7. Rumination

Concerning the SRQ scores, the repeated measures ANOVA (see Figure 11) found no statistical significance for main effect *condition* (F(1,24) = 1.481, p = 0.236, $\eta_p^2 = 0.058$). Main effect *time*, however, was statistically significant (F(2,48) = 5.001, p = 0.011, $\eta_p^2 = 0.172$). A significant interaction between factors *condition* x *time with* a medium effect size could also be revealed (F(2,48) = 3.262, p = 0.047, $\eta_p^2 = 0.120$). Post-hoc paired t-tests indicated that rumination in the anodal group significantly decreased after training (t(13) = 4.039, p = 0.001, d = 1.079). The reduction was no longer significant after follow-up (t(13) = 1.891, p = 0.081, d = 0.505). No change was found in the sham group (t(11) = 0.306, p = 0.765, d = 0.088 after training and t(11) = -1.117, p = 0.288, d = 0.322 after follow-up). Between-group comparisons showed no significant differences in the SRQ scores at pre-session (t(24) = -0.032, p = 0.975, d = 0.013), post-session (t(24) = 1.667, p = 0.108, d = 0.656) or follow-up (t(24) = 1.670, p = 0.108, d = 0.657).

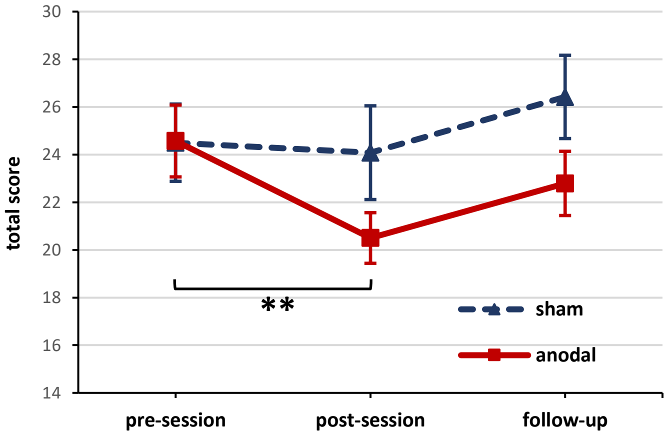


Figure 11. State Rumination Questionnaire (SRQ) – the mean total scores of each group are shown for each session. Standard bars represent standard error of the mean. Possible scores range from 10 = lowest rumination levels to 50 = highest rumination levels.
*** $p < 0.01$*
A reduction of rumination levels after training could be observed in the anodal group.

3.8. Further Questionnaires (SWLS, GDS, STP)

Detailed results from the questionnaires SWLS, GDS and STP are depicted in Table 10.

Regarding life satisfaction as assessed by the SWLS, the repeated measures ANOVA found no statistical significance for main effect *condition* (F(1,24) = 0.502, p = 0.485, η_p^2 = 0.020), *time* (F(2,48) = 0.082, p = 0.922, η_p^2 = 0.003) or for the interaction between *condition* x *time* (F(2,48) = 0.571, p = 0.569, η_p^2 = 0.023).

Table 10. SWLS, GDS and STP scores. The table shows mean total scores from the three questionnaires with standard deviations in parentheses for each session and group.

	Session	**sham**	**anodal**	**t-test**	**p-value**
SWLS	Pre	28.67 (4.68)	27.14 (4.94)	t(24) = 0.803	0.430
	Post	28.83 (3.13)	27.36 (5.76)	t(24) = 0.792	0.436
	follow-up	28.33 (3.77)	27.71 (4.25)	t(24) = 0.390	0.700
GDS	screening	2.00 (1.13)	2.29 (1.33)	t(24) = -0.586	0.563
	Post	1.17 (1.12)	2.07 (1.27)	t(24) = -1.916	0.067
	follow-up	0.92 (0.79)	1.50 (1.45)	t(24) = -1.238	0.228
STP	Pre	19.00 (6.28)	20.86 (2.96)	t(24) = -0.988	0.333
	Post	20.42 (4.54)	22.50 (3.59)	t(24) = -1.306	0.204
	follow-up	18.75 (5.82)	21.36 (3.50)	t(24) = -1.408	0.172

Results from the ANOVA on the GDS revealed statistical significance for main effect *time* (F(2,48) = 9.388, $p < 0.001$, $\eta_p^2 = 0.281$) denoting a slight reduction in total scores over time. Main effect *condition* (F(1,24) = 2.116, p = 0.159, $\eta_p^2 = 0.081$) and the interaction *condition* x *time* (F(2,48) = 1.025, p = 0.366, $\eta_p^2 = 0.041$) were, however, not significant.

For the STP, none of the main effects reached statistical significance: *condition* (F(1,24) = 2.572, p = 0.122, $\eta_p^2 = 0.097$), *time* (F(2,48) = 1.462, p = 0.242, $\eta_p^2 = 0.057$) and *condition* x *time* interaction (F(2,48) = 0.075, p = 0.928, $\eta_p^2 = 0.003$), implying no change in self-rating of task performance over time.

3.9. Correlations

Participants‘ age was found to be negatively correlated with performance in the PASAT and v-2-back at each pre-, post- and follow-up sessions. Similarly, a positive correlation between level of education and PASAT performance at pre-session, as well as v-2-back performance in all sessions was observed. The education duration of participants was, furthermore, negatively correlated with SRQ outcomes at all sessions. See Table 11A for detailed statistical results.

Table 11. Correlation data. Statistical results regarding Pearson correlation coefficients (r) or Spearman correlation coefficients (r_s) and corresponding p-values are reported. Empty cells indicate absence of statistical significance or test relevance.
A. The table shows significant correlations between age of participants or education duration and PASAT, v-2-back or SRQ scores for each session respectively.
B. The table shows significant correlations between SRQ scores and further variables on the left for the corresponding sessions.

A.

	Session	**Age**	**Education**
PASAT	Pre	$r_s(24) = -0.603, p = 0.001$	$r_s(24) = 0.499, p = 0.009$
	Post	$r_s(24) = -0.468, p = 0.016$	/
	follow-up	$r_s(23) = -0.438, p = 0.029$	/
v-2-back	Pre	$r_s(24) = -0.610, p = 0.001$	$r(24) = 0.453, p = 0.020$
	Post	$r_s(24) = -0.580, p = 0.002$	$r(24) = 0.574, p = 0.002$
	follow-up	$r_s(24) = -0.551, p = 0.004$	$r_s(24) = 0.655, p < 0.001$
SRQ	Pre	/	$r(24) = -0.521, p = 0.006$
	Post	/	$r(24) = -0.545, p = 0.004$
	follow-up	/	$r(24) = -0.523, p = 0.006$

B.

		SRQ		
	Session	**pre**	**post**	**follow-up**
PASAT	pre	$r(24)=-0.567,p=0.003$	/	/
	post	/	$r_s(24)=-0.497,p=0.010$	/
	follow-up	/	/	$r_s(23)=-0.484,p=0.014$
v-2-back	pre	$r(24)=-0.642,p<0.001$	/	/
	post	/	$r_s(24)=-0.578,p=0.002$	/
	follow-up	/	/	$r_s(24)=-0.662,p<0.001$
PANAS 2 negative affects	pre	$r_s(24)=0.614,p=0.001$	/	/
	post	/	$r_s(24)=0.531,p=0.005$	/
	follow-up	/	/	$r_s(24)=0.641,p<0.001$
TMT A	pre	$r_s(24)=0.595,p=0.001$	/	/
TMT B	pre	$r_s(24)=0.702,p<0.001$	/	/
STP	pre	$r(24)=-0.478,p=0.013$	/	/
	follow-up	/	/	$r(24)=-0.516,p=0.007$

PASAT performance correlated positively with v-2-back performance at pre-session (r(24) = 0.769, $p < 0.001$), post-session (r(24) = 0.402, p = 0.042) and follow-up ($r_s(23) = 0.593$, p = 0.002). Moreover, there was a negative correlation between PASAT correct trials and TMT A and B completion time at pre-session ($r_s(24) = -0.617$, p = 0.001 and $r_s(24) = -0.688$, $p < 0.001$, respectively).

Negative correlations were revealed between SRQ scores and PASAT performance, as well as between SRQ scores and v-2-back in all corresponding sessions (see Table 11B). SRQ scores were also correlated positively with negative affect scores from PANAS 2 (completed after the PASAT) at all corresponding sessions, with TMTA&B at pre-session, and with STP scores at pre- and follow-up sessions.

No significant correlations were found between the amount of memory concerns or the STAI trait scores at pre-session and any other variables.

3.10. Blinding Efficacy and Adverse Effects of tDCS

"A chi-square test for comparing group-allocation guesses revealed no differences between the two groups (χ^2 (1) = 1.706, p = 0.191) indicating successful blinding of stimulation."(Stoynova et al., 2019).

As shown in Table 12, analysis of the reported tDCS-related adverse effects found no significant differences between groups.

Table 12. "Adverse effects of tDCS. The table shows mean values with standard errors in parentheses from a 5-point Likert scale on adverse sensations of tDCS (1=none, 5=extensive). Ratings from both groups were submitted to independent t-tests." (Stoynova et al., 2019)

Adverse Sensation	**sham**	**anodal**	**t-test**	***p*-value**
Tingling at the site of the electrode	1.92 (0.288)	2.64 (0.440)	t(24) = -1.331	0.196
Tingling elsewhere	1.17 (0.112)	1.21 (0.214)	t(24) = -0.187	0.853
Fatigue	1.42 (0.149)	2.00 (0.296)	t(24) = -1.670	0.108
Itching	1.67 (0.284)	1.64 (0.248)	t(24) = 0.063	0.950
Headache	1.17 (0.112)	1.21 (0.114)	t(24) = -0.296	0.770
Nausea	1.00 (0.000)	1.07 (0.071)	t(24) = -0.923	0.365

The figure is reprinted from Stoynova et al. (2019).

4. Discussion

This study examined the effects of a tDCS-enhanced CC training on the amount of memory concerns in subjects with SCD. We hypothesized that a targeted intervention combining the neuroplasticity-enhancing effects of tDCS and CC training will reduce the negatively biased self-perception of cognitive performance and associated worries in this population. To test this hypothesis, we conducted a randomized, sham-controlled proof-of-principle study with 26 participants above the age of 60 years, who were experiencing memory related concerns. We applied 2mA anodal tDCS to the left dlPFC over 12 sessions during 4 weeks of CC training via PASAT and measured the change in amount of memory concerns by means of a 10-point Likert-Scale at pre-, post- and follow-up session. The described methodological approach was innovative, as this rationale has not been applied to SCD before.

The main findings of our pilot trial were that 1) compared to sham stimulation, anodal tDCS-enhanced CC training significantly reduced the amount of memory concerns in SCD with a large effect size, 2) this effect was maintained for up to 3 months, 3) rumination and trait anxiety levels were significantly reduced in the anodal study group, the latter persisting for up to 3 months, 4) anodal tDCS did not enhance the performance in the PASAT and the transfer tasks compared to sham treatment and did not have an effect on the reported quality of life. Furthermore, little to no adverse effects were reported, proving the safety of this stimulation method in older adults with SCD.

4.1. Memory Concerns Reduction

There is growing evidence that the presence of worries about one’s cognitive abilities in SCD is among the strongest, if not the most important, predictors of future progression to incident dementia (Jessen et al., 2010; Miebach et al., 2019; Pike et al., 2022). Specifically, self-reported memory concerns correlate with an almost twofold elevated risk of incident MCI (van Harten et al., 2018). It is conceivable, that these worries and heightened anxiety represent subtle deficits in cognitive control functions (Bertrams et al., 2013), which in turn is likely to lead to a misallocation of cognitive resources and an acceleration of the occurrence of clinically relevant cognitive impairments (Elfgren et al., 2010). Hence, strengthening cognitive control functions by targeting the symptom of memory concerns might contribute to resilience against cognitive decline in elderly subjects with SCD.

In this study, we demonstrate for the first time, that memory concerns in SCD can be made malleable by a combination of anodal tDCS to the left dlPFC and a four-week CC training. Compared to sham tDCS, this intervention effectively and safely reduced the amount of worries and this change was sustained for up to three months after training. "*The results support our primary hypothesis that memory concerns can be reduced by a targeted activation of the CC network most likely by means of an improved executive control (Plewnia et al., 2015a) on distractive self-focus and negative affect (Plewnia et al., 2015b).*" (Stoynova et al., 2019). As a further explanation, concomitant tDCS may moderate the required cognitive effort by facilitating task-related information processing (Flöel, 2014) with a positive effect on the perception of performance and worries about cognitive decline. Hence, by attenuating memory-related concerns, the attentional resources previously occupied with said concerns might be effectively redirected to better preserving or improving the existing cognitive reserve instead (Hirsch and Mathews, 2012).

Moreover, these findings signify important neuroplastic changes as a result of a tDCS-enhanced CC training. Neuroplasticity is a complex phenomenon, which encompasses the possibility of structural and functional alterations of the brain as an adaptive response to internal or external stimuli (Jones, 2004). This process is essential for, among others, learning, memory consolidation and recovering from brain damage or neurologic and psychiatric symptoms (DeFelipe, 2006; Khan et al., 2017). On the cellular level, neuroplasticity can appear in the form of long-term potentiation (LTP) and long-term depression (LTD), which represent amplified or decreased synaptic transmission, respectively (Bliss and Cooke, 2011). Different NIBS methods hold promise to induce neuroplastic effects under the right circumstances (Polanía et al., 2018). In particular, tDCS is considered to be a modulator of LTP and LTD and its effects are dependent on the endogenous neural activity (Kronberg et al., 2017). This underscores the importance of targeted brain activation during stimulation, for instance in the form of simultaneous cognitive training. Considering these observations, the sustainable reduction of memory concerns in our study most likely reflects lasting beneficial neuroplastic effects through the synergistic impact of tDCS and CC training on ameliorating cognitive control in subjects with SCD. However, the underlying mechanisms and parameters remain to be more thoroughly investigated.

In summary, the prognostically important symptom of memory-related worry in SCD was alleviated through the intervention used in this study, which may open new perspectives to mobilize CC and, at best, delay objective cognitive decline. Importantly, in contrast to the majority of prior research (Roheger et al., 2021; Smart et al., 2017), the primary endpoint of this trial was not the change in SCD or global cognition in general, but specifically the amount of memory concerns. The preregistration of the study and particularly its primary endpoint bolster the reliability of the results.

4.2. Anxiety and Rumination

To date, there is no clear scientific consensus on whether anxiety is a confounding or moderating variable in the context of SCD. On the one hand, anxiety is closely linked to heightened self-focus, worrying and negativity bias (Liu et al., 2019), which aggravate the perception of impaired cognition and medical help-seeking (Boone, 2009). This may partially account for the high percentage of elderly with SCD, who do not experience progression to AD. On the other hand, anxiety might represent an important marker for pre-clinical objective cognitive deterioration before the deficits can be detected by informants or neuropsychological testing (Rabin et al., 2017). In particular, faster progression rates to dementia have been observed in subjects with positive amyloid-beta status and higher levels of anxiety than in those with positive amyloid-beta status but lower levels of anxiety (Pietrzak et al., 2015). Rabin and colleagues postulate a link between increased anxiety and possible dysfunction in the hypothalamic-pituitary-adrenal axis, whereas the latter is considered a risk factors for MCI and AD (Rabin et al., 2017; Joshi and Pratico, 2013).

In our study, the participants did not exhibit higher anxiety state or trait scores in comparison to previously reported age-adjusted normative data as measured by STAI (Bergua et al., 2012). However, trait anxiety levels were significantly reduced in the study group, which received anodal tDCS, but not in the sham treated group. This effect persisted up to three months after training. State anxiety levels were similarly lowered only after anodal tDCS-enhanced CC training, although the change was not observable at follow-up anymore. These results are consistent with the established notion, that anodal tDCS over the left dlPFC can mitigate trait anxiety through strengthening of prefrontal control of the amygdala (Ironside et al., 2019) and weakening attentional bias to threat (Heeren et al., 2015). In a recent randomized controlled trial, Yin et al. demonstrated that decreasing anxiety levels through prior group counselling augments the benefits of memory training in participants with subjective memory complaints, as compared to the group which underwent only memory training without group counselling (Yin et al., 2022). Thus, addressing heightened non-pathological anxiety appears to be important in the management of SCD. While this study suggests beneficial effects of a tDCS-enhanced CC training on anxiety levels in SCD, the implications remain unclear. Of note, trait anxiety scores were significantly higher in the verum group at baseline, which might indicate an accidental selection bias. Hence, this secondary outcome has to be replicated in a larger sample size before further conclusions can be made.

Rumination describes intrusive, repetitive negative thoughts and is considered an important transdiagnostic factor for many psychiatric disorders including depression and anxiety (Watkins and Roberts, 2020). It plays a role in maintaining or even worsening pathological cognitive states, impaired executive function, negativity bias and heightened worrying (Koster et al., 2011). Notably, rumination levels appear to positively correlate with the incidence of SCD in older adults (Schlosser et al., 2020). Some randomized controlled trials have reported favorable effects of tDCS on reducing rumination, especially when the anode is placed over the left dlPFC (Baeken et al., 2017; De Raedt et al., 2017). However, due to protocol heterogeneity, small study samples and short interventions (mostly 1 tDCS session), the results are unclear and often contradictory

(Hoebeke et al., 2021). Additionally, CC training alone has been shown to curtail rumination tendencies in healthy adults (Hoorelbeke et al., 2015). The outcomes of our study seem to partially reflect the current state of research, since a significant, albeit transient, reduction in rumination levels occurred at post-session in the anodal group. Furthermore, the negative correlations between SRQ scores and task performance in all corresponding sessions suggest possible influence of rumination on cognitive processing speed or vice versa.

In general, worry, anxiety and rumination can be viewed as intertwined concepts and, as such, are sometimes summarized under the umbrella term of repetitive negative thinking (Ehring and Watkins, 2008). Accordingly, it may seem natural that the observed reduction of memory concerns in this study will be mirrored in similar decrease in rumination and anxiety levels. Nevertheless, the exact connections between rumination, anxiety and SCD remain unclear and need systematic addressing in future research projects.

4.3. Lack of Effects on Task Performance

In this study, changes in PASAT performance served as one of the secondary outcomes. Based on prior indicative research (Plewnia et al., 2015a; Ruf et al., 2017; Weller et al., 2020), we hypothesized that anodal tDCS applied to the left dlPFC during execution of the PASAT would enhance the training effects compared to sham stimulation. To account for possible pre-existing individual differences such as processing speed or working memory capacity, the overall performance gain during training period was compared between the two study arms. The above-stated hypothesis could not be confirmed by our results, since, although task performance improved over time, it was not ameliorated by anodal tDCS. On a subjective level, these outcomes are reflected in the lack of difference between groups regarding perceived learning success, perceived tDCS-induced performance enhancement and self-rating of task performance.

Naturally, it can be objected, that the reduction in memory concerns in our study is not supported by a measurable improvement in PASAT performance. Indeed, SCD's characteristics present a challenge to scientific research: A merely subjective evaluation of oneself and an absence of measurable cognitive deficits are the essential aspects of this condition (Jessen et al., 2014a), therefore observing an objective, quantifiable cognitive improvement is impeded by SCD’s definition itself. It is presumed that latent cognitive deficits in this condition are still sufficiently functionally compensated (Sperling et al., 2011). Thus, an already intact task performance cannot be further or largely improved in this elderly population, which can lead to so-called ceiling effects.

Although the interaction between pre-training cognitive performance and tDCS effectiveness is complex (Jones et al., 2015), it is increasingly evident that tDCS induces greater effects in clinical settings and in subjects with impaired cognitive abilities (Schwippel et al., 2018). Conversely, healthy individuals with better baseline task performance seem to benefit less from this intervention (Learmonth et al., 2015; Ruf et al., 2017). Accordingly, the lack of visible tDCS-related effects on PASAT outcomes in our study might be due to the mostly preserved working memory functioning in SCD and the little room for improvement via stimulation. This notion is supported by some studies revealing more pronounced effects of tDCS in AD than in MCI (Chen et al., 2022; Šimko et al., 2022). Similarly, de Sousa et al. observed enhancement of cognitive training via anodal tDCS in MCI patients but not in healthy older adults (de Sousa et al., 2020).

Additionally, it has been shown that tDCS effects depend on the task difficulty itself (Jones and Berryhill, 2012; Pope et al., 2015). More challenging tasks generate more cognitive strain and higher activation of different brain regions including the dlPFC, which likely increases susceptibility to tDCS (Hsu et al., 2016). Therefore, a harder version of PASAT or a different task might be required to detect stimulation effects after CC training in SCD. Some researchers argue that, despite its defining subjectivity, SCD might be detected by more sensitive tasks (Wolfsgruber et al., 2020), specifically ones which target associative and visual memory (Bainbridge et al., 2019) like the face-name associative recognition test (Polcher et al., 2017). It might be worth investigating whether utilizing such tasks for cognitive training in combination with tDCS leads to detectable stimulation effects.

The overall improvement in PASAT performance over time in both study groups can be interpreted as a positive outcome of the cognitive training itself. However, we did not observe any transfer effects in related or unrelated tasks. In general, the transferability of cognitive training is considered questionable (Baniqued et al., 2015). Of note, a recent randomized controlled trial on the effectiveness of CC training via PASAT in healthy elderly subjects found no impact of training on far-transfer tasks (Vanderhasselt et al., 2021). Finally, the lack of performance differences between groups regarding the transfer tasks in our study is in accordance with the missing influence of tDCS on PASAT in the first place.

In conclusion, the connection between the objective results of the PASAT and the subjective reports regarding memory complaints in our pilot study is unclear. So far, many studies have examined the effects of tDCS on working memory in healthy older adults (Goldthorpe et al., 2020). The often contradictory results (cf. Manenti et al., 2017; Nilsson et al., 2017; Satorres et al., 2022) might be due to predominantly small sample sizes, heterogenous choice of tasks and outcomes and varying stimulation parameters. As stated above however, our focus differs from mentioned previous research, since we explicitly examined the subjective memory complaints and not memory functions per se.

4.4. Quality of Life and Affective States

SCD is consistently associated with impaired quality of life and wellbeing (Mol et al., 2009; Pusswald et al., 2015; Roehr et al., 2017). In spite of this commonly ascertained correlation, we did not observe lower satisfaction with life as measured by the SWLS in our study. The mean scores of approximately 27-28 points at baseline for both groups were even a little bit higher than the normative SWLS values derived in large German community samples, which range between 25,9 and 26,5 points (Hinz et al., 2018). The missing amelioration in life satisfaction after training is therefore not surprising, since participants did not experience deficits in this regard beforehand. It is conceivable that bigger concerns about memory result in higher impairment of quality of life. The average amount of memory concerns in this study was, however, low to moderate with a mean of 5 on a 10-point Likert-Scale, which possibly explains the lack of noticeable reduction in life satisfaction as well as the absence of improvement after the intervention. Moreover, a different questionnaire assessing quality of life might have been more suitable. Although SWLS is high in reliability and effectiveness (Pavot and Diener, 1993), instruments like the WHOQOL-Bref or the WHO-Five Well-being index may provide a more nuanced and effective measurement of perceived quality of life with emphasis on separate domains and current mental state (Harper et al., 1998; Topp et al., 2015).

Concerning affective states, initial measurements from the PANAS in this study revealed considerably lower means for both positive and negative affects compared to published normative data (Crawford and Henry, 2004). These findings diverge from a previously observed increase in positive to negative affect ratio with age (Diehl et al., 2011). As expected, participants' negative affect consistently rose after completion of the PASAT, most likely due to induced frustration from the task. However, positive affect increased likewise, which might imply a general enhancement of self-perception regarding affect after emotional activation through the task. These changes did not differ between groups, meaning tDCS did not influence affective states. This is in line with many other studies, which could not yield any tDCS effects on mood in healthy participants (Keeser et al., 2011; Plazier et al., 2012; Weller et al., 2020). Modulation of PANAS outcomes via tDCS has been observed predominantly in depressed patients and clinical populations (Brunoni et al., 2014). Since subjects with SCD do not experience detectable structural or functional deficits, their mood may be less easily impacted by tDCS interventions. Conclusions regarding the relationship between affective states and memory concerns cannot be made from this study. Nevertheless, it is worth noting that moods seem to bear very little to no effect on cognitive functioning (Berk et al., 2017; Simpson et al., 2014).

4.5. Conceptualizing SCD

Despite its early introduction in the past century (Reisberg et al., 1982), SCD has only gained surging scientific interest in the last two decades, turning into a widely recognized possible earliest manifestation of cognitive decline preceding AD (Jessen et al., 2014a). The Subjective Cognitive Decline Initiative (SCD-I) proposed a concise definition and conceptual framework for this condition in 2014, which has since been adopted by most researchers. Next to the prerequisite of self-perceived continuous deterioration of cognitive abilities in the absence of objective deficits, additional characteristics were presented, which are linked to higher risk of progression to AD. These are summarized under the term SCD Plus and include, among others, an onset of SCD within 5 years before testing, age at onset above 60 years, concerns about the perceived decline and positive biomarkers associated with AD (Jessen et al., 2014a). Nevertheless, there are still many uncertainties and inconsistencies in respect of the concept of SCD, some of which are discussed below.

Regarding assessment strategies, Rami et al. have recently developed and validated the Subjective Cognitive Decline Questionnaire (Rami et al., 2014). However, when determining the presence of SCD, most studies utilize different approaches and assessments of self-reports, ranging from qualitative to quantitative measurements, single to multi-item questionnaires, different varieties of examined cognitive domains, timeframes and cut-offs (Molinuevo et al., 2017). Moreover, rating methods are often not sufficiently disclosed (Rabin et al., 2017). This high between-study heterogeneity leads to different prevalence rates as well as responses to interventions and hampers the conduction of meta-analyses (Tandetnik et al., 2015). Participants are often sampled from divergent settings such as memory clinics, community-based, volunteers or medical-help seekers cohorts, which can further alter the nature and frequency of expressed concerns (Rabin et al., 2017). Moreover, the merit of informant reports on cognitive functioning is disputed, with some studies showing a predictive value regarding later objective cognitive decline (Valech et al., 2015; van Harten et al., 2018), and others finding no correlation (Amariglio et al., 2012) or warning of additional bias (Hill et al., 2015).

In SCD, subjective experience of memory deterioration is considered a more valuable predictive factor than neuropsychological testing, since rising cognitive deficits can still be sufficiently compensated but self-perception is intact, as opposed to later stages of AD, in which cognitive testing is positive but awareness of illness decreases (Jessen et al., 2014b). However, some researchers suggest that beginning subtle cognitive decline could be detected even in SCD by more advanced and highly sensitive assessment strategies and argue for their wider implementation (Koppara et al., 2015; Rentz et al., 2013; Wolfsgruber et al., 2020). Examples would be focusing more on longitudinal or naturalistic observations (Hertzog et al., 2018; Trull and Ebner-Priemer, 2013). Yet this approach would contradict the subjective nature of the condition and possibly overlook earliest imperceptible stages of the AD continuum.

Another highly relevant research topic is the presence and significance of AD related biomarkers such as amyloidosis, tau pathology and neurodegeneration in SCD (Jessen et al., 2014a). The prevalence of AD biomarker pathology in this condition is currently estimated between 8% and 46% (Jessen et al., 2020; Rostamzadeh et al., 2022) and, more importantly, the combination of SCD and AD biomarkers significantly elevates the risk of progression to objective cognitive deterioration (Rostamzadeh et al., 2022). Some of the SCD Plus features were revealed to correlate with amyloid positivity (Janssen et al., 2022; Miebach et al., 2019). Specifically, concerns and worries about perceived cognitive decline seem most closely linked to the degree of not only amyloid but also tau pathology and neurodegeneration in healthy older individuals (Amariglio et al., 2015; Buckley et al., 2017; Verfaillie et al., 2019). Furthermore, brain atrophy and cortical thinning patterns similar to those in MCI and AD have been observed in magnetic resonance imaging (MRI) studies (Meiberth et al., 2015; Peter et al., 2014; Saykin et al., 2006) as well as in autopsies (Arvanitakis et al., 2018) examining individuals with subjective memory complaints. Finally, the presence of apolipoprotein E4 (the main known genetic risk factor for AD onset (Corder et al., 1993)) in SCD increases the possibility of actual incipient AD pathology (Moreno–Grau et al., 2018). The aforementioned findings suggest that SCD characteristics may propel the identification of cognitively normal individuals with AD biomarker evidence at higher risk of progression to dementia (Janssen et al., 2022) and vice versa, that testing for biomarkers in SCD may aid the separation of preclinical stages of AD from physiological aging (Jessen et al., 2023). Consequently, the presence of SCD in older individuals with amyloid pathology is categorized as stage 2 of the National Institute of Aging-Alzheimer’s Association (NIA-AA) classification system, with stage 1 entailing AD biomarkers with no subjective or objective symptoms and stage 3 corresponding to MCI (Jack et al., 2018). Despite its diagnostic potential, the association of SCD with AD biomarkers should be approached with caution. In fact, there is a lack of large sample studies or longitudinal observations regarding AD pathology in SCD thus far (Jessen et al., 2020) and some research groups have not been able to observe any connection between this condition and amyloidosis (Buckley et al., 2013) or even point to existing biases between knowing one's genetic apolipoprotein genotype and experiencing anticipative subjective memory complaints (Lineweaver et al., 2014). In this study, we decided not to control for AD biomarkers and rather focus on the clinical characteristics of SCD in order to appropriately depict the complexity and range of this condition but also to have a more naturalistic and cost-effective approach to the often unaddressed distressing memory concerns of many elderlies. Furthermore, testing for biomarkers would have raised the ethical issue of disclosing genetic status to healthy individuals (Schicktanz et al., 2014). Nevertheless, in the case of future larger multicentric trials investigating the effects of tDCS on SCD, indicators for preclinical AD can be obtained and included in analysis of response predictors.

The exclusion of patients with clinical depression when screening for SCD has also been increasingly questioned (Rabin et al., 2017). Although depressive symptomatology often induces subjective and objective cognitive worsening (Gorwood et al., 2008; Lindbergh et al., 2016; Zandi, 2004), the relationship between depression and SCD is argued to be much more intricate. On the one hand, there is a convincing body of evidence that especially early-onset depressive episodes can increase the risk of future dementia (Almeida et al., 2017; Bennett and Thomas, 2014). On the other hand, late-life depression has been repeatedly observed to precede dementia, which has led to the assumption that it might be a prodromal symptom or be caused by similar degenerative processes as dementia (Singh-Manoux et al., 2017). In line with this, the prevalence of depressive symptoms in subjects with SCD has been reported significantly higher than in elderly without cognitive complaints (Sabatini et al., 2022). A recent study showed that, in most cases, SCD predates depressive symptoms and that, when depressive symptoms arise in this condition, both amyloid pathology and the risk of progression to dementia are amplified (Kleineidam et al., 2022). Since we decided to adhere to the recommendations of SCD-I (Jessen et al., 2014a) and minimize possible confounding factors, we excluded subjects with clinical depression from this study. However, this approach might have left out an important subgroup of people with SCD at high risk of future dementia. Therefore, it may prove beneficial to adopt more inclusive strategies in future research. Notably, it is worth investigating, whether the established positive effects of anodal tDCS on depression (Lefaucheur et al., 2017) can be utilized in this condition as well.

Additionally, personality traits have been long considered to impact memory complaints in the elderly (Hänninen et al., 1994). Considering that higher neuroticism and lower conscientiousness seem to correlate with an aggravated risk for objective cognitive decline (Low et al., 2013) and occurrence of characteristic neurostructural changes (Kapogiannis et al., 2013), these two traits are of particular interest in the field of dementia. Accordingly, lower conscientiousness was found to be linked with SCD (Reynolds et al., 2022) and higher neuroticism – with the degree of amyloid pathology in this condition (Snitz et al., 2015). In a recent longitudinal analysis, Aschwanden et al. reported, that SCD subjects with lower neuroticism and higher conscientiousness experience lower rates of progression to dementia, thus pointing to these traits as important resilient factors in SCD (Aschwanden et al., 2022). While some interpret the observed associations as a confirmation that higher neuroticism and lower conscientiousness are risk factors for the development of dementia and others view them more as possible incipient symptoms of cognitive decline (Rabin et al., 2017), it is increasingly suggested that personality traits are taken into account and even included in the SCD Plus framework (Muñoz et al., 2020). Further variables that can influence self-reported cognitive decline include, among others, presence of somatic diseases, medication (Jessen et al., 2020), level of education and ethnicity (Aghjayan et al., 2017).

In conclusion, multiple factors play a role in the characterization of SCD and there is predominantly lack of consensus how each of them interacts with this condition, especially when conversion to dementia is concerned. This generally complicates the consistency and transparency of research on SCD. Nevertheless, its potential and suitability for early preventive interventions to slow down cognitive decline remains indisputable, not least because of the higher motivation and treatment adherence in this population compared to later stages on the dementia continuum (Rabin et al., 2017). In order to propel a better understanding of this condition, larger multicentric trials with more standardized operationalization of SCD are to be conducted. The SCD-I acknowledges however, that, due to its multifaceted nature, detailed disclosure of the assessment methods and targeted features of SCD might be more valuable and realistic than aiming for greater homogeneity in future studies (Molinuevo et al., 2017). In accordance with these recommendations, we specifically reported and measured one of the greatest risks for progression to dementia in SCD, namely memory concerns (Jessen et al., 2010), as our main intervention outcome, while recognizing the multitude of possible confounders, which may be addressed in following, more comprehensive trials.

4.6. Stimulation Parameters

The stimulation effects of tDCS depend on numerous parameters, which must be considered during interpretation. These include tDCS-related factors such as current density, polarity, laterality, duration and time of distribution on the one hand, and participants' characteristics such as gender, age, education, motivation levels, brain anatomy, genetic polymorphisms, medication and tobacco consumption on the other hand (Dedoncker et al., 2016). Experiment protocols regarding these parameters vary greatly and sample sizes are commonly small, thus often leading to inconsistent between-studies results and impeding the generalization of a given trial's outcome (Jones et al., 2015). Moreover, the exact interactions and influences of the mentioned variables on the efficacy of tDCS are to a great extent unknown. Some clarifying examples of this are covered below.

It is questionable whether an increase in current intensity results in more pronounced behavioral effects of tDCS. A magnified electric field might in fact activate a wider cortical area and diminish the desired spatial precision, which is already limited due to the standard 35cm^2 size of electrodes. Generally, a non-linear relationship between current intensity, ongoing brain activity and stimulation response is postulated (Batsikadze et al., 2013; Esmaeilpour et al., 2018). However, clinical populations seem to benefit more from the higher ranges of stimulation intensities, as shown in studies on schizophrenia (Hoy et al., 2014) and Parkinson’s disease (Boggio et al., 2006). Similarly, in their recent systematic review of tDCS in MCI and AD, Chen et al. observed greatest stimulation efficacy in trials using 2,5mA (Chen et al., 2022). Whether this can be transferred to SCD or whether lower intensities would be superior remains subject of future research.

The polarity-dependency of tDCS effects especially in cognitive research has also been repeatedly debated (Jacobson et al., 2012), partially due to contradictory findings of improved cognitive functions not only after anodal but also after cathodal stimulation (Christova et al., 2015; Zwissler et al., 2014). These might be explained by beneficial inhibitory processes on distractive network activity (Schroeder et al., 2016) or emerging excitatory effects after longer cathodal stimulation duration (Batsikadze et al., 2013). Likewise, the laterality of cognitive functions renders itself complex and not yet fully understood (Vanderhasselt et al., 2009). Nevertheless, polarity-dependent and laterality-specific tDCS cognitive effects are validated in most studies (Ehlis et al., 2016; Weller et al., 2020).

The state of the brain constitutes another major influence on tDCS effectiveness. The brain state itself is multiply determined via steady factors such as demographics, genetic predispositions and cognitive abilities and more variable state-related factors like current alertness, motivation, mood, medication use, smoking, physical and hormonal activity (Vergallito et al., 2022). The importance of brain activity before and during tDCS application is underpinned by findings of stronger after-effects when tDCS is distributed parallel to a cognitive training task (online) as opposed to offline use (Burton et al., 2023; Martin et al., 2014; Pergher et al., 2022). Accordingly, we used this beneficial combination in our study as well. A further strength of our experiment protocol is the duration of stimulation as well as the length of the total training period, since most conducted trials apply tDCS for approximately 10-15 minutes and implement a single-session methodology (Murugaraja et al., 2017). Of note, as shown in one study, expanding the stimulation time above 20 minutes has not lead to a corresponding increase in cortical excitability (Vignaud et al., 2018), supporting the notion of an optimal stimulation time-window and a non-linear relationship between duration and tDCS effects (Tremblay et al., 2016).

As described in 4.3., the efficacy of tDCS relies on baseline performance (Benwell et al., 2015), which is in turn influenced by education levels (Berryhill and Jones, 2012) and motivation (Jones et al., 2015). Furthermore, certain genetic polymorphisms, specifically in the brain-derived neurotrophic factor (BDNF) and the catechol-O-methyltransferase (COMT) genes, are considered to modulate the susceptibility of tDCS in humans (Chaieb et al., 2014; Polanía et al., 2018), however investigations of the specific impact and interactions are incomplete (Wiegand et al., 2016). Interestingly, the $\text{BDNF}_{\text{Val66Met}}$ polymorphism does not only interact with tDCS effects, but also seems to be associated with greater cognitive deficits in AD patients (Franzmeier et al., 2021).

So far, only a few studies have examined the relationship between age and tDCS efficacy (Habich et al., 2020), but its modulatory impact on the stimulation outcomes is undisputed (Pini et al., 2019). Particularly relevant to this study are previously reported morphological brain changes in subjects with SCD, including reduction in cortical thickness (Meiberth et al., 2015) and aberrations in regional and global neuronal network connectivity (Li et al., 2021), which may affect tDCS receptiveness in this population (Koo et al., 2023; Hanna Lu et al., 2021). In order to ameliorate the potential of tDCS in the elderly, stimulation protocols from studies with younger participants should not be retained unchanged, but rather carefully adjusted to account for the functional and anatomical alterations in aged brains (Habich et al., 2020).

Naturally, all of the above discussed influencing factors lead to a high inter-individual variability in tDCS outcomes, which may be responsible for the observed heterogeneity or lack of effects in some studies. One way to tackle these differences is to employ a within-subject design, in which each group receives sham and verum tDCS consecutively. Considering the apparently longer-lasting effects of the tested intervention still visible after 3 months in this study, a cross-over design would have impeded such observations, which is why a between-group comparison was chosen instead. More reasonably, a shift from group level analysis to a thorough assessment of inter-individual variances in response to tDCS is increasingly being proposed and may be conducted via cluster analysis and computational modeling (Vergallito et al., 2022). This approach is likely to generate more insights into the optimization and personalization of tDCS. However, focusing on that type of investigation was beyond the scope of our pilot study and would be more suitable for future larger samples, which could include genetic and neuroimaging assessments.

In summary, in view of the predominantly non-standardized parameters in SCD and tDCS, conducting research on both subjects simultaneously presents considerable challenges. Nevertheless, the results from this study provide a basis for the development of effective tDCS-enhanced CC training for subjects with memory concerns. In line with published research (Nitsche et al., 2008), they also demonstrate the safety and acceptance of tDCS in an older population, as no strong adverse effects were reported.

4.7. Limitations

The sample size of 26 participants is generally suitable for a pilot study and comparable with most trials in the field of tDCS, however it can still be classified as rather small, thus limiting the power of the study. Nevertheless, the large effect sizes regarding the reduction of memory concerns (as reported in 3.2.) indicate that the stimulation effects were not solely a byproduct of the small sample size.

Another important limitation of the presented experiment is its single-blind design. As described above, due to the use of a multichannel tDCS and stimulation of three subjects at the same time, the person applying tDCS could not be blinded. With this in mind, CERAD-Plus testing and familiarization with the PASAT was conducted before computerized randomization and during tDCS-enhanced training, interaction with the subjects was restricted to a minimum. Therefore, a systematic involuntary influence is highly unlikely, albeit not impossible. The obtained guesses from subjects about their group allocation (see 3.10.) further imply sufficient blinding. Nonetheless, a double-blind design might have been achieved by appointing an additional experimenter, who only controls the stimulation conditions and is not involved in analysis.

Concerning the influence of recruitment, research has shown, that elderly with SCD who actively seek clinical help experience higher levels of subjective memory complaints (Pires et al., 2012) and greater association with AD-related biomarkers in comparison to community samples (Perrotin et al., 2017). Consequently, medical help seeking has been included in the SCD Plus criteria as a risk factor for future progression to objective cognitive decline (Jessen et al., 2020; Slot et al., 2019). The participants in this study were volunteers recruited from the community rather than from memory clinics; thus, there is an increased possibility of having included false positive cases representing memory complaints as part of physiological aging. Notwithstanding this aspect, an even greater risk factor for conversion from SCD to AD was present in our sample, namely persistent memory concerns for at least 1,5 years (Liew, 2020; Wolfsgruber et al., 2016). According to participants' retrospective reports, duration of memory concerns was about 3 years on average.

As outlined above, the effects of tDCS are modulated by an abundance of parameters. For a better understanding of their influence in the context of SCD, more response predictors including BDNF and COMT genotypes, medication and nicotine intake should be obtained in future studies. In addition, functional MRI measurements would be helpful in examining whether the stimulation effects correlate with neuronal changes within the prefrontal control network.

Finally, longer observation on the development of memory concerns and cognitive performance of the participants via later follow-up assessments would have delivered valuable insights into the stability and impact of the presented intervention.

4.8. Conclusion

“This study provides first proof-of-principle for a sustainable beneficial effect of tDCS-enhanced CC training on memory concerns in SCD. Thus, CC training combined with tDCS appears promising as an effective and well tolerated […] approach to reduce the burden of memory related worries in an elderly population.

The results support our primary hypothesis that memory concerns can be reduced by a targeted activation of the CC network most likely by means of an improved executive control (Plewnia et al., 2015a) on distractive self-focus and negative affect (Plewnia et al., 2015b). Based on these prior data it is plausible that a multi-session tDCS-enhanced training program can stabilize the involved CC networks and reduce the concerns about deterioration of cognitive abilities.

The lack of significant effects on processing speed as measured by PASAT performance underlines the inherently subjective nature of SCD (Ossenkoppele and Jagust, 2017) and can most likely be attributed to ceiling effects due to age-related functional limitations. However, the persistent and pronounced reduction of memory concerns by tDCS-enhanced CC training reflects a beneficial effect on prefrontal, executive control. This effect may be useful to recruit available resources to attenuate, at least temporarily, cognitive impairments caused by ongoing neurodegeneration. However, conclusions regarding the efficacy of this approach to delay cognitive decline are premature and beyond the scope of this study. Moreover, testing of optimal stimulation parameters, training schedules and individual genetic, neurophysiological, and neurocognitive response predictors are needed to optimize and stratify potential prophylactic interventions.

In conclusion, this is the first proof of concept for the efficacy of activity enhancing tDCS combined with CC training in reducing the amount of memory concerns in elderly subjects with SCD. Our findings provide a basis for the development of innovative, effective and well tolerated approaches to mobilize CC and alleviate the burden of memory related concerns in a large proportion of the elderly population.” (Stoynova et al., 2019). Future full-scale multicenter trials should aim at providing confirmative evidence of the effectiveness of this intervention in SCD.

The amelioration of detrimental worries in SCD and an empowerment of those affected to take action for cognitive resilience holds promise to reduce help-seeking behaviour and establish a new approach to tackle cognitive decline in its earliest manifestation.

5. Summary

Subjective cognitive decline (SCD), characterized by a self-perceived deterioration of cognitive abilities in the absence of objective deficits, is highly prevalent and attracts growing attention of researchers and clinicians. This condition impairs mental well-being and is considered the earliest clinical manifestation of dementia, especially when worries about SCD are present (Jessen et al., 2014a). As such, it represents a major target for preventive interventions. It is conceivable that in SCD, subtle deficits in cognitive control (CC) functions are linked with a misallocation of cognitive resources and an acceleration of the occurrence of clinically relevant cognitive impairments. Anodal transcranial direct current stimulation (tDCS) to the left dorsolateral prefrontal cortex (dlPFC) can ameliorate CC functions. Specifically, this has been demonstrated by means of a simultaneous challenging and frustrating continuous performance task (Paced Auditory Serial Addition Task; PASAT) (Plewnia et al., 2015a). In this randomized, sham-controlled study, 26 right-handed subjects with SCD aged above 60 years received either anodal or sham tDCS to the left dlPFC over a 4 weeks (12 sessions) CC training with an adaptive PASAT. The amount of concerns regarding memory impairment was quantified by means of a 10-point Likert scale and served as the primary outcome measure. Compared to sham stimulation, anodal tDCS significantly reduced the amount of memory concerns without effects on PASAT performance. This effect was maintained for up to 3 months. Our findings support the hypothesis that activity enhancing anodal tDCS to the left dlPFC combined with CC training can reduce memory concerns in older persons with SCD with a large effect size. This pilot study provides first experimental evidence and estimates for future large-sized clinical trials targeting memory concerns and testing the efficacy of this approach to delay potential subsequent memory impairment in subjects with SCD.

6. Zusammenfassung

Subjektive kognitive Störung (subjective cognitive decline, SCD), die durch eine selbst wahrgenommene Verschlechterung der kognitiven Fähigkeiten bei fehlenden objektiven Defiziten gekennzeichnet ist, ist weit verbreitet und findet bei Forschern und Klinikern zunehmend Beachtung. Dieser Zustand beeinträchtigt das psychische Wohlbefinden und wird oft als die früheste klinische Manifestation von Demenz betrachtet, insbesondere wenn zusätzlich Sorgen um das Gedächtnis vorhanden sind (Jessen et al., 2014a). Als solche stellt sie folglich ein wichtiges Zielsymptom präventiver Interventionen dar. Es ist denkbar, dass bei SCD subtile Defizite in kognitiven Kontrollfunktionen mit einer Fehlverteilung kognitiver Ressourcen und somit einer Beschleunigung des Auftretens klinisch relevanter kognitiver Beeinträchtigungen verbunden sind. Die anodale transkranielle Gleichstromstimulation (tDCS) des linken dorsolateralen präfrontalen Kortex (dlPFC) kann die kognitiven Kontrollfunktionen verbessern. Dies wurde insbesondere unter gleichzeitiger Anwendung einer anspruchsvollen und frustrierenden kontinuierlichen Leistungsaufgabe (Paced Auditory Serial Addition Task; PASAT) nachgewiesen (Plewnia et al., 2015a). In dieser randomisierten kontrollierten Studie erhielten 26 rechtshändige Probanden mit SCD im Alter über 60 Jahre entweder anodale oder Schein-tDCS über dem linken dlPFC während einem 4-wöchigen (12 Sitzungen) Training der kognitiven Kontrolle mittels eines adaptiven PASAT. Das Ausmaß der Sorgen hinsichtlich der Gedächtnisstörung wurde anhand einer 10-Punkte-Likert-Skala quantifiziert und diente als primärer Endpunkt. Im Vergleich zur Scheinstimulation verringerte die anodale tDCS das Ausmaß der Gedächtnissorgen signifikant, dabei ohne Auswirkungen auf die PASAT-Leistung. Dieser Effekt blieb bis zu 3 Monate lang erhalten. Unsere Ergebnisse unterstützen die Hypothese, dass aktivitätssteigernde anodale tDCS über dem linken dlPFC kombiniert mit kognitivem Kontrolltraining die Gedächtnissorgen von älteren Personen mit SCD mit einer großen Effektstärke reduzieren kann. Diese Pilotstudie liefert erste experimentelle Grundlagen die für die Planung größerer klinischer Studien zur Reduktion von Gedächtnissorgen und der Verzögerung des Auftretens objektiver Gedächtnisstörungen bei SCD genutzt werden können.

7. Bibliography

Aghjayan, S.L., Buckley, R.F., Vannini, P., Rentz, D.M., Jackson, J.D., Sperling, R.A., Johnson, K.A., Amariglio, R.E. (2017). The influence of demographic factors on subjective cognitive concerns and beta-amyloid. *Int. psychogeriatrics 29*, 645–652.

Almeida, O.P., Hankey, G.J., Yeap, B.B., Golledge, J., Flicker, L. (2017). Depression as a modifiable factor to decrease the risk of dementia. *Transl. Psychiatry 7*(5), e1117.

Amariglio, R.E., Becker, J.A., Carmasin, J., Wadsworth, L.P., Lorius, N., Sullivan, C., Maye, J.E., Gidicsin, C., Pepin, L.C., Sperling, R.A., Johnson, K.A., Rentz, D.M. (2012). Subjective cognitive complaints and amyloid burden in cognitively normal older individuals. *Neuropsychologia 50*, 2880–2886.

Amariglio, R.E., Buckley, R.F., Mormino, E.C., Marshall, G.A., Johnson, K.A., Rentz, D.M., Sperling, R.A. (2018). Amyloid-associated increases in longitudinal report of subjective cognitive complaints. *Alzheimer's Dement. Transl. Res. Clin. Interv. 4*, 444–449.

Amariglio, R.E., Mormino, E.C., Pietras, A.C., Marshall, G.A., Vannini, P., Johnson, K.A., Sperling, R.A., Rentz, D.M. (2015). Subjective cognitive concerns, amyloid-β, and neurodegeneration in clinically normal elderly. *Neurology 85,* 56–62.

Anderson, M.C., Green, C. (2001). Suppressing unwanted memories by executive control. *Nature 410*, 366–369.

Andrade, S.M., de Oliveira, E.A., Alves, N.T., dos Santos, A.C.G., de Mendonça, C.T.P.L., Sampaio, D.D.A., da Silva, E.E.Q.C., da Fonsêca, É.K.G., de Almeida Rodrigues, E.T., de Lima, G.N.S., Carvalho, J., da Silva, J.A.S., Toledo, M., da Rosa, M.R.D., Gomes, M.Q. de C., de Oliveira, M.M., Lemos, M.T.M., Lima, N.G., Inácio, P., da Cruz Ribeiro e Rodrigues, P.M., Ferreira, R.G.D., Cavalcante, R., de Brito Aranha, R.E.L., Neves, R., da Costa e Souza, R.M., Portugal, T.M., Martins, W.K.N., Pontes, V., de Paiva Fernandes, T.M., Contador, I., Fernández-Calvo, B. (2018). Neurostimulation Combined With Cognitive Intervention in Alzheimer's Disease (NeuroAD): Study Protocol of Double-Blind, Randomized, Factorial Clinical Trial. *Front. Aging Neurosci. 10*:334.

Antal, A., Alekseichuk, I., Bikson, M., Brockmöller, J., Brunoni, A.R., Chen, R., Cohen, L.G., Dowthwaite, G., Ellrich, J., Flöel, A., Fregni, F., George, M.S., Hamilton, R., Haueisen, J., Herrmann, C.S., Hummel, F.C., Lefaucheur, J.P., Liebetanz, D., Loo, C.K., McCaig, C.D., Miniussi, C., Miranda, P.C., Moliadze, V., Nitsche, M.A., Nowak, R., Padberg, F., Pascual-Leone, A., Poppendieck, W., Priori, A., Rossi, S., Rossini, P.M., Rothwell, J., Rueger, M.A., Ruffini, G., Schellhorn, K., Siebner, H.R., Ugawa, Y., Wexler, A., Ziemann, U., Hallett, M., Paulus, W. (2017). Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. *Clin. Neurophysiol. 128*(9):1774-1809

Antonenko, D., Külzow, N., Sousa, A., Prehn, K., Grittner, U., Flöel, A. (2018). Neuronal and behavioral effects of multi-day brain stimulation and memory training. *Neurobiol. Aging 61*, 245–254.

Arvanitakis, Z., Leurgans, S.E., Fleischman, D.A., Schneider, J.A., Rajan, K.B., Pruzin, J.J., Shah, R.C., Evans, D.A., Barnes, L.L., Bennett, D.A. (2018). Memory Complaints, Dementia, and Neuropathology in Older Blacks and Whites. *Ann. Neurol. 83*, 718.

Aschwanden, D., Sutin, A.R., Ledermann, T., Luchetti, M., Stephan, Y., Sesker, A.A., Zhu, X., Terracciano, A., Amariglio, R.E. (2022). Subjective Cognitive Decline: Is a Resilient Personality Protective Against Progression to Objective Cognitive Impairment? Findings from Two Community-Based Cohort Studies. *J. Alzheimers. Dis. 89*, 87–105.

Atkinson, R.C., Shiffrin, R.M. (1968). Human Memory: A Proposed System and its Control Processes. *Psychol. Learn. Motiv. - Adv. Res. Theory 2*, 89–195.

Aupperle, R.L., Melrose, A.J., Stein, M.B., Paulus, M.P. (2012). Executive function and PTSD: disengaging from trauma. *Neuropharmacology 62*, 686–694.

Baeken, C., Remue, J., Vanderhasselt, M.A., Brunoni, A.R., De Witte, S., Duprat, R., Koster, E.H.W., De Raedt, R., Wu, G.R. (2017). Increased left prefrontal brain perfusion after MRI compatible tDCS attenuates momentary ruminative self-referential thoughts. *Brain Stimul. 10*, 1088–1095.

Bainbridge, W.A., Berron, D., Schütze, H., Cardenas-Blanco, A., Metzger, C., Dobisch, L., Bittner, D., Glanz, W., Spottke, A., Rudolph, J., Brosseron, F., Buerger, K., Janowitz, D., Fliessbach, K., Heneka, M., Laske, C., Buchmann, M., Peters, O., Diesing, D., Li, S., Priller, J., Spruth, E.J., Altenstein, S., Schneider, A., Kofler, B., Teipel, S., Kilimann, I., Wiltfang, J., Bartels, C., Wolfsgruber, S., Wagner, M., Jessen, F., Baker, C.I., Düzel, E. (2019). Memorability of photographs in subjective cognitive decline and mild cognitive impairment: Implications for cognitive assessment. *Alzheimer's Dement. 11,* 610–618.

Baniqued, P.L., Allen, C.M., Kranz, M.B., Johnson, K., Sipolins, A., Dickens, C., Ward, N., Geyer, A., Kramer, A.F. (2015). Working Memory, Reasoning, and Task Switching Training: Transfer Effects, Limitations, and Great Expectations? *PLoS One 10*, e0142169.

Barbey, A.K., Koenigs, M., Grafman, J. (2013). Dorsolateral prefrontal contributions to human working memory. Cortex. 49, 1195–1205.

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M.F., Nitsche, M.A. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *J. Physiol. 591,* 1987–2000.

Beard, J.R., Officer, A.M., Cassels, A.K. (2016). The World Report on Ageing and Health. *Gerontologist 56*, S163–S166.

Beck, A. (1967). Depression: clinical, experimental, and theoretical aspects. Hoeber Medical Division Harper & Row, New York.

Beck, A.T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *Am. J. Psychiatry 165*, 969–977.

Begemann, M.J., Brand, B.A., Curčić-Blake, B., Aleman, A., Sommer, I.E. (2020). Efficacy of non-invasive brain stimulation on cognitive functioning in brain disorders: a meta-analysis. *Psychol. Med. 50*(15), 2465-2486.

Bennett, S., Thomas, A.J. (2014). Depression and dementia: cause, consequence or coincidence? *Maturitas 79*, 184–190.

Benwell, C.S.Y., Learmonth, G., Miniussi, C., Harvey, M., Thut, G. (2015). Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralized attention bias. *Cortex. 69*, 152–165.

Bergua, V., Meillon, C., Potvin, O., Bouisson, J., Le Goff, M., Rouaud, O., Ritchie, K., Dartigues, J.F., Amieva, H. (2012). The STAI-Y trait scale: psychometric properties and normative data from a large population-based study of elderly people. *Int. psychogeriatrics 24*, 1163–1171.

Berk, L., van Boxtel, M., Köhler, S., van Os, J. (2017). Positive affect and cognitive decline: a 12-year follow-up of the Maastricht Aging Study. *Int. J. Geriatr. Psychiatry 32*, 1305–1311.

Berres, M., Monsch, A.U., Bernasconi, F., Thalmann, B., Stähelin, H.B. (2000). Normal ranges of neuropsychological tests for the diagnosis of Alzheimer's disease. *Stud Heal. Technol Inf. 77*, 195–204.

Berryhill, M.E., Jones, K.T. (2012). tDCS selectively improves working memory in older adults with more education. *Neurosci. Lett. 521*, 148–151.

Berryhill, M.E., Martin, D. (2018). Cognitive Effects of Transcranial Direct Current Stimulation in Healthy and Clinical Populations: An Overview. *J. ECT 34*, e25–e35.

Berryhill, M.E., Peterson, D., Jones, K., Stephens, J. (2014). Hits and misses: leveraging tDCS to advance cognitive research. *Front. Psychol. 5*, 800.

Bertrams, A., Englert, C., Dickhäuser, O., Baumeister, R.F. (2013). Role of self-control strength in the relation between anxiety and cognitive performance. *Emotion 13*, 668–680.

Bikson, M., Datta, A., Rahman, A., Scaturro, J. (2010). Electrode montages for tDCS and weak transcranial electrical stimulation: role of "return" electrode's position and size. *Clin. Neurophysiol. 121*, 1976–1978.

Bikson, M., Grossman, P., Thomas, C., Zannou, A.L., Jiang, J., Adnan, T., Mourdoukoutas, A.P., Kronberg, G., Truong, D., Boggio, P., Brunoni, A.R., Charvet, L., Fregni, F., Fritsch, B., Gillick, B., Hamilton, R.H., Hampstead, B.M., Jankord, R., Kirton, A., Knotkova, H., Liebetanz, D., Liu, A., Loo, C., Nitsche, M.A., Reis, J., Richardson, J.D., Rotenberg, A., Turkeltaub, P.E., Woods, A.J. (2016a). Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. *Brain Stimul. 9*, 641–661.

Bikson, M., Paneri, B., Giordano, J. (2016b). The off-label use, utility and potential value of tDCS in the clinical care of particular neuropsychiatric conditions. *J. Law Biosci. 3*, 642–646.

Bikson, M., Rahman, A. (2013). Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms. *Front. Hum. Neurosci. 7*:688.

Bliss, T.V.P., Cooke, S.F. (2011). Long-term potentiation and long-term depression: a clinical perspective. *Clinics 66* Suppl 1:3-17.

Boggio, P.S., Ferrucci, R., Rigonatti, S.P., Covre, P., Nitsche, M., Pascual-Leone, A., Fregni, F. (2006). Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *J. Neurol. Sci. 249*, 31–38.

Boone, K.B. (2009). Fixed belief in cognitive dysfunction despite normal neuropsychological scores: neurocognitive hypochondriasis? *Clin. Neuropsychol. 23,* 1016–1036.

Braver, T.S., Paxton, J.L., Locke, H.S., Barch, D.M. (2009). Flexible neural mechanisms of cognitive control within human prefrontal cortex. *Proc. Natl. Acad. Sci. USA 106*, 7351–7356.

Brunoni, A.R., Amadera, J., Berbel, B., Volz, M.S., Rizzerio, B.G., Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int. J. Neuropsychopharmacol. 14*, 1133–1145.

Brunoni, A.R., Moffa, A.H., Fregni, F., Palm, U., Padberg, F., Blumberger, D.M., Daskalakis, Z.J., Bennabi, D., Haffen, E., Alonzo, A., Loo, C.K. (2016). Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. *Br. J. Psychiatry 208*, 522–531.

Brunoni, A.R., Nitsche, M.A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., Edwards, D.J., Valero-Cabre, A., Rotenberg, A., Pascual-Leone, A., Ferrucci, R., Priori, A., Boggio, P.S., Fregni, F. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul. 5*, 175–195.

Brunoni, A.R., Vanderhasselt, M.A. (2014). Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. *Brain Cogn. 86*, 1–9.

Brunoni, A.R., Zanao, T.A., Vanderhasselt, M.A., Valiengo, L., De Oliveira, J.F., Boggio, P.S., Lotufo, P.A., Benseñor, I.M., Fregni, F. (2014). Enhancement of affective processing induced by bifrontal transcranial direct current stimulation in patients with major depression. *Neuromodulation 17*, 138–142.

Buckley, R., Saling, M.M., Ames, D., Rowe, C.C., Lautenschlager, N.T., MacAulay, S.L., Martins, R.N., Masters, C.L., O'Meara, T., Savage, G., Szoeke, C., Villemagne, V.L., Ellis, K.A. (2013). Factors affecting subjective memory complaints in the AIBL aging study: biomarkers, memory, affect, and age. *Int. psychogeriatrics 25*, 1307–1315.

Buckley, R.F., Hanseeuw, B., Schultz, A.P., Vannini, P., Aghjayan, S.L., Properzi, M.J., Jackson, J.D., Mormino, E.C., Rentz, D.M., Sperling, R.A., Johnson, K.A., Amariglio, R.E. (2017). Region-Specific Association of Subjective Cognitive Decline With Tauopathy Independent of Global β-Amyloid Burden. *JAMA Neurol. 74,* 1455.

Burton, C.Z., Garnett, E.O., Capellari, E., Chang, S.E., Tso, I.F., Hampstead, B.M., Taylor, S.F. (2023). Combined Cognitive Training and Transcranial Direct Current Stimulation in Neuropsychiatric Disorders: A Systematic Review and Meta-analysis. *Biol. psychiatry. Cogn. Neurosci. Neuroimaging 8*, 151–161.

Cabeza, R., Albert, M., Belleville, S., Craik, F.I.M., Duarte, A., Grady, C.L., Lindenberger, U., Nyberg, L., Park, D.C., Reuter-Lorenz, P.A., Rugg, M.D., Steffener, J., Rajah, M.N. (2018). Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nat. Rev. Neurosci. 19*, 701–710.

Cabeza, R., Dennis, N.A. (2013). Reuter-Lorenz, Patricia A. and others (eds), 'Frontal Lobes and Aging: Deterioration and Compensation', in Donald T. Stuss, and Robert T. Knight (eds), Principles of Frontal Lobe Function (Oxford University Press, 1 Sept. 2013). Pages 628–652.

Calkins, A.W., McMorran, K.E., Siegle, G.J., Otto, M.W. (2015). The Effects of Computerized Cognitive Control Training on Community Adults with Depressed Mood. *Behav. Cogn. Psychother. 43*, 578–589.

Chaieb, L., Antal, A., Ambrus, G.G., Paulus, W. (2014). Brain-derived neurotrophic factor: Its impact upon neuroplasticity and neuroplasticity inducing transcranial brain stimulation protocols. *Neurogenetics 15*, 1–11.

Chaieb, L., Antal, A., Paulus, W. (2008). Gender-specific modulation of short-term neuroplasticity in the visual cortex induced by transcranial direct current stimulation. *Vis. Neurosci. 25*, 77–81.

Chase, H.W., Boudewyn, M.A., Carter, C.S., Phillips, M.L. (2020). Transcranial direct current stimulation: a roadmap for research, from mechanism of action to clinical implementation. *Mol. Psychiatry 25,* 397–407.

Chen, J., Wang, Z., Chen, Q., Fu, Y., Zheng, K. (2022). Transcranial Direct Current Stimulation Enhances Cognitive Function in Patients with Mild Cognitive Impairment and Early/Mid Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Brain Sci. 12*(5):562.

Christova, M., Rafolt, D., Gallasch, E. (2015). Cumulative effects of anodal and priming cathodal tDCS on pegboard test performance and motor cortical excitability. *Behav. Brain Res. 287*, 27–33.

Chu, C.S., Li, C.T., Brunoni, A.R., Yang, F.C., Tseng, P.T., Tu, Y.K., Stubbs, B., Carvalho, A.F., Thompson, T., Rajji, T.K., Yeh, T.C., Tsai, C.K., Chen, T.Y., Li, D.J., Hsu, C.W., Wu, Y.C., Yu, C.L., Liang, C.S. (2021). Cognitive effects and acceptability of non-invasive brain stimulation on Alzheimer's disease and mild cognitive impairment: a component network meta-analysis. *J. Neurol. Neurosurg. Psychiatry 92*, 195–203.

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A. (1993). Gene Dose of Apolipoprotein E Type 4 Allele and the Risk of Alzheimer's Disease in Late Onset Families. *Science 261*(5123), 921–923.

Coutlee, C.G., Huettel, S.A. (2012). The functional neuroanatomy of decision making: prefrontal control of thought and action. *Brain Res. 1428*, 3–12.

Crawford, J.R., Henry, J.D. (2004). The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. *Br. J. Clin. Psychol. 43*, 245–265.

Creutzfeldt, O.D., Fromm, G.H., Kapp, H. (1962). Influence of transcortical d-c currents on cortical neuronal activity. *Exp. Neurol. 5*, 436–452.

Cruz Gonzalez, P., Fong, K.N.K., Brown, T. (2018). The Effects of Transcranial Direct Current Stimulation on the Cognitive Functions in Older Adults with Mild Cognitive Impairment: A Pilot Study. *Behav. Neurol. 2018:*5971385*.*

DaSilva, A.F., Volz, M.S., Bikson, M., Fregni, F. (2011). Electrode Positioning and Montage in Transcranial Direct Current Stimulation. *J. Vis. Exp. 51:*2744.

Datta, A., Elwassif, M., Battaglia, F., Bikson, M. (2008). Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis. *J. Neural Eng. 5*, 163–174.

De Raedt, R., Remue, J., Loeys, T., Hooley, J.M., Baeken, C. (2017). The effect of transcranial direct current stimulation of the prefrontal cortex on implicit self-esteem is mediated by rumination after criticism. *Behav. Res. Ther. 99*, 138–146.

de Sousa, A.V.C., Grittner, U., Rujescu, D., Külzow, N., Flöel, A. (2020). Impact of 3-Day Combined Anodal Transcranial Direct Current Stimulation-Visuospatial Training on Object-Location Memory in Healthy Older Adults and Patients with Mild Cognitive Impairment. *J. Alzheimer's Dis. 75*, 223–244.

Dedoncker, J., Brunoni, A.R., Baeken, C., Vanderhasselt, M.-A. (2016). A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) Over the Dorsolateral Prefrontal Cortex in Healthy and Neuropsychiatric Samples: Influence of Stimulation Parameters. *Brain Stimul. 9*(4):501-17.

DeFelipe, J., (2006). Brain plasticity and mental processes: Cajal again. *Nat. Rev. Neurosci. 7*, 811–817.

Diamond, A. (2013). Executive Functions. *Annu Rev Psychol 64*:135-168.

Diehl, M., Hay, E.L., Berg, K.M. (2011). The ratio between positive and negative affect and flourishing mental health across adulthood. *Aging Ment. Health 15*, 882–893.

Dockery, C.A., Hueckel-Weng, R., Birbaumer, N., Plewnia, C. (2009). Enhancement of planning ability by transcranial direct current stimulation. J. *Neurosci. 29*, 7271–7277.

Dodich, A., Carli, G., Cerami, C., Iannaccone, S., Magnani, G., Perani, D. (2017). Social and cognitive control skills in long-life occupation activities modulate the brain reserve in the behavioural variant of frontotemporal dementia. *Cortex 99*:311-318.

Dolcos, F., McCarthy, G. (2006). Brain systems mediating cognitive interference by emotional distraction. *J. Neurosci. 26*, 2072–2079.

Duecker, F., de Graaf, T.A., Sack, A.T. (2014). Thinking caps for everyone? The role of neuro-enhancement by non-invasive brain stimulation in neuroscience and beyond. *Front. Syst. Neurosci. 8*, 71.

Duverne, S., Koechlin, E. (2017). Hierarchical Control of Behaviour in Human Prefrontal Cortex. *Wiley Handb. Cogn. Control* 207–220.

Egner, T., Hirsch, J. (2005). Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. *Nat. Neurosci. 8*, 1784–1790.

Ehlis, A.C., Haeussinger, F.B., Gastel, A., Fallgatter, A.J., Plewnia, C., 2016. Task-dependent and polarity-specific effects of prefrontal transcranial direct current stimulation on cortical activation during word fluency. *Neuroimage 140*, 134–140.

Ehring, T., Watkins, E.R. (2008). Repetitive Negative Thinking as a Transdiagnostic Process. *Int. J. Cogn. Ther. 1*, 192–205.

Elfgren, C., Gustafson, L., Vestberg, S., Passant, U. (2010). Subjective memory complaints, neuropsychological performance and psychiatric variables in memory clinic attendees: A 3-year follow-up study. *Arch. Gerontol. Geriatr. 51*(3):e110-4.

Erk, S., Spottke, A., Meisen, A., Wagner, M., Walter, H., Jessen, F. (2011). Evidence of neuronal compensation during episodic memory in subjective memory impairment. *Arch. Gen. Psychiatry 68*, 845–52.

Esmaeilpour, Z., Marangolo, P., Hampstead, B.M., Bestmann, S., Galletta, E., Knotkova, H., Bikson, M. (2018). Incomplete evidence that increasing current intensity of tDCS boosts outcomes. *Brain Stimul. 11*, 310–321.

Eysenck, M.W., Derakshan, N., Santos, R., Calvo, M.G. (2007). Anxiety and cognitive performance: Attentional control theory. *Emotion 7*(2):336-53

Fales, C.L., Barch, D.M., Rundle, M.M., Mintun, M.A., Snyder, A.Z., Cohen, J.D., Mathews, J., Sheline, Y.I. (2008). Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. *Biol. Psychiatry*

63, 377–384.

Feeser, M., Prehn, K., Kazzer, P., Mungee, A., Bajbouj, M. (2014). Transcranial Direct Current Stimulation Enhances Cognitive Control During Emotion Regulation. *Brain Stimul. 7*, 105–112.

Fernández-Blázquez, M.A., Ávila-Villanueva, M., Maestú, F., Medina, M. (2016). Specific Features of Subjective Cognitive Decline Predict Faster Conversion to Mild Cognitive Impairment. *J. Alzheimers. Dis. 52*, 271–81.

Ferrucci, R., Mameli, F., Guidi, I., Mrakic-Sposta, S., Vergari, M., Marceglia, S., Cogiamanian, F., Barbieri, S., Scarpini, E., Priori, A. (2008). Transcranial direct current stimulation improves recognition memory in Alzheimer disease. *Neurology 71*, 493–498.

Fertonani, A., Ferrari, C., Miniussi, C. (2015). What do you feel if I apply transcranial electric stimulation? Safety, sensations and secondary induced effects. *Clin. Neurophysiol. 126*, 2181–2188.

Flöel, A. (2014). tDCS-enhanced motor and cognitive function in neurological diseases. *Neuroimage 85* Pt 3, 934–947.

Franzmeier, N., Ren, J., Damm, A., Monté-Rubio, G., Boada, M., Ruiz, A., Ramirez, A., Jessen, F., Düzel, E., Rodríguez Gómez, O., Benzinger, T., Goate, A., Karch, C.M., Fagan, A.M., McDade, E., Buerger, K., Levin, J., Duering, M., Dichgans, M., Suárez-Calvet, M., Haass, C., Gordon, B.A., Lim, Y.Y., Masters, C.L., Janowitz, D., Catak, C., Wolfsgruber, S., Wagner, M., Milz, E., Moreno-Grau, S., Teipel, S., Grothe, M.J., Kilimann, I., Rossor, M., Fox, N., Laske, C., Chhatwal, J., Falkai, P., Perneczky, R., Lee, J.H., Spottke, A., Boecker, H., Brosseron, F., Fliessbach, K., Heneka, M.T., Nestor, P., Peters, O., Fuentes, M., Menne, F., Priller, J., Spruth, E.J., Franke, C., Schneider, A., Westerteicher, C., Speck, O., Wiltfang, J., Bartels, C., Araque Caballero, M.Á., Metzger, C., Bittner, D., Salloway, S., Danek, A., Hassenstab, J., Yakushev, I., Schofield, P.R., Morris, J.C., Bateman, R.J., Ewers, M. (2021). The BDNFVal66Met SNP modulates the association between beta-amyloid and hippocampal disconnection in Alzheimer's disease. *Mol. Psychiatry 26*, 614–628.

Gandiga, P.C., Hummel, F.C., Cohen, L.G. (2006). Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin. Neurophysiol. 117*, 845–850.

Gazzaley, A., Rissman, J., D'Esposito, M. (2004). Functional connectivity during working memory maintenance. *Cogn. Affect. Behav. Neurosci. 4*, 580–599.

Goldthorpe, R.A., Rapley, J.M., Violante, I.R. (2020). A Systematic Review of Non-invasive Brain Stimulation Applications to Memory in Healthy Aging. *Front. Neurol. 11*:57507.

Gonsalvez, I., Baror, R., Fried, P., Santarnecchi, E., Pascual-Leone, A., (2017). Therapeutic Noninvasive Brain Stimulation in Alzheimer's Disease. *Curr. Alzheimer Res. 14*(4):362-376.

Gonzalez, R., Grant, I., Miller, S.W., Taylor, M.J., Schweinsburg, B.C., Carey, C.L., Woods, S.P., Norman, M.A., Rippeth, J.D., Martin, E.M., Heaton, R.K. (2006). Demographically adjusted normative standards for new indices of performance on the Paced Auditory Serial Addition Task (PASAT). *Clin. Neuropsychol. 20*, 396–413.

Gorwood, P., Corruble, E., Falissard, B., Goodwin, G.M. (2008). Toxic effects of depression on brain function: impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. *Am. J. Psychiatry 165*, 731–739.

Goschke, T. (2014). Dysfunctions of decision-making and cognitive control as transdiagnostic mechanisms of mental disorders: advances, gaps, and needs in current research. *Int. J. Methods Psychiatr. Res. 23* (Suppl 1), 41–57.

Goschke, T. (2003). Voluntary action and cognitive control from a cognitive neuroscience perspective. In S. Maasen, W. Prinz, G. Roth (Eds.), *Voluntary action: Brains, minds, and sociality* (pp. 49–85). Oxford University Press.

Grahek, I., Everaert, J., Krebs, R.M., Koster, E.H.W. (2018). Cognitive Control in Depression: Toward Clinical Models Informed by Cognitive Neuroscience: *Clinical Psychological Science, 6*(4), 464–480.

Groenewold, N.A., Opmeer, E.M., de Jonge, P., Aleman, A., Costafreda, S.G. (2013). Emotional valence modulates brain functional abnormalities in depression: evidence from a meta-analysis of fMRI studies. *Neurosci. Biobehav. Rev. 37*, 152–163.

Gronwall, D.M. (1977). Paced auditory serial-addition task: a measure of recovery from concussion. *Percept. Mot. Skills 44*, 367–73.

Gross, J.J., John, O.P. (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *J. Pers. Soc. Psychol. 85*, 348–362.

Haatveit, B.C., Sundet, K., Hugdahl, K., Ueland, T., Melle, I., Andreassen, O.A. (2010). The validity of d prime as a working memory index: Results from the “Bergen n-back task.” *J. Clin. Exp. Neuropsychol. 32*, 871–880.

Habich, A., Fehér, K.D., Antonenko, D., Boraxbekk, C.J., Flöel, A., Nissen, C., Siebner, H.R., Thielscher, A., Klöppel, S. (2020). Stimulating aged brains with transcranial direct current stimulation: Opportunities and challenges. *Psychiatry Res. Neuroimaging 306*:111179.

Hänninen, T., Reinikainen, K.J., Helkala, E. -L, Koivisto, K., Mykkänen, L., Laakso, M., Pyörälä, K., Riekkinen, P.J. (1994). Subjective memory complaints and personality traits in normal elderly subjects. *J. Am. Geriatr. Soc. 42*, 1–4.

Harper, A., Power, M., Orley, J., Herrman, H., Schofield, H., Murphy, B., Metelko, Z., Szabo, S., Pibernik-Okanovic, M., Quemada, N., Caria, A., Rajkumar, S., Kumar, S., Saxena, S., Chandiramani, K., Amir, M., Bar-On, D., Tazaki, M., Noji, A., Van Heck, G., De Vries, J., Sucre, J.A., Picard-Ami, L., Kabanov, M., Lomachenkov, A., Burkovsky, G., Carrasco, R.L., Bodharamik, Y., Meesapya, K., Skevington, S., Patrick, D., Martin, M., Wild, D., Acuda, W., Mutambirwa, J., Bonicaato, S., Yongping, G., Fleck, M., Angermeyer, M.C., Kilian, R., Kwok-fai, L., Billington, R., Bullinger, M., Kuyken, W., Sartorius, N. (1998). Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. *Psychol. Med. 28*, 551–558.

Heeren, A., Baeken, C., Vanderhasselt, M.A., Philippot, P., De Raedt, R. (2015). Impact of Anodal and Cathodal Transcranial Direct Current Stimulation over the Left Dorsolateral Prefrontal Cortex during Attention Bias Modification: An Eye-Tracking Study. *PLoS One 10*(4):e0124182.

Herrington, J.D., Mohanty, A., Koven, N.S., Fisher, J.E., Stewart, J.L., Banich, M.T., Webb, A.G., Miller, G.A., Heller, W. (2005). Emotion-modulated performance and activity in left dorsolateral prefrontal cortex. *Emotion 5*, 200–207.

Hertzog, C., Hülür, G., Gerstorf, D., Pearman, A.M. (2018). Is subjective memory change in old age based on accurate monitoring of age-related memory change? Evidence from two longitudinal studies. *Psychol. Aging 33*, 273–287.

Hill, A.T., Fitzgerald, P.B., Hoy, K.E. (2016). Effects of Anodal Transcranial Direct Current Stimulation on Working Memory: A Systematic Review and Meta-Analysis of Findings From Healthy and Neuropsychiatric Populations. *Brain Stimul. 9*, 197–208.

Hill, N.L., Mogle, J.M., Munoz, E., Wion, R., Colancecco, E.M. (2015). Assessment of subjective cognitive impairment among older adults. *J. Gerontol. Nurs. 41*, 28–35.

Hinz, A., Conrad, I., Schroeter, M.L., Glaesmer, H., Brähler, E., Zenger, M., Kocalevent, R.D., Herzberg, P.Y. (2018). Psychometric properties of the Satisfaction with Life Scale (SWLS), derived from a large German community sample. *Qual. Life Res. 27*, 1661–1670.

Hirsch, C.R., Mathews, A. (2012). A cognitive model of pathological worry. *Behav. Res. Ther. 50*, 636–646.

Hoebeke, Y., Desmedt, O., Özçimen, B., Heeren, A. (2021). The impact of transcranial Direct Current stimulation on rumination: A systematic review of the sham-controlled studies in healthy and clinical samples. *Compr. Psychiatry 106*:152226.

Hoorelbeke, K., Koster, E.H.W., Vanderhasselt, M.A., Callewaert, S., Demeyer, I. (2015). The influence of cognitive control training on stress reactivity and rumination in response to a lab stressor and naturalistic stress. *Behav. Res. Ther. 69*, 1–10.

Horne, K.S., Filmer, H.L., Nott, Z.E., Hawi, Z., Pugsley, K., Mattingley, J.B., Dux, P.E. (2021). Evidence against benefits from cognitive training and transcranial direct current stimulation in healthy older adults. *Nat. Hum. Behav. 5*, 146–158.

Horvath, J.C., Carter, O., Forte, J.D. (2014). Transcranial direct current stimulation: five important issues we aren’t discussing (but probably should be). *Front. Syst. Neurosci. 8*:2.

Hoy, K.E., Arnold, S.L., Emonson, M.R.L., Daskalakis, Z.J., Fitzgerald, P.B. (2014). An investigation into the effects of tDCS dose on cognitive performance over time in patients with schizophrenia. *Schizophr. Res. 155*, 96–100.

Hsu, T.Y., Juan, C.H., Tseng, P. (2016). Individual Differences and State-Dependent Responses in Transcranial Direct Current Stimulation. *Front. Hum. Neurosci. 10*:643.

Hsu, W.-Y., Ku, Y., Zanto, T.P., Gazzaley, A. (2015). Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer’s disease: a systematic review and meta-analysis. *Neurobiol. Aging 36*, 2348–59.

Hunter, M.A., Coffman, B.A., Trumbo, M.C., Clark, V.P. (2013). Tracking the neuroplastic changes associated with transcranial direct current stimulation: a push for multimodal imaging. *Front. Hum. Neurosci. 7:* 495.

Huo, L., Zheng, Z., Li, Jin, Wan, W., Cui, X., Chen, S., Wang, W., Li, J. (2018). Long-Term Transcranial Direct Current Stimulation Does Not Improve Executive Function in Healthy Older Adults. *Front. Aging Neurosci. 10*:298.

Inagawa, T., Narita, Z., Sugawara, N., Maruo, K., Stickley, A., Yokoi, Y., Sumiyoshi, T.

(2019). A Meta-Analysis of the Effect of Multisession Transcranial Direct Current Stimulation on Cognition in Dementia and Mild Cognitive Impairment. *Clin. EEG Neurosci. 50*, 273–282.

IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.

Ironside, M., Browning, M., Ansari, T.L., Harvey, C.J., Sekyi-Djan, M.N., Bishop, S.J., Harmer, C.J., O'Shea, J. (2019). Effect of Prefrontal Cortex Stimulation on Regulation of Amygdala Response to Threat in Individuals With Trait Anxiety: A Randomized Clinical Trial. *JAMA psychiatry 76*, 71–78.

Iyer, M.B., Mattu, U., Grafman, J., Lomarev, M., Sato, S., Wassermann, E.M. (2005). Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology 64*, 872–875.

Jack, C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R., Elliott, C., Masliah, E., Ryan, L., Silverberg, N. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's Dement. 14*(4):535-562

Jacobson, L., Koslowsky, M., Lavidor, M. (2012). tDCS polarity effects in motor and cognitive domains: a meta-analytical review. *Exp. brain Res. 216*, 1–10.

Jaeggi, S.M., Studer-Luethi, B., Buschkuehl, M., Su, Y.F., Jonides, J., Perrig, W.J. (2010). The relationship between n-back performance and matrix reasoning — implications for training and transfer. *Intelligence 38*, 625–635.

Janssen, O., Jansen, W.J., Vos, S.J.B., Boada, M., Parnetti, L., Gabryelewicz, T., Fladby, T., Molinuevo, J.L., Villeneuve, S., Hort, J., Epelbaum, S., Lleó, A., Engelborghs, S., van der Flier, W.M., Landau, S., Popp, J., Wallin, A., Scheltens, P., Rikkert, M.O., Snyder, P.J., Rowe, C., Chételat, G., Ruíz, A., Marquié, M., Chipi, E., Wolfsgruber, S., Heneka, M., Boecker, H., Peters, O., Jarholm, J., Rami, L., Tort-Merino, A., Binette, A.P., Poirier, J., Rosa-Neto, P., Cerman, J., Dubois, B., Teichmann, M., Alcolea, D., Fortea, J., Sánchez-Saudinós, M.B., Ebenau, J., Pocnet, C., Eckerström, M., Thompson, L., Villemagne, V., Buckley, R., Burnham, S., Delarue, M., Freund-Levi, Y., Wallin, Å.K., Ramakers, I., Tsolaki, M., Soininen, H., Hampel, H., Spiru, L., Tijms, B., Ossenkoppele, R., Verhey, F.R.J., Jessen, F., Visser, P.J.(2022).Characteristics of subjective cognitive decline associated with amyloid positivity. *Alzheimers. Dement.18*, 1832–1845.

Jessen, F., Amariglio, R.E., Buckley, R.F., van der Flier, W.M., Han, Y., Molinuevo, J.L., Rabin, L., Rentz, D.M., Rodriguez-Gomez, O., Saykin, A.J., Sikkes, S.A.M., Smart, C.M., Wolfsgruber, S., Wagner, M. (2020). The characterisation of subjective cognitive decline. *Lancet Neurol. 19*(3):271-278.

Jessen, F., Amariglio, R.E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chételat, G., Dubois, B., Dufouil, C., Ellis, K.A., van der Flier, W.M., Glodzik, L., van Harten, A.C., de Leon, M.J., McHugh, P., Mielke, M.M., Molinuevo, J.L., Mosconi, L., Osorio, R.S., Perrotin, A., Petersen, R.C., Rabin, L.A., Rami, L., Reisberg, B., Rentz, D.M., Sachdev, P.S., de la Sayette, V., Saykin, A.J., Scheltens, P., Shulman, M.B., Slavin, M.J., Sperling, R.A., Stewart, R., Uspenskaya, O., Vellas, B., Visser, P.J., Wagner, M., Subjective Cognitive Decline Initiative (SCD-I) Working Group. (2014a). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers. Dement. 10*, 844–

52.

Jessen, F., Wiese, B., Bachmann, C., Eifflaender-Gorfer, S., Haller, F., Kölsch, H., Luck, T., Mösch, E., Van Den Bussche, H., Wagner, M., Wollny, A., Zimmermann, T., Pentzek, M., Riedel-Heller, S.G., Romberg, H.P., Weyerer, S., Kaduszkiewicz, H., Maier, W., Bickel, H. (2010). Prediction of dementia by subjective memory impairment effects of severity and temporal association with cognitive impairment. *Arch. Gen. Psychiatry 67*, 414–422.

Jessen, F., Wolfsgruber, S., Kleineindam, L., Spottke, A., Altenstein, S., Bartels, C., Berger, M., Brosseron, F., Daamen, M., Dichgans, M., Dobisch, L., Ewers, M., Fenski, F., Fliessbach, K., Freiesleben, S.D., Glanz, W., Görß, D., Gürsel, S., Janowitz, D., Kilimann, I., Kobeleva, X., Lohse, A., Maier, F., Metzger, C., Munk, M., Preis, L., Sanzenbacher, C., Spruth, E., Rauchmann, B., Vukovich, R., Yakupov, R., Weyrauch, A.S., Ziegler, G., Schmid, M., Laske, C., Perneczky, R., Schneider, A., Wiltfang, J., Teipel, S., Bürger, K., Priller, J., Peters, O., Ramirez, A., Boecker, H., Heneka, M.T., Wagner, M., Düzel, E. (2023). Subjective cognitive decline and stage 2 of Alzheimer disease in patients from memory centers. *Alzheimers. Dement. 19*, 487–497.

Jessen, F., Wolfsgruber, S., Wiese, B., Bickel, H., Mösch, E., Kaduszkiewicz, H., Pentzek, M., Riedel-Heller, S.G., Luck, T., Fuchs, A., Weyerer, S., Werle, J., van den Bussche, H., Scherer, M., Maier, W., Wagner, M., German Study on Aging, Cognition and Dementia in Primary Care Patients. (2014b). AD dementia risk in late MCI, in early MCI, and in subjective memory impairment. *Alzheimer's Dement. 10*, 76–83.

Jones, E.G. (2004). Plasticity and neuroplasticity. *J. Hist. Neurosci. 13*, 293.

Jones, K.T., Berryhill, M.E. (2012). Parietal contributions to visual working memory depend on task difficulty. *Front. psychiatry 3*:81.

Jones, K.T., Gözenman, F., Berryhill, M.E. (2015). The strategy and motivational influences on the beneficial effect of neurostimulation: a tDCS and fNIRS study. *Neuroimage 105*, 238–247.

Jones, N.P., Siegle, G.J., Muelly, E.R., Haggerty, A., Ghinassi, F. (2010). Poor performance on cognitive tasks in depression: Doing too much or not enough? *Cogn. Affect. Behav. Neurosci. 10*, 129–140.

Joormann, J., D'Avanzato, C. (2010). Emotion regulation in depression: Examining the role of cognitive processes. *Cognition and Emotion, 24*(6), 913–939.

Joshi, Y.B., Praticò, D. (2013). Stress and HPA axis dysfunction in Alzheimer's disease. In: Praticò D, Mecocci P, editors. Studies on Alzheimer's Disease Oxidative Stress in Applied Basic Research and Clinical Practice. New York: Springer; pp. 159-165.

Kabakov, A.Y., Muller, P.A., Pascual-Leone, A., Jensen, F.E., Rotenberg, A. (2012). Contribution of axonal orientation to pathway-dependent modulation of excitatory transmission by direct current stimulation in isolated rat hippocampus. *J. Neurophysiol. 107*, 1881–1889.

Kapogiannis, D., Sutin, A., Davatzikos, C., Costa, P., Resnick, S. (2013). The five factors of personality and regional cortical variability in the Baltimore longitudinal study of aging. *Hum. Brain Mapp. 34*, 2829–2840.

Keeser, D., Padberg, F., Reisinger, E., Pogarell, O., Kirsch, V., Palm, U., Karch, S., Möller, H.J., Nitsche, M.A., Mulert, C. (2011). Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA) study. *Neuroimage 55*, 644–657.

Kekic, M., Boysen, E., Campbell, I.C., Schmidt, U.(2016). A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. *J. Psychiatr. Res. 74*, 70–86.

Khan, F., Amatya, B., Galea, M.P., Gonzenbach, R., Kesselring, J. (2017). Neurorehabilitation: applied neuroplasticity. *J. Neurol. 264*, 603–615.

Khedr, E.M., Gamal, N.F. El, El-Fetoh, N.A., Khalifa, H., Ahmed, E.M., Ali, A.M., Noaman, M., El-Baki, A.A., Karim, A.A. (2014). A Double-Blind Randomized Clinical Trial on the Efficacy of Cortical Direct Current Stimulation for the Treatment of Alzheimer's Disease. *Front. Aging Neurosci. 6*, 275.

Kim, J.H., Kim, D.W., Chang, W.H., Kim, Y.H., Kim, K., Im, C.H. (2014). Inconsistent outcomes of transcranial direct current stimulation may originate from anatomical differences among individuals: electric field simulation using individual MRI data. *Neurosci. Lett. 564*, 6–10.

Kim, S., Stephenson, M.C., Morris, P.G., Jackson, S.R. (2014). tDCS-induced alterations in GABA concentration within primary motor cortex predict motor learning and motor memory: a 7 T magnetic resonance spectroscopy study. *Neuroimage 99*, 237–243.

Kirchner, W.K. (1958). Age differences in short-term retention of rapidly changing information. *J. Exp. Psychol.* 352–358.

Kleineidam, L., Wagner, M., Guski, J., Wolfsgruber, S., Miebach, L., Bickel, H., König, H.H., Weyerer, S., Lühmann, D., Kaduszkiewicz, H., Luppa, M., Röhr, S., Pentzek, M., Wiese, B., Maier, W., Scherer, M., Kornhuber, J., Peters, O., Frölich, L., Wiltfang, J., Lewczuk, P., Hüll, M., Ramirez, A., Jessen, F., Riedel-Heller, S.G., Heser, K. (2022). Disentangling the relationship of subjective cognitive decline and depressive symptoms in the development of cognitive decline and dementia. *Alzheimers. Dement 19*(5):2056-2068.

Koechlin, E., Ody, C., Kouneiher, F. (2003). The architecture of cognitive control in the human prefrontal cortex. *Science 302*, 1181–1185.

Koenigs, M., Grafman, J. (2009). The functional neuroanatomy of depression: Distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behav. Brain Res. 201*, 239.

Koo, G.K., Gaur, A., Tumati, S., Kusumo, R.W., Bawa, K.K., Herrmann, N., Gallagher, D., Lanctôt, K.L. (2023). Identifying factors influencing cognitive outcomes after anodal transcranial direct current stimulation in older adults with and without cognitive impairment: A systematic review. *Neurosci. Biobehav. Rev. 146,*105047.

Koppara, A., Wagner, M., Lange, C., Ernst, A., Wiese, B., König, H.H., Brettschneider, C., Riedel-Heller, S., Luppa, M., Weyerer, S., Werle, J., Bickel, H., Mösch, E., Pentzek, M., Fuchs, A., Wolfsgruber, S., Beauducel, A., Scherer, M., Maier, W., Jessen, F. (2015). Cognitive performance before and after the onset of subjective cognitivedecline in old age. *Alzheimer's Dement. 1*(2), 194–205.

Koster, E.H.W., De Lissnyder, E., Derakshan, N., De Raedt, R. (2011). Understanding depressive rumination from a cognitive science perspective: the impaired disengagement hypothesis. *Clin. Psychol. Rev. 31*, 138–145.

Koster, E.H.W., Hoorelbeke, K., Onraedt, T., Owens, M., Derakshan, N. (2017). Cognitive control interventions for depression: A systematic review of findings from training studies. *Clin. Psychol. Rev. 53*, 79–92.

Krause, B., Kadosh, R.C. (2014). Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation. *Front. Syst. Neurosci. 8*:25.

Kronberg, G., Bridi, M., Abel, T., Bikson, M., Parra, L.C. (2017). Direct Current Stimulation Modulates LTP and LTD: Activity Dependence and Dendritic Effects. *Brain Stimul. 10*, 51–58.

Kuo, M.F., Paulus, W., Nitsche, M.A. (2014). Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *Neuroimage 85* Pt 3:948-60

Lawton, M.P., Brody, E.M. (1969). Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living. *Gerontologist 9*, 179–186.

Lazeron, R.H.C., Rombouts, S.A.R.B., de Sonneville, L., Barkhof, F., Scheltens, P. (2003). A paced visual serial addition test for fMRI. *J. Neurol. Sci. 213*, 29–34.

Learmonth, G., Thut, G., Benwell, C.S.Y., Harvey, M. (2015). The implications of state-dependent tDCS effects in aging: Behavioural response is determined by baseline performance. *Neuropsychologia 74,* 108–119.

Lefaucheur, J.P. (2016). A comprehensive database of published tDCS clinical trials (2005-2016). *Neurophysiol. Clin. 46*, 319–398.

Lefaucheur, J.P., Antal, A., Ayache, S.S., Benninger, D.H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B., Marangolo, P., Mylius, V., Nitsche, M.A., Padberg, F., Palm, U., Poulet, E., Priori, A., Rossi, S., Schecklmann, M., Vanneste, S., Ziemann, U., Garcia-Larrea, L., Paulus, W. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin. Neurophysiol. 128, 56–92*.

Lejuez, C., Kahler, C. W., and Brown, R.A. (2003). A modified computer version of the Paced Auditory Serial Addition Task (PASAT) as a laboratory-based stressor. *Behav. Ther. 26* (4), 290– 293.

LeMoult, J., Arditte, K.A., D'Avanzato, C., Joormann, J. (2013). State Rumination: Associations with Emotional Stress Reactivity and Attention Biases. *J. Exp. Psychopathol. 4*, 471.

Li, S., Daamen, M., Scheef, L., Gaertner, F.C., Buchert, R., Buchmann, M., Buerger, K., Catak, C., Dobisch, L., Drzezga, A., Ertl-Wagner, B., Essler, M., Fliessbach, K., Haynes, J.D., Incesoy, E.I., Kilimann, I., Krause, B.J., Lange, C., Laske, C., Priller, J., Ramirez, A., Reimold, M., Rominger, A., Roy, N., Scheffler, K., Maurer, A., Schneider, A., Spottke, A., Spruth, E.J., Teipel, S.J., Tscheuschler, M., Wagner, M., Wolfsgruber, S., Düzel, E., Jessen, F., Peters, O., Boecker, H. (2021). Abnormal Regional and Global Connectivity Measures in Subjective Cognitive Decline Depending on Cerebral Amyloid Status. *J. Alzheimers. Dis. 79*, 493–509.

Liebetanz, D., Koch, R., Mayenfels, S., König, F., Paulus, W., Nitsche, M.A. (2009). Safety limits of cathodal transcranial direct current stimulation in rats. *Clin. Neurophysiol. 120*, 1161–1167.

Liew, T.M. (2020). Trajectories of subjective cognitive decline, and the risk of mild cognitive impairment and dementia. *Alzheimers. Res. Ther. 12*(1):135.

Lindbergh, C.A., Dishman, R.K., Miller, L.S. (2016). Functional Disability in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis. *Neuropsychol. Rev. 26*, 129–159.

Lineweaver, T.T., Bondi, M.W., Galasko, D., Salmon, D.P. (2014). Effect of knowledge of APOE genotype on subjective and objective memory performance in healthy older adults. *Am. J. Psychiatry 171*, 201–208.

Liu, J., Shen, K., Li, H. (2019). How state anxiety and attentional bias interact with each other: The moderating effect of cognitive appraisal. *Atten. Percept. Psychophys. 81*, 694–706.

Low, L.F., Harrison, F., Lackersteen, S.M. (2013). Does personality affect risk for dementia? A systematic review and meta-analysis. *Am. J. Geriatr. Psychiatry 21*, 713–728.

Lu, Hongliang, Gong, Y., Huang, P., Zhang, Y., Guo, Z., Zhu, X., You, X. (2021). Effect of Repeated Anodal HD-tDCS on Executive Functions: Evidence From a Pilot and Single-Blinded fNIRS Study. *Front. Hum. Neurosci. 14*:583730.

Lu, Hanna, Li, J., Zhang, L., Chan, S.S.M., Lam, L.C.W. (2021). Dynamic changes of region-specific cortical features and scalp-to-cortex distance: implications for transcranial current stimulation modeling. *J. Neuroeng. Rehabil. 18*(1):2.

Luck, T., Roehr, S., Jessen, F., Villringer, A., Angermeyer, M.C., Riedel-Heller, S.G. (2015). Mortality in Individuals with Subjective Cognitive Decline: Results of the Leipzig Longitudinal Study of the Aged (LEILA75). *J. Alzheimer's Dis. 48*, 33–42.

Mackie, M.A., Van Dam, N.T., Fan, J. (2013). Cognitive control and attentional functions. *Brain Cogn. 82*, 301–312.

Manenti, R., Sandrini, M., Gobbi, E., Cobelli, C., Brambilla, M., Binetti, G., Cotelli, M. (2017). Strengthening of Existing Episodic Memories Through Non-invasive Stimulation of Prefrontal Cortex in Older Adults with Subjective Memory Complaints. *Front. Aging Neurosci. 9*, 401.

Marceglia, S., Mrakic-Sposta, S., Rosa, M., Ferrucci, R., Mameli, F., Vergari, M., Arlotti, M., Ruggiero, F., Scarpini, E., Galimberti, D., Barbieri, S., Priori, A. (2016). Transcranial Direct Current Stimulation Modulates Cortical Neuronal Activity in Alzheimer's Disease. *Front. Neurosci. 10*, 134.

Martin, D.M., Liu, R., Alonzo, A., Green, M., Loo, C.K., (2014). Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. *Exp. brain Res. 232*, 3345–3351.

McEvoy, P.M., Watson, H., Watkins, E.R., Nathan, P. (2013). The relationship between worry, rumination, and comorbidity: evidence for repetitive negative thinking as a transdiagnostic construct. *J. Affect. Disord. 151*, 313–320.

McGuire, J.T., Botvinick, M.M. (2010). Prefrontal cortex, cognitive control, and the registration of decision costs. *Proc. Natl. Acad. Sci. USA. 107*, 7922–7926.

McTeague, L.M., Huemer, J., Carreon, D.M., Jiang, Y., Eickhoff, S.B., Etkin, A. (2017). Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. *Am. J. Psychiatry 174*, 676–685.

Meiberth, D., Scheef, L., Wolfsgruber, S., Boecker, H., Block, W., Träber, F., Erk, S., Heneka, M.T., Jacobi, H., Spottke, A., Walter, H., Wagner, M., Hu, X., Jessen, F.

(2015). Cortical thinning in individuals with subjective memory impairment. *J. Alzheimers. Dis. 45*, 139–146.

Meron, D., Hedger, N., Garner, M., Baldwin, D.S. (2015). Transcranial direct current stimulation (tDCS) in the treatment of depression: Systematic review and meta-analysis of efficacy and tolerability. *Neurosci. Biobehav. Rev. 57,* 46–62.

Miebach, L., Wolfsgruber, S., Polcher, A., Peters, O., Menne, F., Luther, K., Incesoy, E., Priller, J., Spruth, E., Altenstein, S., Buerger, K., Catak, C., Janowitz, D., Perneczky, R., Utecht, J., Laske, C., Buchmann, M., Schneider, A., Fliessbach, K., Kalbhen, P., Heneka, M.T., Brosseron, F., Spottke, A., Roy, N., Teipel, S.J., Kilimann, I., Wiltfang, J., Bartels, C., Düzel, E., Dobisch, L., Metzger, C., Meiberth, D., Ramirez, A., Jessen, F., Wagner, M.(2019). Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. *Alzheimer's Res. Ther. 11*(1), 66.

Miller, E.K. (2000). The prefrontal cortex and cognitive control. *Nat. Rev. Neurosci. 1*, 59–65.

Miniussi, C., Harris, J.A., Ruzzoli, M. (2013). Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci. *Biobehav. Rev. 37*, 1702–1712.

Mitchell, A.J., Beaumont, H., Ferguson, D., Yadegarfar, M., Stubbs, B. (2014). Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. *Acta Psychiatr. Scand. 130*, 439–51.

Mol, M.E.M., Van Boxtel, M.P.J., Willems, D., Verhey, F.R.J., Jolles, J. (2009). Subjective forgetfulness is associated with lower quality of life in middle-aged and young-old individuals: A 9-year follow-up in older participants from the Maastricht Aging Study. *Aging Ment. Heal. 13*, 699–705.

Molinuevo, J.L., Rabin, L.A., Amariglio, R., Buckley, R., Dubois, B., Ellis, K.A., Ewers, M., Hampel, H., Klöppel, S., Rami, L., Reisberg, B., Saykin, A.J., Sikkes, S., Smart, C.M., Snitz, B.E., Sperling, R., van der Flier, W.M., Wagner, M., Jessen, F., Subjective Cognitive Decline Initiative (SCD-I) Working Group (2017). Implementation of subjective cognitive decline criteria in research studies. *Alzheimer's Dement. 13*, 296–311.

Monte-Silva, K., Liebetanz, D., Grundey, J., Paulus, W., Nitsche, M.A. (2010). Dosage-dependent non-linear effect of L-dopa on human motor cortex plasticity. *J. Physiol. 588*, 3415–3424.

Moreno–Grau, S., Rodríguez-Gómez, O., Sanabria, Á., Pérez-Cordón, A., Sánchez-Ruiz, D., Abdelnour, C., Valero, S., Hernández, I., Rosende-Roca, M., Mauleón, A., Vargas, L., Lafuente, A., Gil, S., Santos-Santos, M.Á., Alegret, M., Espinosa, A., Ortega, G., Guitart, M., Gailhajanet, A., de Rojas, I., Sotolongo-Grau, Ó., Ruiz, S., Aguilera, N., Papasey, J., Martín, E., Peleja, E., Lomeña, F., Campos, F., Vivas, A., Gómez-Chiari, M., Tejero, M.Á., Giménez, J., Serrano-Ríos, M., Orellana, A., Tárraga, L., Ruiz, A., Boada, M., Alzheimer's Disease Neuroimaging Initiative, FACEHBI study group. (2018). Exploring APOE genotype effects on Alzheimer's disease risk and amyloid β burden in individuals with subjective cognitive decline: The FundacioACE Healthy Brain Initiative (FACEHBI) study baseline results. *Alzheimer's Dement. 14*, 634–643.

Morris, J.C., Heyman, A., Mohs, R.C., Hughes, J.P., van Belle, G., Fillenbaum, G., Mellits, E.D., Clark, C. (1989). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology 39*, 1159–65.

Muñoz, N., Gomà-I-Freixanet, M., Valero, S., Rodríguez-Gómez, O., Sanabria, A., Pérez-Cordón, A., Hernández, I., Marquié, M., Mir, I., Martín, E., Benaque, A., Ruiz, A., Tarraga, L., Boada, M., Alegret, M. (2020). Personality Factors and Subjective Cognitive Decline: The FACEHBI Cohort. *Behav. Neurol. 2020*, e5232184.

Murugaraja, V., Shivakumar, V., Sinha, P., Venkatasubramanian, G., Sivakumar, P. (2017). Transcranial direct current stimulation for mild cognitive impairment. *J. Geriatr. Ment. Heal. 4*, 106.

Nelson, J., McKinley, R.A., Phillips, C., McLntire, U., Goodyear, C., Kreiner, A., Montorton, L. (2016). The Effects of Transcranial Direct Current Stimulation (tDCS) on Multitasking Throughput Capacity. *Front. Hum. Neurosci. 10*:589.

Nguyen, L., Murphy, K., Andrews, G. (2019). Immediate and long-term efficacy of executive functions cognitive training in older adults: A systematic review and meta-analysis. *Psychol. Bull. 145*, 698–733.

Niendam, T.A., Laird, A.R., Ray, K.L., Dean, Y.M., Glahn, D.C., Carter, C.S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cogn. Affect. Behav. Neurosci. 12*, 241–268.

Nilsson, J., Lebedev, A. V., Rydström, A., Lövdén, M. (2017). Direct-Current Stimulation Does Little to Improve the Outcome of Working Memory Training in Older Adults. *Psychol. Sci. 28*(7):907-920.

Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P.S., Fregni, F., Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimul. 1*, 206–223.

Nitsche, M.A., Müller-Dahlhaus, F., Paulus, W., Ziemann, U. (2012). The pharmacology of neuroplasticity induced by non-invasive brain stimulation: building models for the clinical use of CNS active drugs. *J. Physiol. 590*, 4641–62.

Nitsche, M.A., Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J. Physiol. 527* Pt 3, 633–9.

Nord, C.L., Lally, N., Charpentier, C.J. (2013). Harnessing electric potential: DLPFC tDCS induces widespread brain perfusion changes. *Front. Syst. Neurosci. 7:*99.

Ochsner, K.N., Bunge, S.A., Gross, J.J., Gabrieli, J.D.E. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *J. Cogn. Neurosci. 14*, 1215–1229.

Ochsner, K.N., Gross, J.J. (2005). The cognitive control of emotion. *Trends Cogn. Sci. 9*, 242–249.

Ohn, S.H., Park, C. Il, Yoo, W.K., Ko, M.H., Choi, K.P., Kim, G.M., Lee, Y.T., Kim, Y.H., (2008). Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. *Neuroreport 19*, 43–47.

Oldfield, R.C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia 9,* 97–113.

Ossenkoppele, R., Jagust, W.J. (2017). The Complexity of Subjective Cognitive Decline. *JAMA Neurol. 74*, 1400.

Parazzini, M., Rossi, E., Ferrucci, R., Liorni, I., Priori, A., Ravazzani, P. (2014). Modelling the electric field and the current density generated by cerebellar transcranial DC stimulation in humans. *Clin. Neurophysiol. 125*, 577–584.

Parker, A.F., Ohlhauser, L., Scarapicchia, V., Smart, C.M., Szoeke, C., Gawryluk, J.R. (2022). A Systematic Review of Neuroimaging Studies Comparing Individuals with Subjective Cognitive Decline to Healthy Controls. *J. Alzheimers. Dis. 86*(4):1545-1567.

Paulus, W. (2004). Outlasting excitability shifts induced by direct current stimulation of the human brain. Suppl. *Clin. Neurophysiol. 57*, 708–714.

Paulus, W., Opitz, A. (2013). Ohm's law and tDCS over the centuries. *Clin. Neurophysiol. 124*, 429–430.

Pavot, W., Diener, E. (1993). Review of the Satisfaction With Life Scale. *Psychol. Assess. 5*, 164–172.

Peirce, J.W., 2009. Generating Stimuli for Neuroscience Using PsychoPy. *Front. Neuroinform. 2*:10.

Pergher, V., Au, J., Alizadeh Shalchy, M., Santarnecchi, E., Seitz, A., Jaeggi, S.M., Battelli, L. (2022). The benefits of simultaneous tDCS and working memory training on transfer outcomes: A systematic review and meta-analysis. *Brain Stimul. 15*, 1541–1551.

Perrotin, A., La Joie, R., de La Sayette, V., Barré, L., Mézenge, F., Mutlu, J., Guilloteau, D., Egret, S., Eustache, F., Chételat, G. (2017). Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: Differential affective and imaging correlates. *Alzheimer's Dement. 13*, 550–560.

Pessoa, L. (2008). On the relationship between emotion and cognition. *Nat. Rev. Neurosci. 9*, 148–158.

Peter, J., Scheef, L., Abdulkadir, A., Boecker, H., Heneka, M., Wagner, M., Koppara, A., Klöppel, S., Jessen, F. (2014). Gray matter atrophy pattern in elderly with subjective memory impairment. *Alzheimers. Dement. 10*, 99–108.

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.

Pietrzak, R.H., Lim, Y.Y., Neumeister, A., Ames, D., Ellis, K.A., Harrington, K., Lautenschlager, N.T., Restrepo, C., Martins, R.N., Masters, C.L., Villemagne, V.L., Rowe, C.C., Maruff, P. (2015). Amyloid-β, anxiety, and cognitive decline in preclinical Alzheimer disease: a multicenter, prospective cohort study. *JAMA psychiatry 72*, 284–291.

Pike, K.E., Cavuoto, M.G., Li, L., Wright, B.J., Kinsella, G.J., (2022). Subjective Cognitive Decline: Level of Risk for Future Dementia and Mild Cognitive Impairment, a Meta-Analysis of Longitudinal Studies. *Neuropsychol. Rev. 32*, 703–735.

Pini, L., Manenti, R., Cotelli, M., Pizzini, F.B., Frisoni, G.B., Pievani, M. (2019). Non-Invasive Brain Stimulation in Dementia: A Complex Network Story. *Neurodegener. Dis. 18*, 281–301.

Pires, C., Silva, D., Maroco, J., Ginó, S., Mendes, T., Schmand, B.A., Guerreiro, M., De Mendonça, A. (2012). Memory Complaints Associated with Seeking Clinical Care. *Int. J. Alzheimers. Dis. 2012*:725329.

Plazier, M., Joos, K., Vanneste, S., Ost, J., De Ridder, D. (2012). Bifrontal and bioccipital transcranial direct current stimulation (tDCS) does not induce mood changes in healthy volunteers: a placebo controlled study. *Brain Stimul. 5*, 454–

461.

Plewnia, C., Schroeder, P.A., Kunze, R., Faehling, F., Wolkenstein, L. (2015a). Keep calm and carry on: improved frustration tolerance and processing speed by transcranial direct current stimulation (tDCS). *PLoS One 10*(4), e0122578.

Plewnia, C., Schroeder, P.A., Wolkenstein, L. (2015b). Targeting the biased brain: non-invasive brain stimulation to ameliorate cognitive control. *Lancet Psychiatry 2*(4), 351–6.

Plewnia, C., Zwissler, B., Längst, I., Maurer, B., Giel, K., Krüger, R. (2013). Effects of transcranial direct current stimulation (tDCS) on executive functions: Influence of COMT Val/Met polymorphism. *Cortex 49*, 1801–1807.

Polanía, R., Nitsche, M.A., Ruff, C.C. (2018). Studying and modifying brain function with non-invasive brain stimulation. *Nat. Neurosci. 21*(2):174-187.

Polcher, A., Frommann, I., Koppara, A., Wolfsgruber, S., Jessen, F., Wagner, M. (2017). Face-Name Associative Recognition Deficits in Subjective Cognitive Decline and Mild Cognitive Impairment. *J. Alzheimers. Dis. 56*, 1185–1196.

Pope, P.A., Brenton, J.W., Miall, R.C. (2015). Task-Specific Facilitation of Cognition by Anodal Transcranial Direct Current Stimulation of the Prefrontal Cortex. Cereb. *Cortex 25*, 4551–4558.

Posner, M.I., Petersen, S.E. (1990). The attention system of the human brain. *Annu. Rev. Neurosci. 13*, 25–42.

Prehn, K., Flöel, A. (2015). Potentials and limits to enhance cognitive functions in healthy and pathological aging by tDCS. Front. Cell. Neurosci. 9:355.

Priori, A. (2003). Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. *Clin. Neurophysiol. 114*, 589–595.

Pusswald, G., Tropper, E., Kryspin-Exner, I., Moser, D., Klug, S., Auff, E., Dal-Bianco, P., Lehrner, J. (2015). Health-Related Quality of Life in Patients with Subjective Cognitive Decline and Mild Cognitive Impairment and its Relation to Activities of Daily Living. *J. Alzheimer's Dis. 47*, 479–486.

R., R. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Ski.* 271–276.

R Core Team (2018). Nlme: linear and nonlinear mixed effects models. R Foundation for Statistical Computing, Vienna, Austria. URL https://CRAN.R-project.org/package=nlme.

R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Rabin, L.A., Smart, C.M., Amariglio, R.E. (2017). Subjective Cognitive Decline in Preclinical Alzheimer's Disease. *Annu. Rev. Clin. Psychol. 13*, 369–396.

Rahman, A., Reato, D., Arlotti, M., Gasca, F., Datta, A., Parra, L.C., Bikson, M. (2013). Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. *J. Physiol. 591*, 2563–2578.

Rami, L., Mollica, M.A., Garcfa-Sanchez, C., Saldafia, J., Sanchez, B., Sala, I., Valls-Pedret, C., Castellvi, M., Olives, J., Molinuevo, J.L. (2014). The subjective cognitive decline questionnaire (SCD-Q): A validation study. *J. Alzheimer's Dis.*

41, 453–466.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb. Cortex 15*, 1676–1689.

Razza, L.B., De Smet, S., Moffa, A., Sudbrack-Oliveira, P., Vanderhasselt, M.A., Brunoni, A.R. (2021). Follow-up effects of transcranial direct current stimulation (tDCS) for the major depressive episode: A systematic review and meta-analysis. *Psychiatry Res. 302*:114024.

Reisberg, B., Ferris, S.H., De Leon, M.J., Crook, T. (1982). The Global Deterioration Scale for assessment of primary degenerative dementia. *Am. J. Psychiatry 139*, 1136–1139.

Rentz, D.M., Parra Rodriguez, M.A., Amariglio, R., Stern, Y., Sperling, R., Ferris, S. (2013). Promising developments in neuropsychological approaches for the detection of preclinical Alzheimer’s disease: a selective review. *Alzheimers. Res. Ther. 5*(6):58.

Reynolds, G.O., Manning, L., Kirn, D., Klein, H., Hampton, O., Burke, O., Buckley, R., Rentz, D., Sperling, R., Marshall, G.A., Amariglio, R.E. (2022). Subjective Cognitive Decline in a Registry Sample: Relation to Psychiatric History, Loneliness, and Personality. *J. Prev. Alzheimer’s Dis. 9*, 435.

Roehr, S., Luck, T., Pabst, A., Bickel, H., König, H.-H., Lühmann, D., Fuchs, A., Wolfsgruber, S., Wiese, B., Weyerer, S., Mösch, E., Brettschneider, C., Mallon, T., Pentzek, M., Wagner, M., Mamone, S., Werle, J., Scherer, M., Maier, W., Jessen, F., Riedel-Heller, S.G., AgeCoDe study group. (2017). Subjective cognitive decline is longitudinally associated with lower health-related quality of life. *Int. Psychogeriatrics 29*(12):1939-1950.

Roheger, M., Hennersdorf, X.S., Riemann, S., Flöel, A., Meinzer, M. (2021). A systematic review and network meta-analysis of interventions for subjective cognitive decline. *Alzheimer’s Dement. 7*(1):e12180.

Röhr, S., Pabst, A., Riedel-Heller, S.G., Jessen, F., Turana, Y., Handajani, Y.S., Brayne, C., Matthews, F.E., Stephan, B.C.M., Lipton, R.B., Katz, M.J., Wang, C., Guerchet, M., Preux, P.M., Mbelesso, P., Ritchie, K., Ancelin, M.L., Carrière, I., Guaita, A., Davin, A., Vaccaro, R., Kim, K.W., Han, J.W., Suh, S.W., Shahar, S., Din, N.C., Vanoh, D., van Boxtel, M., Köhler, S., Ganguli, M., Jacobsen, E.P., Snitz, B.E., Anstey, K.J., Cherbuin, N., Kumagai, S., Chen, S., Narazaki, K., Ng, T.P., Gao, Q., Gwee, X., Brodaty, H., Kochan, N.A., Trollor, J., Lobo, A., López-Antón, R., Santabárbara, J., Crawford, J.D., Lipnicki, D.M., Sachdev, P.S. (2020). Estimating prevalence of subjective cognitive decline in and across international cohort studies of aging: a COSMIC study. *Alzheimers. Res. Ther. 12*(1), 39.

Roiser, J.P., Elliott, R., Sahakian, B.J., (2012). Cognitive mechanisms of treatment in depression. *Neuropsychopharmacology 37*, 117–136.

Rostamzadeh, A., Bohr, L., Wagner, M., Baethge, C., Jessen, F. (2022). Progression of Subjective Cognitive Decline to MCI or Dementia in Relation to Biomarkers for Alzheimer Disease: A Meta-analysis. *Neurology 99*, E1866–E1874.

Rotenberg, S., Maeir, A., Dawson, D.R., (2020). Changes in Activity Participation Among Older Adults With Subjective Cognitive Decline or Objective Cognitive Deficits. *Front. Neurol. 10*:1393.

Roy, A.K., Shehzad, Z., Margulies, D.S., Kelly, A.M.C., Uddin, L.Q., Gotimer, K., Biswal, B.B., Castellanos, F.X., Milham, M.P. (2009). Functional connectivity of the human amygdala using resting state fMRI. *Neuroimage 45*, 614–626.

Ruf, S.P., Fallgatter, A.J., Plewnia, C. (2017). Augmentation of working memory training by transcranial direct current stimulation (tDCS). *Sci. Rep. 7*, 876.

Rush, S., Driscoll, D.A. (1968). Current distribution in the brain from surface electrodes. *Anesth Analg 47*, 717–723.

Sabatini, S., Woods, R.T., Ukoumunne, O.C., Ballard, C., Collins, R., Clare, L. (2022). Associations of subjective cognitive and memory decline with depression, anxiety, and two-year change in objectively-assessed global cognition and memory. *Neuropsychol. Dev. Cogn. B. Aging. Neuropsychol. Cogn. 29*, 840–866.

Saldanha, J.S., Zortea, M., Deliberali, C.B., Nitsche, M.A., Kuo, M.F., Torres, I.L. da S., Fregni, F., Caumo, W. (2020). Impact of Age on tDCS Effects on Pain Threshold and Working Memory: Results of a Proof of Concept Cross-Over Randomized Controlled Study. *Front. Aging Neurosci. 12:*189.

Satorres, E., Meléndez, J.C., Pitarque, A., Real, E., Abella, M., Escudero, J. (2022). Enhancing Immediate Memory, Potential Learning, and Working Memory with Transcranial Direct Current Stimulation in Healthy Older Adults. *Int. J. Environ. Res. Public Health 19* (19):12716.

Saykin, A.J., Wishart, H.A., Rabin, L.A., Santulli, R.B., Flashman, L.A., West, J.D., McHugh, T.L., Mamourian, A.C. (2006). Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. *Neurology 67*, 834–842.

Scheef, L., Spottke, A., Daerr, M., Joe, A., Striepens, N., Kölsch, H., Popp, J., Daamen, M., Psych, D., Gorris, D., Heneka, M.T., Boecker, H., Biersack, H.J., Maier, W., Schild, H.H., Wagner, M., Jessen, F. (2012). Glucose metabolism, gray matter structure, and memory decline in subjective memory impairment. *Neurology 79*, 1332–1339.

Schicktanz, S., Schweda, M., Ballenger, J.F., Fox, P.J., Halpern, J., Kramer, J.H., Micco, G., Post, S.G., Thompson, C., Knight, R.T., Jagust, W.J. (2014). Before it is too late: professional responsibilities in late-onset Alzheimer's research and pre-symptomatic prediction. *Front. Hum. Neurosci. 8*, 921.

Schlosser, M., Demnitz-King, H., Whitfield, T., Wirth, M., Marchant, N.L. (2020). Repetitive negative thinking is associated with subjective cognitive decline in older adults: a cross-sectional study. *BMC Psychiatry 20*, 500.

Schmid, N.S., Ehrensperger, M.M., Berres, M., Beck, I.R., Monsch, A.U. (2014). The Extension of the German CERAD Neuropsychological Assessment Battery with Tests Assessing Subcortical, Executive and Frontal Functions Improves Accuracy in Dementia Diagnosis. *Dement. Geriatr. Cogn. Dis. Extra 4*, 322–34.

Schroeder, P.A., Pfister, R., Kunde, W., Nuerk, H.C., Plewnia, C. (2016). Counteracting Implicit Conflicts by Electrical Inhibition of the Prefrontal Cortex. *J. Cogn. Neurosci. 28*, 1737–1748.

Schwippel, T., Papazova, I., Strube, W., Fallgatter, A.J., Hasan, A., Plewnia, C. (2018). Beneficial effects of anodal transcranial direct current stimulation (tDCS) on spatial working memory in patients with schizophrenia. *Eur. Neuropsychopharmacol. 28*, 1339–1350.

Segrave, R.A., Arnold, S., Hoy, K., Fitzgerald, P.B. (2014). Concurrent cognitive control training augments the antidepressant efficacy of tDCS: A pilot study. *Brain Stimul. 7*, 325–331.

Semendeferi, K., Damasio, H., Frank, R., Van Hoesen, G.W. (1997). The evolution of the frontal lobes: A volumetric analysis based on three-dimensional reconstructions of magnetic resonance scans of human and ape brains. *J. Hum. Evol. 32*, 375–388.

Sendi, M.S.E., Zendehrouh, E., Fu, Z., Liu, J., Du, Y., Mormino, E., Salat, D.H., Calhoun, V.D., Miller, R.L. (2021). Disrupted Dynamic Functional Network Connectivity Among Cognitive Control Networks in the Progression of Alzheimer's Disease. *Brain Connectivity* ahead of print.

Sheehan, D. V, Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J. Clin. Psychiatry 59 Suppl 20*, 22-33;quiz 34-57.

Shi, R., Sharpe, L., Abbott, M. (2019). A meta-analysis of the relationship between anxiety and attentional control. *Clin. Psychol. Rev. 72*:101754.

Shiozawa, P., Fregni, F., Benseñor, I.M., Lotufo, P.A., Berlim, M.T., Daskalakis, J.Z., Cordeiro, Q., Brunoni, A.R. (2014). Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. *Int. J. Neuropsychopharmacol. 17*, 1443–1452.

Shulman, K.I., Shedletsky, R., Silver, I.L. (1986). The challenge of time: Clock-drawing and cognitive function in the elderly. *Int. J. Geriatr. Psychiatry 1*, 135–140.

Siegert, A., Diedrich, L., Antal, A. (2021). New Methods, Old Brains-A Systematic Review on the Effects of tDCS on the Cognition of Elderly People. *Front. Hum. Neurosci. 15*: 730134.

Siegle, G.J., Ghinassi, F., Thase, M.E. (2007a). Neurobehavioral Therapies in the 21st Century: Summary of an Emerging Field and an Extended Example of Cognitive Control Training for Depression. *Cognit. Ther. Res. 31*, 235–262.

Siegle, G.J., Thompson, W., Carter, C.S., Steinhauer, S.R., Thase, M.E. (2007b). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biol. Psychiatry 61*, 198–209.

Silvanto, J., Muggleton, N., Walsh, V. (2008). State-dependency in brain stimulation studies of perception and cognition. *Trends Cogn. Sci. 12*, 447–454.

Šimko, P., Kent, J.A., Rektorova, I. (2022). Is non-invasive brain stimulation effective for cognitive enhancement in Alzheimer's disease? An updated meta-analysis. *Clin. Neurophysiol. 144*, 23–40.

Simpson, E.E., Maylor, E.A., McConville, C., Stewart-Knox, B., Meunier, N., Andriollo-Sanchez, M., Polito, A., Intorre, F., McCormack, J.M., Coudray, C. (2014). Mood and cognition in healthy older European adults: the Zenith study. *BMC Psychol. 2*(1):11.

Singh-Manoux, A., Dugravot, A., Fournier, A., Abell, J., Ebmeier, K., Kivimäki, M., Sabia, S., (2017). Trajectories of Depressive Symptoms Before Diagnosis of Dementia: A 28-Year Follow-up Study. *JAMA psychiatry 74*, 712–718.

Slot, R.E.R., Sikkes, S.A.M., Berkhof, J., Brodaty, H., Buckley, R., Cavedo, E., Dardiotis, E., Guillo-Benarous, F., Hampel, H., Kochan, N.A., Lista, S., Luck, T., Maruff, P., Molinuevo, J.L., Kornhuber, J., Reisberg, B., Riedel-Heller, S.G., Risacher, S.L., Roehr, S., Sachdev, P.S., Scarmeas, N., Scheltens, P., Shulman, M.B., Saykin, A.J., Verfaillie, S.C.J., Visser, P.J., Vos, S.J.B., Wagner, M., Wolfsgruber, S., Jessen, F., van der Flier, W.M., Alzheimer's Disease Neuroimaging Initiative, DESCRIPA working group; INSIGHT-preAD study group, SCD-I working group. (2019). Subjective cognitive decline and rates of incident Alzheimer's disease and non–Alzheimer's disease dementia. *Alzheimer's Dement. 15*, 465–476.

Smart, C.M., Karr, J.E., Areshenkoff, C.N., Rabin, L.A., Hudon, C., Gates, N., Ali, J.I., Arenaza-Urquijo, E.M., Buckley, R.F., Chetelat, G., Hampel, H., Jessen, F., Marchant, N.L., Sikkes, S.A.M., Tales, A., van der Flier, W.M., Wesselman, L. and the Subjective Cognitive Decline Initiative (SCD-I) Working Group. (2017). Non-Pharmacologic Interventions for Older Adults with Subjective Cognitive Decline: Systematic Review, Meta-Analysis, and Preliminary Recommendations. *Neuropsychol. Rev. 27*(3), 245–257.

Snitz, B.E., Weissfeld, L.A., Cohen, A.D., Lopez, O.L., Nebes, R.D., Aizenstein, H.J., McDade, E., Price, J.C., Mathis, C.A., Klunk, W.E. (2015). Subjective Cognitive Complaints, Personality and Brain Amyloid-beta in Cognitively Normal Older Adults. *Am. J. Geriatr. Psychiatry 23*, 985–993.

Snyder, H.R., Hankin, B.L. (2016). Spiraling out of control: Stress generation and subsequent rumination mediate the link between poorer cognitive control and internalizing psychopathology. *Clin. Psychol. Sci. 4*(6), 1047–1064.

Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., Iwatsubo, T., Jack, C.R., Kaye, J., Montine, T.J., Park, D.C., Reiman, E.M., Rowe, C.C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M.C., Thies, B., Morrison-Bogorad, M., Wagster, M. V., Phelps, C.H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement. 7*, 280–292.

Spielberger, C.D. (1983). *Manual for the State-Trait Anxiety Inventory.* Palo Alto, California: Consulting Psychologists Press.

Stagg, C.J., Best, J.G., Stephenson, M.C., O'Shea, J., Wylezinska, M., Kineses, Z.T., Morris, P.G., Matthews, P.M., Johansen-Berg, H. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *J. Neurosci. 29*, 5202–5206.

Stagg, C.J., Lin, R.L., Mezue, M., Segerdahl, A., Kong, Y., Xie, J., Tracey, I. (2013). Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. *J. Neurosci. 33*, 11425–11431.

Stagg, C.J., Nitsche, M.A. (2011). Physiological basis of transcranial direct current stimulation. *Neuroscientist 17*, 37–53.

Stanislaw, H., Todorov, N. (1999). Calculation of signal detection theory measures. *Behav. Res. Methods, Instruments, Comput. 31*, 137–149.

Stogmann, E., Moser, D., Klug, S., Gleiss, A., Auff, E., Dal-Bianco, P., Pusswald, G., Lehrner, J. (2016). Activities of Daily Living and Depressive Symptoms in Patients with Subjective Cognitive Decline, Mild Cognitive Impairment, and Alzheimer's Disease. *J. Alzheimer's Dis. 49*, 1043–1050.

Stoynova, N., Laske, C., Plewnia, C. (2019). Combining electrical stimulation and cognitive control training to reduce concerns about subjective cognitive decline. *Brain Stimul. 12*(4): 1083-1085

Tandetnik, C., Farrell, M.T., Cary, M.S., Cines, S., Emrani, S., Karlawish, J., Cosentino, S. (2015). Ascertaining Subjective Cognitive Decline: A Comparison of Approaches and Evidence for Using an Age-Anchored Reference Group. *J. Alzheimers. Dis. 48*:43–55.

Thirugnanasambandam, N., Grundey, J., Adam, K., Drees, A., Skwirba, A.C., Lang, N., Paulus, W., Nitsche, M.A. (2011). Nicotinergic impact on focal and non-focal neuroplasticity induced by non-invasive brain stimulation in non-smoking humans. *Neuropsychopharmacology 36*, 879–886.

Topp, C.W., Østergaard, S.D., Søndergaard, S., Bech, P. (2015). The WHO-5 Well-Being Index: a systematic review of the literature. Psychother. *Psychosom. 84*, 167–176.

Tremblay, S., Larochelle-Brunet, F., Lafleur, L.P., El Mouderrib, S., Lepage, J.F., Théoret, H. (2016). Systematic assessment of duration and intensity of anodal transcranial direct current stimulation on primary motor cortex excitability. *Eur. J. Neurosci. 44*, 2184–90.

Trull, T.J., Ebner-Priemer, U. (2013). Ambulatory assessment. *Annu. Rev. Clin. Psychol. 9*, 151–176.

Trumbo, M.C., Matzen, L.E., Coffman, B.A., Hunter, M.A., Jones, A.P., Robinson, C.S.H., Clark, V.P. (2016). Enhanced working memory performance via transcranial direct current stimulation: The possibility of near and far transfer. *Neuropsychologia 93*, 85–96.

Valech, N., Mollica, M.A., Olives, J., Tort, A., Fortea, J., Lleo, A., Belén, S.S., Molinuevo, J.L., Rami, L. (2015). Informant's Perception of Subjective Cognitive Decline Helps to Discriminate Preclinical Alzheimer's Disease from Normal Aging. *J. Alzheimer's Dis. 48*, S87–S98.

Van den Bergh, N., Vermeersch, S., Hoorelbeke, K., Vervaeke, J., De Raedt, R., Koster, E.H.W., 2020. Cognitive Control Training as an Augmentation Strategy to CBT in the Treatment of Fear of Failure in Undergraduates. *Cognit. Ther. Res. 44*, 1199–1212.

van Harten, A.C., Mielke, M.M., Swenson-Dravis, D.M., Hagen, C.E., Edwards, K.K., Roberts, R.O., Geda, Y.E., Knopman, D.S., Petersen, R.C. (2018). Subjective cognitive decline and risk of MCI: The Mayo Clinic Study of Aging. *Neurology 91*, e300–e312.

Vanderhasselt, M.A., Baeken, C., Van Schuerbeek, P., Luypaert, R., De Mey, J., De Raedt, R. (2013). How brooding minds inhibit negative material: An event-related fMRI study. *Brain Cogn. 81*, 352–359.

Vanderhasselt, M.A., de Raedt, R., Baeken, C. (2009). Dorsolateral prefrontal cortex and Stroop performance: tackling the lateralization. *Psychon. Bull. Rev. 16*, 609–612.

Vanderhasselt, M.A., De Raedt, R., Namur, V., Lotufo, P.A., Bensenor, I.M., Boggio, P.S., Brunoni, A.R. (2015). Transcranial electric stimulation and neurocognitive training in clinically depressed patients: a pilot study of the effects on rumination. *Prog. Neuropsychopharmacol. Biol. Psychiatry 57*, 93–99.

Vanderhasselt, M.A., Demeyer, I., Van Imschoot, L., Hoorelbeke, K., De Raedt, R. (2021). Cognitive Control Training in Healthy Older Adults: A Proof of Concept Study on the Effects on Cognitive Functioning, Emotion Regulation and Affect. *Cognit. Ther. Res. 45*, 959–968.

Vaqué-Alcázar, L., Mulet-Pons, L., Abellaneda-Pérez, K., Solé-Padullés, C., Cabello-Toscano, M., Macià, D., Sala-Llonch, R., Bargalló, N., Solana, J., Cattaneo, G., Tormos, J.M., Pascual-Leone, A., Bartrés-Faz, D. (2021). tDCS-Induced Memory Reconsolidation Effects and Its Associations With Structural and Functional MRI Substrates in Subjective Cognitive Decline. *Front. Aging Neurosci. 13*:695232.

Verfaillie, S.C.J., Timmers, T., Slot, R.E.R., Van Der Weijden, C.W.J., Wesselman, L.M.P., Prins, N.D., Sikkes, S.A.M., Yaqub, M., Dols, A., Lammertsma, A.A., Scheltens, P., Ossenkoppele, R., Van Berckel, B.N.M., Van Der Flier, W.M., 2019. Amyloid-β load is related to worries, but not to severity of cognitive complaints in individuals with subjective cognitive decline: The science project. *Front. Aging Neurosci. 11*, 7.

Vergallito, A., Feroldi, S., Pisoni, A., Lauro, L.J.R. (2022). Inter-Individual Variability in tDCS Effects: A Narrative Review on the Contribution of Stable, Variable, and Contextual Factors. *Brain Sci. 12*(5):522.

Vicario, C.M., Salehinejad, M.A., Felmingham, K., Martino, G., Nitsche, M.A. (2019). A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders. *Neurosci. Biobehav. Rev. 96*, 219–231.

Vignaud, P., Mondino, M., Poulet, E., Palm, U., Brunelin, J. (2018). Duration but not intensity influences transcranial direct current stimulation (tDCS) after-effects on cortical excitability. *Neurophysiol. Clin. 48*, 89–92.

Wang, T., Guo, Z., Du, Y., Xiong, M., Yang, Z., Ren, L., He, L., Jiang, Y., McClure, M.A., Mu, Q. (2021). Effects of Noninvasive Brain Stimulation (NIBS) on Cognitive Impairment in Mild Cognitive Impairment and Alzheimer Disease: A Meta-analysis. *Alzheimer Dis. Assoc. Disord. 35*, 278–288.

Wang, X.T., Wang, Z.T., Hu, H.Y., Qu, Y., Wang, M., Shen, X.N., Xu, W., Dong, Q., Tan, L., Yu, J.T. (2021). Association of Subjective Cognitive Decline with Risk of Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis of Prospective Longitudinal Studies. *J. Prev. Alzheimer’s Dis. 8*, 277–285.

Watkins, E.R., Roberts, H. (2020). Reflecting on rumination: Consequences, causes, mechanisms and treatment of rumination. *Behav. Res. Ther. 127*, 103573.

Wei, Y.C., Huang, L.Y., Chen, C.K., Lin, C., Shyu, Y.C., Chen, Y.L., Huang, W.Y., Lin, C.P. (2019). Subjective Cognitive Decline in the Community Is Affected at Multiple Aspects of Mental Health and Life Quality: A Cross-Sectional Study of the Community Medicine of Keelung Chang Gung Memorial Hospital. *Dement. Geriatr. Cogn. Dis. Extra 9*, 152–162.

Weller, S. (2016). Effects of Left Prefrontal Transcranial Direct Current Stimulation on Cognitive Control Training. Master Thesis. Tübingen.

Weller, S., Nitsche, M.A., Plewnia, C. (2020). Enhancing cognitive control training with transcranial direct current stimulation: a systematic parameter study. *Brain Stimul. 13*, 1358–1369.

Wen, C., Bi, Y.L., Hu, H., Huang, S.Y., Ma, Y.H., Hu, H.Y., Tan, L., Yu, J.T. (2022). Association of Subjective Cognitive Decline with Cerebrospinal Fluid Biomarkers of Alzheimer’s Disease Pathology in Cognitively Intact Older Adults: The CABLE Study. *J. Alzheimers. Dis. 85*, 1143–1151.

Wiegand, A., Nieratschker, V., Plewnia, C. (2016). Genetic modulation of transcranial direct current stimulation effects on cognition. *Front. Hum. Neurosci. 10*, 651.

Wiegand, A., Sommer, A., Nieratschker, V., Plewnia, C. (2019). Improvement of cognitive control and stabilization of affect by prefrontal transcranial direct current stimulation (tDCS). *Sci. Rep. 9*(1):6797.

Wolfsgruber, S., Kleineidam, L., Guski, J., Polcher, A., Frommann, I., Roeske, S., Spruth, E.J., Franke, C., Priller, J., Kilimann, I., Teipel, S., Buerger, K., Janowitz, D., Laske, C., Buchmann, M., Peters, O., Menne, F., Casan, M.F., Wiltfang, J., Bartels, C., Düzel, E., Metzger, C., Glanz, W., Thelen, M., Spottke, A., Ramirez, A., Kofler, B., Fließbach, K., Schneider, A., Heneka, M.T., Brosseron, F., Meiberth, D., Jessen, F., Wagner, M. (2020). Minor neuropsychological deficits in patients with subjective cognitive decline. *Neurology 95*, E1134–E1143.

Wolfsgruber, S., Kleineidam, L., Wagner, M., Mösch, E., Bickel, H., Lühmann, D., Ernst, A., Wiese, B., Steinmann, S., König, H.H., Brettschneider, C., Luck, T., Stein, J., Weyerer, S., Werle, J., Pentzek, M., Fuchs, A., Maier, W., Scherer, M., Riedel-Heller, S.G., Jessen, F. (2016). Differential Risk of Incident Alzheimer’s Disease Dementia in Stable Versus Unstable Patterns of Subjective Cognitive Decline. *J. Alzheimer’s Dis. 54*, 1135–1146.

Wolkenstein, L., Plewnia, C., 2013. Amelioration of Cognitive Control in Depression by Transcranial Direct Current Stimulation. *Biol. Psychiatry 73*, 646–651.

Wolkenstein, L., Zeiller, M., Kanske, P., Plewnia, C. (2014). Induction of a depression-like negativity bias by cathodal transcranial direct current stimulation. *Cortex 59*, 103–112.

Woods, A.J., Antal, A., Bikson, M., Boggio, P.S., Brunoni, A.R., Celnik, P., Cohen, L.G., Fregni, F., Herrmann, C.S., Kappenman, E.S., Knotkova, H., Liebetanz, D., Miniussi, C., Miranda, P.C., Paulus, W., Priori, A., Reato, D., Stagg, C., Wenderoth, N., Nitsche, M.A. (2016). A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clin. Neurophysiol. 127*(2):1031-1048.

Woods, A.J., Cohen, R., Marsiske, M., Alexander, G.E., Czaja, S.J., Wu, S. (2018). Augmenting cognitive training in older adults (The ACT Study): Design and Methods of a Phase III tDCS and cognitive training trial. *Contemp. Clin. Trials 65*, 19–32.

Woodworth, R.S., Thorndike, E.L., 1901. The influence of improvement in one mental function upon the efficiency of other functions. (I). *Psychol. Rev. 8*, 247–261.

Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M., Leirer, V.O. (1982). Development and validation of a geriatric depression screening scale: A preliminary report. *J. Psychiatr. Res. 17*, 37–49.

Yin, S., Zhu, X., Li, R., Huo, L., Ren, W., Niu, Y., Li, J. (2022). Alleviated Anxiety Boosts Memory Training Gain in Older Adults with Subjective Memory Complaints: A Randomized Controlled Trial. *Am. J. Geriatr. Psychiatry 30*, 184–194.

Yun, K., Song, I.-U., Chung, Y.-A. (2016). Changes in cerebral glucose metabolism after 3 weeks of noninvasive electrical stimulation of mild cognitive impairment patients. *Alzheimers. Res. Ther. 8*, 49.

Zandi, T. (2004). Relationship between subjective memory complaints, objective memory performance, and depression among older adults. *Am. J. Alzheimers. Dis. Other Demen. 19*, 353–360.

Ziemann, U., Paulus, W., Nitsche, M.A., Pascual-Leone, A., Byblow, W.D., Berardelli, A., Siebner, H.R., Classen, J., Cohen, L.G., Rothwell, J.C. (2008). Consensus: Motor cortex plasticity protocols. *Brain Stimul. 1*, 164–182.

Zwissler, B., Sperber, C., Aigeldinger, S., Schindler, S., Kissler, J., Plewnia, C. (2014). Shaping memory accuracy by left prefrontal transcranial direct current stimulation. *J. Neurosci. 34*, 4022–4026.

8. Declaration of contribution

The work was carried out in the University Clinic for Psychiatry and Psychotherapy Tübingen in the workgroup “Neurophysiology and Interventional Neuropsychiatry” under the supervision of Prof. Dr. Christian Plewnia.

The experiment was conceptualized and planned by Prof. Plewnia and me in collaboration with Prof. Dr. Christoph Laske. After an initial training in the implementation of the CERAD-Plus neuropsychological battery by Christian Mychajliw as well as introductory guidance of other members from the workgroup (Simone Weller, Anja Sommer, Jan-Philipp Schinkel and Tobias Schwippel) regarding the application of tDCS and PASAT, all screenings and experiments were conducted by me.

Statistical analysis and interpretation of the data was carried out in collaboration with Prof. Plewnia. Evaluation of the CERAD-NAB-Plus results was supervised by Prof. Laske.

The manuscript for the publication “Combining electrical stimulation and cognitive control training to reduce concerns about subjective cognitive decline“ was drafted by me and completed in collaboration with Prof. Plewnia and Prof. Laske.

I assure that I have written this dissertation completely independently and that I have not used any other sources than those cited in this dissertation.

9. Publication

Parts of this dissertation have already been published in the following publication:

Stoynova, N., Laske, C., Plewnia, C. (2019). Combining electrical stimulation and cognitive control training to reduce concerns about subjective cognitive decline. Brain Stimulation; 12(4): 1083-1085.

Text passages that are identical to those in the publication are written in quotation marks followed by the citation and formatted in italics. Square brackets (e.g. [word]) indicate newly inserted words/characters in the quotation while three dots ([…]) indicate omission of words.

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