Transcranial direct current stimulation effects on auditory event-related potentials in Schizophrenia

A thesis submitted to the University of Newcastle, NSW, Australia for the degree of Doctor of Philosophy (Psychiatry)

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STATEMENT OF ORIGINALITY

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STATEMENT OF COLLABORATION

I hereby certify that the work embodied in this thesis has been done in collaboration with other researchers, or carried out in other institutions. I have included as part of the thesis a statement clearly outlining the extent of collaboration, with whom and under what auspices.

Lilly Knechtel
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ABSTRACT

Transcranial direct current stimulation (tDCS) is considered a non-invasive and well-tolerated brain stimulation technique with very few adverse side effects. Importantly, tDCS does not directly evoke neuronal firing (as induced by electroconvulsive or transcranial magnetic stimulation), but instead alters the resting membrane potential of pre- and post-synaptic neurons dependent on the current polarity in the stimulated brain region. Animal studies suggest that changes in long-term potentiation occur via glutamate release in response to anodal tDCS, thereby affecting learning and memory. In clinical studies, a current not exceeding 2 mA/cm² is applied for 10–30 min via electrodes placed above the target brain region. To date, a number of clinical studies have reported some promising effects when treating patients with depression, chronic pain, schizophrenia, dementia, Parkinson’s disease and cerebral stroke. However, appropriately designed randomized controlled clinical trials are scarce and reported intervention effect sizes only vary from small to moderate, with little evidence for sustained long-term effects.

Particularly the effects of tDCS on human cognition are poorly understood, including the underlying neurophysiological mechanisms. Hence, the current thesis investigated the effects of anodal tDCS over the prefrontal cortex on auditory event-related potentials (ERPs) and related changes in the neurochemistry of the stimulated brain tissue with high-field proton magnetic resonance spectroscopy (MRS) in healthy volunteers.

The effects of a single session of 20 min of 2 mA left-prefrontal anodal versus sham stimulation on auditory ERPs was investigated by employing a randomized single-blind crossover design. Stimulation effects on cortical glutamate (Glu) and glutamine (Glx) levels were subsequently measured in a 3 Tesla MRS scan. tDCS
was associated with a significant increase of N1 amplitudes while smaller P3b amplitudes correlated with higher cortical Glu and Glx levels in the stimulated brain area when performing an auditory go/no-go discrimination task. tDCS did not change mismatch negativity, nor task performance or cortical Glu/Glx levels. Cortical Glu/Glx levels and N1 amplitudes were both depended on stimulation order (“sham” vs “active”).

Notwithstanding, increased N1 amplitudes with anodal tDCS support the notion of increased cortical excitability, thereby potentially supporting impaired cognitive processes in neuropsychiatric conditions. Hence, the effects of tDCS on ERPs were also investigated in schizophrenia. Schizophrenia patients usually present with significantly smaller N1, MMN and P3 amplitudes when compared to their healthy counterparts. This was also confirmed in the current study. However, anodal tDCS had no effect on any ERPs in schizophrenia patients and did not affect the performance in the go/no go task. In fact, both groups, healthy controls and schizophrenia patients, performed equally well on this task.

Taken together, these findings indicate that a single application of tDCS increases cortical excitability in healthy subjects as indicated by larger N1 amplitudes but not in schizophrenia patients. However, it is important to emphasize that the current study only investigated the short term effects of a single tDCS application whereas therapeutic effects usually take place following repeated tDCS over several weeks. The repeated application of tDCS is more likely to induce changes in neuronal plasticity (e.g. via long-term potentiation), which in turn is thought to facilitate recovery and to support re-learning as well as other cognitive processes. Hence, tDCS may be a useful tool when combined with cognitive behaviour therapy. Carry-over effects from active to sham trials can potentially interfere with tDCS effects on cortical excitability and should be taken into account by future studies (e.g. by employing a between-subjects study design).
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INTRODUCTORY LIST OF ABBREVIATIONS

EEG = Electroencephalography
ERP = Event-related Potential
Glu = Glutamate
Glx = Glutamate and Glutamine
MMN = Mismatch Negativity
MRS = Magnetic Resonance Spectroscopy
SAPS = Scale for the Assessment of Positive Symptoms
SANS = Scale for the Assessment of Negative Symptoms
tDCS = Transcranial Direct Current Stimulation
1. TRANSCRANIAL DIRECT CURRENT STIMULATION: NEUROPHYSIOLOGY AND CLINICAL APPLICATIONS

1.1. Transcranial brain stimulation

Electrical brain stimulation is a well-established form of treatment for various psychiatric and neurological conditions. It ranges from electroconvulsive therapy to treat severe forms of depression and schizophrenia, to deep brain stimulation to treat conditions such as Parkinson's disease via intracranial implanted electrodes. While these forms of interventions are highly effective, their applications are limited by potentially severe adverse side effects, which are associated with general anesthesia and neurosurgery. Hence, the search for less invasive and less costly methods of brain stimulation has been under investigation for a while and has produced two potential alternatives to date: transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Both methods can be applied without invasive procedures as they use either brief high-intensity magnetic pulses or a low-intensity current to stimulate circumscribed brain tissue via extra cranial devices. Both methods are well tolerated and do not have severe adverse side effects. However, are they actually an effective method of intervention? This question will be reviewed here for tDCS in clinical studies.

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that have recently gained significant scientific attention.

1.2. How does tDCS work?

Neurophysiologic mechanisms have been predominantly investigated using animal research and *in vivo* brain slice recordings, while human studies have largely relied on measures of tDCS-induced metabolic changes in brain tissue measured via magnetic resonance spectroscopy and associated changes in electroencephalographic recordings of brain activity.

The findings essentially point to a neural mechanism of tDCS, whereby the anodal current shifts the resting membrane potential of pre- and post-synaptic neurons toward depolarization, thus resulting in hyperexcitability, while the cathodal current shifts membrane potentials in the opposite direction, resulting in neuronal hypoexcitability [1, 2]. This notion is supported by the respective changes in response to anodal and cathodal stimulation when altering membrane thresholds by introducing agents acting on calcium or sodium ion channels [1, 3].

Recent studies have investigated underlying physiological mechanisms of tDCS more directly by using epidural recordings of corticospinal activity in response to transcranial magnetic stimulation before and after tDCS [4, 5]. Di Lazzaro *et al.* suggest that tDCS works via increased excitability of corticospinal axons, thereby increasing activity levels in cortico–cortical projections onto pyramidal tract neurons, thus resulting in motor cortex excitability modulation with both synaptic (I wave) and nonsynaptic (D wave) mechanisms [4].

Hence, tDCS is considered a noninvasive brain stimulation technique that influences neuronal excitability by altering membrane thresholds but without
evoking neural firing directly as occurs with electroconvulsive stimulation, for example. Directly evoking neural firing is also highly unlikely given the low intensities of the currents employed, usually not more than 2 mA/cm² [6], which is significantly below action potential thresholds [7].

Excitability changes can also be recorded as motor-evoked potentials from peripheral muscles. Consistent with the notion of tDCS-induced response threshold modulation, anodal stimulation of the motor cortex increases and cathodal stimulation decreases response magnitude [8]. This also affects motor skill learning, as reported in the largest study conducted to date investigating tDCS effects on motor skill learning in 93 healthy right-handed subjects in response to left, right and sham stimulation of the primary motor cortex [9]. The authors found improved motor skill learning following three sessions of anodal stimulation of the left (dominant) motor cortex versus sham stimulation, with intermediate effects for anodal stimulation over the right motor cortex.

These findings exemplify tDCS effects on learning and memory, and point to changes in synaptic functions (i.e., long-term potentiation or depression) in response to anodal (more responsive) or cathodal (less responsive) neural networks [10-13]. A crucial neurotransmitter for long-term potentiation and learning is glutamate acting via the N-methyl-d-aspartate receptor [14]. Magnetic resonance spectroscopy studies have confirmed an increase in glutamine/glutamate signal in brain tissue with anodal stimulation [15], which would explain some of the beneficial effects on learning as well as its therapeutic potential for neuropsychiatric conditions that are characterized by hypofunctional brain regions (e.g., due to reduced cortical metabolism and/or abnormal neurotransmission as in the frontal and prefrontal
cortex of patients suffering from depression [16]).

Dockery et al. examined the effects of tDCS of the left dorsolateral prefrontal cortex on planning function by using the Tower of London task to evaluate performance during and after anodal, cathodal (15 min of 1 mA) and sham tDCS in 24 healthy volunteers [17]. Better performance was reported for cathodal tDCS applied during acquisition and early consolidation when preceding anodal tDCS, but not in the later training session. By contrast, anodal tDCS enhanced performance when applied in the later sessions following cathodal tDCS. These findings suggest that both anodal and cathodal tDCS can improve executive performance but with training phase-specific results. The authors concluded that their findings were due to excitability-decreasing cathodal tDCS producing noise reduction of neuronal activity in the early training phase, whereas a further adaptive configuration of specific neuronal connections is supported by excitability-enhancing anodal tDCS in the later training phase, thus enhancing the efficacy of active connections. This improvement in function was sustained at 6 and 12 months after training.

Iyer et al. studied the effects of tDCS of the left prefrontal cortex in 30 healthy participants using different intensities of tDCS [18]. The authors reported no effect on emotion, psychomotor speed and global measures of processing compared with sham stimulation. Verbal fluency performance however improved with anodal tDCS (20 min of 2 mA) whereas cathodal tDCS had the opposite effect [18].

The findings of this brief review of tDCS studies in healthy subjects are consistent with preclinical data, which suggests a modulatory and polarity-dependent effect on the neural responsiveness in stimulated brain tissue. However, hemispheric specialization of cognitive functions, as well as the interplay of the left and right
brain, has to be taken into account when applying tDCS. Chi and Snyder, for example, investigated the effect of tDCS polarity in 60 healthy participants by stimulating the anterior temporal lobes while participants conducted a demanding insight problem-solving task that could only be solved by 20% of the study participants when receiving sham stimulation [19]. The authors reported that only the combination of left-hemispheric cathodal tDCS and right-hemispheric anodal tDCS improved cognitive performance, whereas switching polarities did not change performance [19]. The authors subscribed to the theory, that inhibition to the left anterior temporal lobe can lead to a cognitive style that is less influenced by mental templates and that the right anterior temporal lobe could be associated with insight or novel meaning.

A meta-analytical review by Jacobson et al. found homogeneity in motor studies for anodal-excitation and cathodal-inhibition effects, but heterogeneity in cognitive studies. The anodal-excitation effect is still observed in most cognitive studies, however the cathode rarely causes inhibition effects, which might reflect on compensation processes within the rich brain networks that typically support cognitive functions [20].

1.3. Adverse side effects of tDCS

tDCS is a safe procedure with many studies not reporting adverse side effects at all; although this could be a result of ‘absence of evidence rather than evidence of absence’ [21]. When reviewing 102 participants who underwent a total of 567 tDCS sessions, mild tingling sensations at the stimulation site (70.6%), moderate fatigue (35.3%) and itching (30.4%) were reported as the most common side effects,
followed by headaches (11.8%), nausea (2.9%) and insomnia (<1%) as less common adverse events [22]. These rates do not appear to be different to sham stimulation according to a review of reports published between 1998 and 2010 [21]. However, the authors of this review also noted that adverse side-effect profiles may differ dependent on electrode placements and type of neuropsychiatric condition, but the published data do not support more detailed analyses in this respect [21].

1.4. Clinical applications of tDCS

A PubMed search identified 1,146 publications for the period 2000 – 2013 when using the search phrase ‘transcranial direct current stimulation’ (Figure 1).

Figure 1: PubMed identified 1,146 publications when using the search phrase ‘transcranial direct current stimulation’. Publications per annum are given between 2000 and December 2013.

However, the methods and study designs vary considerably, without a comprehensive meta-analytical approach, other than perhaps for intervention in
depression [23]. Hence, this qualitative review will focus on clinical studies published in the past 5 years (i.e., 2007–2012) with a sufficient sample size to detect at least moderate effects and a single- or double-blind study design when comparing tDCS effects to sham stimulation. When applying these criteria, identified studies were relevant to depression, pain, cerebral stroke, neurodegenerative brain disorders (e.g., Parkinson’s disease) and schizophrenia. In addition, anecdotal evidence from studies not meeting these inclusion criteria will be reported where relevant.

1.4.1. Depression

The first studies on tDCS effects on mood, dating back to the 1960s and 1970s, reported mood elevation, giddiness and talkativeness following bifrontal stimulation in depressed patients [24-27]. By contrast, emotional state, affect, emotional decision-making, arousal and psychomotor functions remained unchanged with bi-frontal anodal and cathodal tDCS in mentally healthy volunteers (n = 25) when tested in a double-blind crossover study [27]. These findings suggest that mood-elevating effects of frontal tDCS are more likely to occur in patients suffering from a depressive disorder.

93 publications from 2007 to 2012 were identified when entering the search phrase major ‘depressive disorder’ OR ‘depression’ AND ‘transcranial direct current stimulation’ OR ‘tDCS’. Most studies apply the anode to the left dorso-lateral prefrontal region and the cathode to the right supraorbital region, aiming to re-establish a balance between left and right frontal cortex activation when
assuming a link between depression, executive impairment and hypoactivity in
the left dorsolateral prefrontal cortex. This is based on several studies
connecting prefrontal cortex asymmetry - with hyperactivation on the right and
hypoactivation on the left prefrontal cortex – with subjects with depression [27-29]. This tDCS setup can act simultaneously in both areas.

Kalu et al. identified six randomized trials and four open-label studies published
from 1998 to May 2011 for their meta-analysis [23]. The authors concluded that
depression symptom severity is significantly reduced with frontal tDCS versus
sham stimulation, while four studies [30-33] also reported sustained effects or
further symptom improvement over a 4-week follow-up period. However, a lack
of homogeneity following meta-regression points to patient sampling bias due to
the absence/presence of medication or inter-individual differences in symptom
severity at study inclusion.

Since then, and following on from an earlier study [34], the largest controlled
clinical trial using tDCS as a treatment for depression was performed on 64
patients by an Australian team and published in 2012 [31]. Patients underwent
15 sessions of anodal left prefrontal stimulation versus sham, followed by 3
weeks of open-label treatment. Clinical ratings on the Montgomery–Asberg
Depression Rating Scale significantly improved in the active treatment versus
sham stimulation arm, as did processing speed (Symbol Digit Modalities Test)
after the first session. However, other mood ratings did not confirm an
advantage of active tDCS versus sham stimulation, whereas an advantage has
been demonstrated for various other neuropsychological tests across multiple
cognitive domains after the initial 15 sessions. In addition, the number of actual
responders was small, as was the overall intervention effect size. However, the
open-label phase suggests more benefits of repeated tDCS on mood but no additional cumulative effects on cognition.

While more sustained and larger effects with repeated tDCS on mood have also been reported by others [33, 35] – including trials without concurrent antidepressant treatment [33, 34] – the published findings to date are still limited. In particular, randomized and controlled clinical trials comparing tDCS (active vs sham) with other established forms of intervention (e.g., pharmacotherapy and cognitive behaviour therapy) are missing. Therefore, tDCS as a treatment for depression should be considered in line with other forms of physical intervention, such as light-exposure therapy for seasonal depression or sleep-deprivation therapy, until findings from larger clinical trials become available. While the lack of serious adverse side effects seems to favour tDCS – even without unequivocal evidence of its effectiveness – caution should be exerted with respect to suicidality as with any other mode of intervention.

1.4.2. Pain

Pain and depression symptoms often present as concurrent phenomena [36]. Moreover, antidepressant pharmacotherapy (i.e., in the multimodal treatment of chronic pain [37]) also offers additional benefits via modulatory effects on central pathways associated with pain processing [38, 39]. Therefore, tDCS may also offer an alternative method of intervention by modulating pain processing in these central pathways.

Various studies have investigated this approach in a variety of chronic pain conditions, such as spinal cord injury [40], fibromyalgia [41, 42] and migraine
For example, Fregni et al. investigated anodal motor cortex stimulation in a small group of 17 patients suffering from chronic pain following traumatic spinal injury [40-42]. Patients were randomly assigned to active (n = 11) and sham stimulation (n = 6), which was performed in a double-blind fashion. The authors reported a significant cumulative decrease of pain rating scores in response to successive anodal tDCS versus sham stimulation.

Repeated anodal stimulation of the motor cortex also appears to be beneficial for fibromyalgia patients (n = 32) [41]. The reported effect was side specific for the motor cortex and tDCS was not effective when stimulating the dorsolateral prefrontal cortex. Finally, repeated cathodal stimulation (n = 13) of the visual cortex (vs sham; n = 13) over 6 weeks appears to reduce the intensity and duration but not the frequency of migraine attacks when comparing 2 months pre- versus 2 months post-treatment [43].

While the reported preliminary findings are promising, sample sizes were very small and often heterogeneous in respect to baseline pain measures, treatment history and other concurrent treatment or coexisting morbidities. Furthermore, pain is a very complex phenomenon and it remains unclear how tDCS interferes with central pain processing. Hence, more systematic research is required to draw firm conclusions on the effectiveness of tDCS for chronic pain treatment.

These previous clinical applications of tDCS are largely passive in their nature; that is, patients are not required to perform tasks while receiving tDCS. This approach, however, neglects the potential benefits of tDCS on learning and memory, which has applications for brain injury, cerebral stroke and degenerative brain disorders.
1.4.3. Cerebral Stroke

Cerebral stroke usually affects unilateral circumscribed brain regions. This often results in a functional interhemispheric imbalance that hinders rehabilitation efforts. tDCS may be used to selectively down- and/or up-regulate affected brain regions in the respective hemisphere in order to support neural reorganization in combination with active rehabilitation therapy after stroke or traumatic brain injury.

Wu et al. investigated tDCS in 90 inpatients suffering from upper limb spasticity after cerebral stroke [45]. Twenty sessions of cathodal stimulation were applied to the primary sensory and motor cortex area of the stroke-affected hemisphere while the patients concurrently underwent conventional physiotherapy. The authors found a better response in patients receiving active tDCS versus sham stimulation, using Modified Ashworth Scale of muscle spasticity, Fugl-Meyer Assessment of Motor Recovery and Barthel Index. This advantage was maintained at follow-up after 4 weeks. By contrast, early intervention in acute stroke - applying anodal tDCS over ipsilesional M1, starting on second day after stroke onset - does not appear to benefit from tDCS [46]. While these findings are promising, they still require replication in sufficiently large controlled clinical trials.

More recently, Meinzer et al. investigated tDCS effects on language function in 20 healthy volunteers using functional MRI [47]. Anodal stimulation of the left inferior frontal gyrus significantly improved semantic word retrieval while resting-state functional MRI showed increased connectivity [45]. Further research using a combination of repeated functional and structural brain imaging may be helpful to better understand the potential effects of tDCS on
neuroplasticity.

Animal research is equally important to systematically investigate the potential effects of an electrical current on neural repair.

1.4.4. Neurodegenerative & neurodevelopmental brain disorders

The loss of dopamine-synthesizing neurons in substantia nigra characterises Parkinson's disease. Motor symptoms such as rigidity, tremor, bradykinesia and gait instability are the defining neurological symptoms. However, reduced processing speed and impaired executive function (i.e., attention and working memory), along with mood and vegetative symptoms, complicate the complex clinical presentation of Parkinson's disease.

tDCS applied to various cortical regions (i.e., to the motor, frontal and prefrontal cortex) may be beneficial in treating some of the motor and cognitive symptoms as they occur in this disorder; for instance, via retrograde cortical stimulation of the dopamine-depleted midbrain structures. Moreover, working memory performance correlates with prefrontal dopamine levels [48]. Dopamine release in the caudate nucleus can be facilitated by high-frequency repetitive transcranial magnetic stimulation of the prefrontal cortex [49]. Hence, prefrontal tDCS may mediate similar mechanisms.

However, the available data from sufficiently large clinical trials are still scarce and largely limited to investigating effects on motor performance. Benninger et al. undertook a randomized double-blind and sham-controlled study on 25 Parkinson's disease patients, stimulating motor and prefrontal cortices [50]. They reported small effects on gait and bradykinesia versus sham stimulation, but no effects on self-assessed mobility, physical and mental wellbeing, nor in
reaction time or symptoms as rated on the Unified Parkinson’s Disease Rating Scale.

Increasing prefrontal dopamine may also be beneficial when targeting hypofrontality and associated cognitive and negative symptoms in schizophrenia (e.g. via increased caudate dopamine release in response to prefrontal cortex stimulation [49]). However, reports are still scarce or have revealed limited effects [51]. More promising effects have been reported by Brunelin et al., when targeting medication-refractory auditory hallucinations with tDCS in 30 schizophrenia patients [52]. The authors placed the anode left prefrontally and the cathode left temporoparietally and stimulated twice a day over 5 consecutive days. They were able to find a significant reduction of auditory verbal hallucinations versus the sham condition along with improved negative and other positive symptoms. These beneficial effects lasted for up to 3 months. These findings are awaiting replication.

The cholinergic system appears to play an important role in the interneuronal circuits, modulating the efficacy of neuronal intracortical synaptic transmission. To explain anodal tDCS effects in pathological conditions, it is interesting to assess, whether tDCS interferes with cholinergic circuits. It has been shown that anodal tDCS increases the activity of cortical cholinergic interneurons, with increasing short latency afferent inhibition [53], but also decreasing excitatory after-effects [54]. This may represent a promising therapeutic target for patients diagnosed with Alzheimer’s disease, which is associated with decreased cholinergic function, in particular when combining tDCS with cognitive training. However, study populations to date remain too small and too heterogeneous to support a critical review.
1.5. Conclusion

tDCS is inexpensive, safe to administer and based on plausible biological mechanisms. However, its effects on brain functions associated with mood and cognition are still poorly understood. Nevertheless, our review suggests small-to-moderate effects when treating some neuropsychiatric conditions. Hence, tDCS may be considered a complementary form of treatment, specifically targeting mood and executive function, and perhaps auditory hallucinations in schizophrenia. However, large-scale randomized controlled clinical trials are still required to evaluate its effectiveness in comparison to other more established forms of intervention. Also, a more systematic approach comparing stimulation sites, altering polarity, and varying duration, current intensity and number of repeats is critical. These investigations should consider adding functional brain imaging, magnetic resonance spectroscopy and EEG-based tools to further our understanding of tDCS effects in clinical populations. In particular, tDCS effects on learning and memory, and its clinical applications in cognitive remediation and stroke recovery, are promising and warrant further research. As a first step in this direction, the following chapter aims to further our understanding of tDCS effects on brain function in healthy volunteers.
2. TRANSCRANIAL DIRECT CURRENT STIMULATION OF PREFRONTAL CORTEX: AN AUDITORY EVENT-RELATED POTENTIAL AND PROTON MAGNETIC RESONANCE SPECTROSCOPY STUDY

2.1. Introduction

Little is known how tDCS-induced changes of cortical glutamate (Glu) levels affect auditory event-related potentials (ERPs) as measures of neural excitability. Hence, the current study investigated the effects of tDCS on auditory ERPs as well as tDCS-induced changes of Glu levels in the stimulated prefrontal cortex.

An ERP is the time-locked electrophysiological brain response to a specific sensory, cognitive or motor event that can be measured via electroencephalography (EEG) as waveforms. ERP waveforms contain positive and negative voltage deflections within different components, mostly referred to by a letter indicating polarity (N for negative, P for positive) and a number indicating either the latency after a stimulus in milliseconds or the ordinal

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position in the waveform [55]. The ERPs of most interest for the current study were N1 and P3.

N1, the first substantial negative peak in the waveform, occurs about 100 milliseconds after a presented stimulus; it is mostly distributed over the fronto-central region of the scalp and is involved in perception. The amplitude of N1 depends on several factors, such as rise time of the onset of a sound, its loudness, inter-stimulus interval and frequency [56, 57].

The P3 component is involved in the process of decision-making, as it is thought to reflect processes involved in stimulus evaluation or categorization; it contains two distinguishable subcomponents: P3a (also called novelty P3), with shorter latency and more frontally displayed amplitude and the classic P3/P300, later renamed to P3b. The P3a has been mainly associated with engagement of attention, (especially the orienting, involuntary shifts to changes in the environment), and the processing of novelty stimuli [58]. It is triggered by an unexpected event. However, P3b involves active cognitive processing, linked to the task at hand, e.g. counting oddballs. It is triggered by improbable events - the less probable the event, the larger the P3b amplitude.

Glu and its precursor glutamine are usually difficult to quantify separately \textit{in vivo} by proton magnetic resonance spectroscopy (MRS). Hence, both are usually expressed as (combined) glutamine/glutamate (Glx) signal [59-61]. \textit{In vivo} human proton MRS investigations to date have provided some evidence that tDCS induces changes to the Glx signal. For instance, Stagg et al. [62] reported reduced Glx with cathodal cortex stimulation but no change of the Glx signal following anodal tDCS. Clark et al., [63] reported increased Glx levels after 30
minutes of 2 mA parietal anodal tDCS. However, the authors tested the effect of tDCS following a baseline MRS scan without controlling for potential order effects or non-specific (placebo-like) effects as they may occur based on participant expectations.

Notwithstanding, the reports are largely consistent with the preclinical findings as reviewed in chapter 1, and suggest a Glu-mediated mechanism that is altering cortical excitability in response to tDCS. This mechanism seems to be the physiological basis of the beneficial effects of repeated prefrontal cortex stimulation when, for instance, treating depressive symptoms [64].

Previous in vivo human studies have investigated the effects of tDCS on the excitability of the motor cortex [65, 66]. It has also been demonstrated that tDCS alters visual working memory performance (i.e. improved error rate, accuracy, and faster reaction time when using the n-back task) following 20 min of 2 mA of anodal dorsolateral prefrontal tDCS with the cathode positioned contra laterally in the suborbital region [67]. The reported behavioural changes were accompanied by reduced frontal delta activity, increased P2 and P3 ERP amplitudes, and enhanced current source density in parahippocampal gyrus.

The current study investigated tDCS effects on pre-attentive and attentive auditory discrimination performance and associated ERPs and tDSC-induced changes in Glu/Glx signal. An increase of N1 amplitudes was predicted, indicative of higher levels of cortical excitability and hence alertness [68, 69] in response to increased Glu activity following prefrontal tDCS. It was further hypothesised that higher levels of cortical excitability decrease P3b amplitude (e.g. [70, 71]) and therefore affect auditory discrimination performance (i.e. improving hit rates
and/or facilitating errors of commission) due to a higher level of alertness and uncertainty along with increased Glu activity [72].

Potential changes of Mismatch Negativity (MMN), which represents an ERP measure of non-attentive auditory discrimination performance [73-77], calculated by subtracting ERPs in response to frequent standard stimuli from ERPs in response to rare deviant stimuli, were also explored. MMN peaks occur with a frontocentral maximum about 200ms after presentation of deviant stimulus. MMN generation has been linked to Glu neurotransmission [75, 78]. While MMN is predominantly generated in the primary auditory cortex, a secondary generator has been located in the inferior prefrontal cortex [74, 79-81]. It has been proposed that the prefrontal MMN component is associated with the attention shift towards the oddball, thus triggering further contextual evaluation of its relevance. This cognitive process produces a P3a ERP proportional to the salience of the oddball [76, 82], thus signalling an attention shift towards the oddball, which is predicted to be facilitated with increased Glu activity.

2.2. Materials and methods

The study was approved by the University of Newcastle Human Research Ethics Committee (Reference H-2011-0075) and took place at the University of Newcastle Priority Centre for Translational Neuroscience & Mental Health Research in 2012 and 2013.

2.2.1. Subjects
Ten male and 6 female volunteers (13 right and 2 left-handed, 1 ambidextrous, assessed with Edinburgh Handedness Inventory [83]) with a mean age of 29.9 (SD 6.1) years were recruited from the local community by advertisement. All subjects gave informed written consent before participating.

Study exclusion criteria were suffering from a chronic medical condition or reporting a history of epilepsy, previous head injury with unconsciousness, or mental illness and/or alcohol/illicit drug abuse/dependence (according to DSM-IV diagnostic criteria; [84]). Subjects were also tested for intact hearing and screened for standard MRI exclusion criteria (e.g. claustrophobia, metal implants, etc.).

### 2.2.2. Study design and tDCS procedure

tDCS effects were tested by employing a randomized and counterbalanced repeated measurement crossover design by comparing “active” versus “sham” stimulation on two separate occasions (i.e. as an EEG and MRS session at least several weeks apart). Eight subjects underwent “sham” stimulation first whereas 8 subjects underwent “active” tDCS first for the EEG session. Respectively, the time difference between sham and active tDCS was between 60 and 90 minutes at both, EEG and MRS session.

On each occasion, tDCS was applied via 3.5 cm² saline-soaked sponge electrodes (Transcranial Direct Current Stimulator PLUS, Magstim). The anodal electrode was placed left prefrontally at F3 (International 10-20 System) and the cathodal electrode at the right supraorbital region. In the “active” condition, the current
was gradually increased over 30 sec to 2 mA and maintained for 20 min while no stimulation was applied after the initial 30-sec stimulation (i.e. 10 sec of gradually increasing to 2 mA, followed by maintaining 2 mA for 10 sec before gradually decreasing the current over 10 sec from 2 mA to 0 mA) in the “sham” condition. The “active” condition also ended with gradually reducing the current from 2 mA to 0 mA over 10 sec. “Sham” and “active” tDCS took place one hour apart in both the ERP and MRS session, respectively.

2.2.3. Stimuli, EEG recording, and ERP extraction

EEGs were recorded 10.0 (SD 2.0) min after “sham” and “active” tDCS while subjects were presented with acoustic stimuli via calibrated headphones (Sennheiser HD 280). A randomized tone sequence with a stimulus-onset asynchrony (SOA) of 600 msec with three types of pure tones were generated (Presentation Software, Neurobehavioral Systems Inc.): (1) a frequent (p=0.9) 1 kHz-tone of 100 msec duration together with (2) a rare (p=0.1) duration-deviant tone of 1 kHz and 50 msec duration or, alternatively, (3) with a rare (p=0.1) pitch-deviant tone of 1.2 kHz and 100 msec duration. Tones were presented in two separate recording sessions of 700 stimulus presentations of 630 frequent standard stimuli and 70 rare deviant stimuli, respectively. Two deviant tones were never presented consecutively. Duration and pitch deviant sessions were alternated between the repeat sessions of “sham” or “active” tDCS. During EEG recordings, subjects were asked to watch a silent movie and to ignore the tones. This passive listening task was followed by an active auditory “go/no-go” discrimination task. Subjects were presented with a random sequence of
frequent \((p=0.9)\) 1 kHz tone with 100 msec duration and rare \((p=0.1)\) digitally composed complex sound with a high frequency cut-off at 11 kHz at 1,000 msec SOA (Presentation Software, Neurobehavioral Systems Inc.). Individual sound stimuli were never presented consecutively. The sound stimuli served as the target stimuli in the “go/no-go” discrimination task and required a simultaneous button-press response with both thumbs.

Continuous EEG was recorded (NuAmps, Neuroscan Ltd.) against a nose reference with tin electrodes (Quick-cap, Compumedics Ltd.) with a 500 Hz sampling rate (high pass 0.1 Hz, low pass 30 Hz, and 50 Hz notch filter) from FZ, CZ, PZ, F3, C3, P3, F4, C4, and P4 (International 10-20 System) and from left and right mastoid. Potential eye movement artifacts were recorded via vertical and horizontal EOG. Impedance was kept below 5 kΩ. The EEG was recorded after “active” and “sham” stimulation and analysed off-line.

Raw data were corrected for eye-blink artefacts [85] and high pass-filtered (0.2 Hz/12 dB). Epochs were created for -422 msec to 600 msec intervals relative to stimulus onset and rejected for EEGs exceeding ±100 μV. Epochs were then low-pass filtered at 20 Hz and ERPs calculated and averaged relative to a 200 msec pre-stimulus onset baseline.

MMN was extracted in the passive listening task by subtracting ERPs in response to the frequent standard stimuli from ERPs in response to the rare deviant stimuli (duration and pitch oddballs, respectively). Post-stimulus onset intervals for mean ERP amplitude measures were calculated at Fz [74] for N1 between 100-140 msec, 140-240 msec for MMN in response to pitch deviance, 150-250 msec for MMN in response to duration deviance, 240-450 msec for P3a (passive
listening task), and 174-470 msec at Pz for P3b (“go/no-go” discrimination task [70]), respectively. A minimum of 70 trials for N1, MMN and P3a, respectively and a minimum of 30 trials for P3b recordings were accepted as sufficient signal to noise separation.

2.2.4. MRS acquisition

Proton MRS data was acquired after “sham” and “active” tDCS, respectively, in a separate session, several weeks after the EEG study. MRS data was available from 12 of the 16 study participants (8 males and 4 females, 9 right and 2 left-handed and 1 ambidextrous; mean age 28.6 years SD 6.5). MRS commenced 16.2 min (SD 4.1) after “sham” or “active” tDCS. Six subjects underwent “sham” stimulation first, whereas 6 subjects underwent “active” tDCS as their first session.

Point-resolved spectroscopy [PRESS; 86] was performed on a 3 Tesla Magnetom Verio System (Siemens AG, Erlangen, Germany) with a 70 cm diameter bore (software version VB17A) and a 32 channel head coil (Siemens AG, Erlangen, Germany) with operating proton resonant frequency at 123.25 MHz. A set of orthogonal three-plane localizer images was acquired to allow for spectroscopic voxel localization in left dorsolateral prefrontal cortex as shown in Figure 2.
One-dimensional spectroscopic data was acquired with the following parameters: voxel size of 2.5 x 2.5 x 2.5 cm$^3$ at approximately L 325, A 176, and F 213; number of averages of 128; acquisition vector of 2,048 data points, echo time (TE) of 30 ms; spectral width of 2,000 Hz; repetition time of 2 s, 4 preparation scans; 3.7 ppm RF offset frequency (on resonance with glutamate). WET water suppression was applied prior to sequence [87] and a separate non-water-suppressed acquisition was acquired for water processing in LCModel (16 scans, Version 6.2.). Automated and interactive voxel shimming was undertaken to yield a water FWHM of 12-20 Hz. Raw spectroscopic data was taken off-line to LCModel [88] and processed using an appropriate metabolite basis set for processing and quantification. The metabolites aspartate, Glu and Glx are reported in mmol units.

Three-dimensional volumes (MP-RAGE, TE=2.57ms, TR=1500ms, FOV: 250x250mm$^2$, Matrix: 256x256 mm$^2$ voxel size of 1 x 1 x 1 cm$^3$) were acquired to allow for correction of differing components of pre/post-tDCS grey versus white matter ratios in each proton MRS voxel. Quantification of grey to white matter
ratio was calculated using FSLMATHS and FSLSTATS Software (http://fsl.fmrib.ox.ac.uk/fsl; Oxford, United Kingdom). Each three-dimensional volumetric dataset was processed with FSLFAST image segmentation to correct for white to grey matter ratios (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FAST). Each of the tissue types (grey matter, white matter and cerebrospinal fluid) was presented on separate files, along with partial volume estimates for each of these tissue types. By overlaying the files for each of the tissue types on to the voxel using the FSLMATHS, the voxel composition of grey matter, white matter and cerebrospinal fluid was determined and used to correct the individual spectrographic data according to the respective tissue proportions in that voxel. Proton MRS data quantification for glutamate (Glu), Glutamine (Glx) and aspartate was performed using LCModel corrected by the individual voxel tissue composition.

2.2.5. Statistical analyses

As a quality-assurance measure, LCModel produces a Cramer–Rao lower bound (CRLB) of the fit to the peak of interest. If this value was greater than 15%, the fit was deemed unreliable and was excluded from analyses. ERP amplitude (N1, MMN, P3a and P3b) and metabolite (Glu, Glx) differences for “sham” versus “active” tDCS were tested non-parametrically (SPSS Version 19) at $p<0.05$ (two-sided) with Wilcoxon Signed-Rank Test and order effects of “sham/active” versus “active/sham” were tested with the Mann-Whitney U-Test. Spearman Correlation Coefficients were calculated to test associations at $p<0.05$ (two-
sided) of metabolite concentration differences of “active” minus “sham” tDCS with the corresponding ERP amplitude changes.

2.3. Results

2.3.1. Behavioural Data

tDCS did not alter the hit rate in the auditory “go/no-go” discrimination task with 97.0% in the “active” versus 98.4% in the “sham” condition. Likewise, the low false alarm rate remained unchanged with less than 0.01% in both conditions.

2.3.2. ERP data

N1 amplitudes significantly increased from -0.75 μV (SD 0.79) in the “sham” condition to -1.15 μV (SD 1.01) with tDCS ($z = 2.35; p=0.019$; Figure 3). This effect on N1 amplitude was also dependent on the order of stimulation conditions ($z = -2.36; p=0.018$) with a significant N1 augmentation only when “active” tDCS was taking place first ($z = -2.52; p=0.012$). No significant differences for “sham” versus “active” stimulation or any order effects were statistically confirmed for MMN, P3a and P3b amplitudes.
Figure 3: N1 auditory ERPs (grand averages recorded at Fz) in response to standard stimuli in the duration-deviant condition (passive listening task) significantly increase with tDCS ($p<0.02$). Arrow marks stimulus onset; negative polarity is upwards.

2.3.3. MRS data

CRLB was <15 % for Glu and Glx, respectively. Glu levels did not significantly differ between “sham” and “active” tDCS (Glu: 2.25 [SD 0.67] mmol with “sham” versus 2.12 [SD 0.61] mmol with “active” tDCS). Likewise, Glx with 2.28 [SD 0.66] mmol in the “sham” condition did not significantly change to 2.13 [SD 0.61] mmol with “active” tDCS. Glu and Glx response to tDCS, however, depended on the order of “sham” and “active” conditions (Glu: $z=-2.40$; $p=0.016$; Glx: $z=-2.242$; $p=0.025$) with a significant decrease of Glu ($z=-1.99$; $p=0.046$) and Glx ($z=-1.99$, $p=0.046$) with “active” tDCS when the “sham” condition was conducted first.
amplitude changes did not correlate with changes of Glu and Glx levels except for P3b amplitudes (Glu: \( r_s = -0.75; p=0.005 \); Glx: \( r_s = -0.68; p=0.014 \)).

### 2.4. Discussion

The results partially support the hypotheses; that is N1 amplitudes at Fz increased with left prefrontal anodal tDCS consistent with increased excitability [68, 69], while Glu and Glx metabolites remained unchanged in the stimulated brain area as well as the auditory discrimination performance and related ERPs (MMN, P3a and P3b). The order in which sham and active tDCS were applied played an important role, as Glu and Glx decreased after active tDCS when it was applied subsequently to sham tDCS. However, overall tDCS effects could have been potentially masked by order effects, which may be due to increased excitability when first exposed to the scanner environment and tDCS or to carry-over tDCS effects in the “sham” condition when the “active” stimulation was conducted first. Assuming that acute tDCS effects last no longer than one hour [89], 60 to 90 minutes were left between the active and sham tDCS applications. tDCS carry-over effects are therefore unlikely, though they cannot be completely eliminated. It has also been reported that Glx levels decrease initially (i.e. within 30 min post stimulation when employing transcranial magnetic stimulation [90] before increasing above baseline levels thereafter). A similar time course may also be present with tDCS. In this respect, balancing the order of “sham” and “active” tDCS at approximate one-hour intervals may have been a sub-optimal design feature of the current study.
Neuronal firing rates regulation in the cerebral cortex relies strongly on coordination between glutamatergic excitatory neurons and γ-amino butyric acid (GABA) inhibitory interneurons [91]. Due to insufficient data quality for GABA spectra, it was not possible to investigate the excitation/inhibition balance (i.e. measured by ratios of glutamate/GABA), which may have provided a more complex interpretation of the stimulation effects on brain function than looking at Glu and/or Glx alone [92].

No tDCS effect on the ERPs MMN and P3a/P3b were found. Since various regions are involved in generating ERPs - such as hippocampus and temporal-parietal junction for P3 [93-96], as well as the superior temporal gyrus for P3, N1 and MMN [97-99] – different stimulation locations should be considered in future studies.

Nevertheless, the increase of N1 amplitudes with tDCS, even stronger so when “active” tDCS came first, is a robust finding and consistent with increased cortical excitability following anodal left-prefrontal cortex stimulation.

However, a corresponding association of N1 amplitudes with changes in Glu or Glx signal in the stimulated brain area was statistically not confirmed. By contrast, P3b amplitudes appear to mirror Glu and Glx levels but irrespective of tDCS effects; that is smaller P3b amplitudes with higher levels of Glu and Glx as hypothesized. The also hypothesized concurrent effects on auditory discrimination performance were not observed. In this respect, the task was probably too easy to detect a potential tDCS effect.
3. TRANSCRANIAL DIRECT CURRENT STIMULATION OF PREFRONTAL CORTEX: AN AUDITORY EVENT-RELATED POTENTIAL STUDY IN SCHIZOPHRENIA

3.1. Introduction

The investigation of tDCS effects on event-related potentials in schizophrenia was conducted in two parts. In the first part, described in the previous chapter, tDCS effects were investigated on healthy participants with the aim to further the knowledge about tDCS effectiveness. These participants also constituted the control group to the clinical group of schizophrenia patients, investigated in the second part of the study, described in this chapter.

The glutamate system has been one of the focus points in schizophrenia research for the last few years. Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS). The glutamate hypothesis of schizophrenia is pointing to a hypofunction of glutamatergic signaling via glutamate (N-methyl D-aspartate –NMDA) receptor. It has been suggested that the application of tDCS can alter and increase glutamate levels (e.g.[63]). This leads to the question, whether tDCS could be used as a potential treatment tool.

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The symptoms of schizophrenia can be distinguished between positive and negative symptoms. The positive symptoms or psychosis often occur episodically and are characterized by delusions and hallucinations. Negative symptoms are closely associated with hypofrontality, which represents a global down-regulation of brain function in the frontal brain. They constitute the most debilitating feature of schizophrenia by affecting working memory, social cognition, affect regulation, communication, and motivation, thus resulting in impaired global functioning. Negative symptoms show little response to antipsychotic drug treatment. Moreover, antipsychotic medication is likely to aggravate hypofrontality via D2 dopamine receptor blockade.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique which effects regional neuronal excitability [14] through the application of a weak electrical current (e.g. 2 mA for 20 min) without directly evoking action potentials [6]. Preclinical studies suggest that tDCS shifts resting membrane potentials of both pre- and postsynaptic neurons, thereby resulting in hyper-excitability with anodal or hypo-excitability with cathodal stimulation [1, 14].

When applied in clinical populations, the procedure is proven to be safe and well tolerated [32, 64]. Clinical studies to date, as reviewed in chapter 1, have provided some evidence for beneficial effects when treating depression symptoms while there are also promising effects reported suggesting better cerebral stroke recovery as well as improved pain treatment and cognitive remediation outcomes with tDCS in neurodegenerative and neurodevelopmental conditions (reviewed by [64]). Improving the efficacy of cognitive remediation in
conditions like schizophrenia would be particularly important since cognitive symptoms are one of the most significant factors determining the long-term rehabilitation prospects of patients suffering from this condition.

Little is known, however, how tDCS effects neural processing in schizophrenia. Hence, the current study investigated the effects of prefrontal tDCS on auditory event-related potentials (ERPs), which are known to be reduced in schizophrenia patients and have also been described as being linked to cognitive deficits of the disorder [98, 100-102].

It was hypothesised that anodal prefrontal tDCS increases cortical excitability along with increased “negativity” in “pre-attentive” ERPs such as N1 [68, 69] and Mismatch Negativity (MMN; [73-77]). It was further hypothesised that increased cortical excitability facilitates subsequent “attentive” information processing (i.e. improving hit rates and increasing errors of commission whilst performing an auditory discrimination task) along with associated ERPs, such as P3a and P3b amplitudes [67, 70].

3.2. Methods

The study was approved by the University of Newcastle Human Research Ethics Committee (Reference H-2011-0075, H-2011-0367) and took place at the University of Newcastle’s Priority Centre for Translational Neuroscience & Mental Health Research in 2012 and 2013.

3.2.1. Subjects

Healthy subjects participated in the previous study (Chapter 2). Patient participants were recruited from the local community by advertisement: 9 males
and 5 females (12 right and 2 left-handed) with a mean age of 46.7 (SD 6.4) meeting DSM-IV criteria for schizophrenia [84]. Patient symptoms were rated on the Scale for the Assessment of Positive Symptoms (SAPS; [103]) and the Scale for the Assessment of Negative Symptoms (SANS; [104]). Study participation exclusion criteria were a history of epilepsy and/or alcohol/illicit drug abuse/dependence, a previous head injury with unconsciousness, or a hearing impairment.

3.2.2. tDCS procedure and study design
Brain stimulation effects were tested single blind by employing a randomized and counterbalanced repeated measurement crossover design comparing “active” versus “sham” stimulation as described in Chapter 3.

3.2.3. EEG recording and analyses
EEG recording and data processing was identical to the methods described in Chapter 3.

3.3. Results

3.3.1. Demographic and clinical data
All 14 patients were symptomatically stable at the time of data collection and on antipsychotic medication. Patients were rated 4.0 (SD 5.2) for positive symptoms (SAPS) and 5.5 (SD 4.9) for negative symptoms (SANS). Four patients were treated with clozapine, three with quetiapine, two with risperidone, two with aripiprazole, and three patients each with ziprasidone, paliperidone, or flupentixol. Five patients received antidepressant co-medication (i.e. paroxetine, venlafaxine, desvenlafaxine, escitalopram, or duloxetine) whereas one patient
was also treated with sodium valproate and one patient with lithium carbonate. Patients were well educated with 14 of 16 having completed secondary or tertiary tuition. However, the majority of patients were unemployed or part-time or casually employed at the time of study participation. All 16 healthy volunteers completed secondary or tertiary education and were significantly younger than the patient sample ($F_{1,28} = 61.8, p<0.0001$).

### 3.3.2. Behavioural Data

Patients and healthy subjects performed equally well on the go/no-go auditory discrimination task (hit rate 96.0% [SD 10.3] versus 98.2% [SD 1.4]: $U= 68.5; Z= -0.84; p = 0.40$); omission error rate 4.38 % versus 1.78 %: $U= 81.5; Z= -0.13; p= 0.89$; commission error rate 1.61% versus 0.63 %: $U= 67.5; Z= -0.95; p= 0.34$; reaction time 390 msec versus 378 msec: $U= 82.0; Z= -0.10; p= 0.92$). tDCS did not significantly alter any of the aforementioned behavioural performance measures in both groups.

### 3.3.3. ERP data

Patient ERP amplitudes were significantly smaller when compared to healthy subjects (N1 at Cz when recorded in the go/no-go discrimination task: $-5.11 \mu V$ [SD 3.23] versus $-1.91 \mu V$ [SD 2.07], $z=-2.58; p=0.009$; MMN at Fz when recorded in the duration-deviant condition: $-0.67 \mu V$ [SD 2.22] versus $-2.27 \mu V$ [SD 1.93] $z=-2.33; p=0.019$; P3b at Pz when recorded in the go/no-go discrimination task: $2.49 \mu V$ [SD 3.21] versus $6.60 \mu V$ [SD 3.54], $z=-2.45; p=0.013$; **Figure 4 A & B**). tDCS significantly increased the N1 amplitude in healthy subjects at Fz from $-0.75 \mu V$ [SD 0.79] to $-1.15 \mu V$ [SD 1.01] ($z=2.35; p=0.019$) in the passive listening task, as described in chapter 3; **Figure 4 C**). This effect was dependent on
stimulation order \((z = -2.36; p = 0.018)\) and significant when tDCS took place prior to sham stimulation \((z = -2.52; p = 0.012)\). tDCS did not significantly change any other ERP in healthy subjects. Also, tDCS did not alter any ERP in patients.

Figure 4: Event-related potentials (ERPs; negative up) recorded whilst performing an auditory go/no-go discrimination task (A) or a passive auditory listening task (B & C). Patient ERPs are presented as thick lines whereas healthy subject data are presented as thin lines. Grey represents “sham” stimulation and black tDCS data. Arrow marks stimulus onset. (A) P3b amplitudes at Pz in response to target stimuli and (B) Mismatch Negativity (MMN) at Fz in response to duration deviants were significantly smaller in patients. (C) N1 amplitudes at Fz significantly increased with tDCS in healthy subjects only.
3.4. Discussion

As hypothesised, N1, MMN and P3b amplitudes were significantly smaller in schizophrenia patients than in healthy controls.

Against previous expectations, tDCS only significantly increased the N1 amplitude in the passive listening task in healthy subjects, not in schizophrenia patients. Furthermore, this effect was dependent on stimulation order and significant when tDCS took place prior to sham stimulation. No other tDCS related ERP changes were found in healthy subjects or schizophrenia patients. Despite a significant age difference, no changes in behavioural data between control and clinical group were detected.

As expected, MMN amplitudes at Fz in response to duration deviants and P3b amplitudes at Pz in response to target sounds in the auditory discrimination task were significantly smaller in the schizophrenia group when compared to their younger healthy counterparts (e.g. reviewed by Todd et al., [105]).

Positive effects of tDCS in schizophrenia have been reported for psychotic symptoms (i.e., auditory hallucinations) and, to a lesser extend, for cognitive symptoms (reviewed by Agarwal et al., [106]). Investigating ERPs for their high temporal resolution when assessing the various stages of neural processing, this study did not replicate a positive effect of tDCS in schizophrenia. N1 amplitude increase in healthy subjects is consistent with the notion of increased cortical excitability in response to anodal prefrontal tDCS. However, prefrontal tDCS did not alter N1, MMN and P3b amplitudes in the schizophrenia group. The fact that patients were treated with psychotropic medication at the time of testing, which may have altered neuronal responsiveness to tDCS should be considered.
However, little empirical evidence supports the assertion of antipsychotics affecting those ERPs, which were selected for the current experiments.

Furthermore, no effect of tDCS on MMN and P3b was recorded in healthy study participants. Multiple brain regions can be of importance for ERP generation. Two main generators for MMN have been located in the primary auditory cortex and in the inferior prefrontal cortex [74, 79-81]. However, it is possible that anodal tDCS administered from F3 did not sufficiently enhance MMN generation. Further research needs to be conducted in order to precisely ascertain the optimal location for tDCS application to ERPs.

Meta-analytical data suggest an effect of prefrontal tDCS predominantly on reaction time and to a lesser extent on cognitive performance when compared to other non-invasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS; [107]). The authors also noted that studies are often lacking appropriate control conditions or are insufficiently powered due to small sample size. Also, the heterogeneity of the various outcome measures limits comparability between studies. Our study, however, indicates that tDCS does not alter reaction time as both of our groups performed equally well on the go/no-go auditory discrimination task. Patients are usually performing with longer reaction times and higher error rates, but not in the current study. This could be partially explained by the low level of difficulty in the go/no-go auditory discrimination task.

In summary, tDCS appears to acutely change cortical excitability only in our healthy sample, as indicated by increased N1 amplitudes, which however, does
not translate into faster reaction times or performance changes, such as increased rates errors of commission [108]. The lack of behavioural changes along with the physiological signs of increased cortical excitability may be limited by a ceiling effect in the overall very well performing study participants.

Further limitations of this study that may have contributed to these results will be discussed in the next chapter.
4. PROJECT SUMMARY, LIMITATIONS AND CONCLUSION

Transcranial direct current stimulation alters neural plasticity by modulating neuronal excitability of pre- and postsynaptic neuron populations and is a well-tolerated brain stimulation technique with very few adverse side effects. tDCS, in contrast to methods such as electroconvulsive or transcranial magnetic stimulation, does not directly evoke neuronal firing. Achieved effects depend on current polarity and derive from the alteration of the resting membrane potential of pre- and post-synaptic neurons.

The ERP and MRS experiments followed the notion of anodal stimulation increasing and cathodal stimulation decreasing neuronal firing thresholds, thereby modulating glutamate-mediated cortical excitability and synaptic functions associated with long-term potentiation. This notion is supported by animal studies suggesting changes in long-term potentiation via glutamate release in response to anodal tDCS, thereby affecting learning and memory.

Cognitive impairment is one of the most significant factors determining the long-term rehabilitation prospects of schizophrenia patients. Cognitive training has been shown to be beneficial; however, effect sizes of cognitive remediation remain relatively low. tDCS may boost intervention efficacy when applied in combination with cognitive training.
The first experiment, using a healthy sample, investigated the effect of a single tDCS application of 20 min left-prefrontal anodal 2 mA tDCS versus sham stimulation on event-related potentials (i.e. N1, MMN, and P3), which are commonly linked to cognitive deficits in schizophrenia. Neurochemical changes in response to tDCS in the stimulated brain tissue were measured with MRS in a separate session by employing a randomized single-blind crossover design on both occasions.

N1 amplitudes increased with tDCS in our healthy sample consistent with the notion of increased neuronal excitability; however, N1 amplitude changes were not related to changes of prefrontal glutamate/glutamine levels. By contrast, smaller P3b amplitudes correlated with higher glutamate and glutamine levels in the stimulated brain but did not affect performance in a go/no-go task when recording P3b. All other ERPs were unaffected by tDCS and no significant changes in glutamate/glutamine levels in response to tDCS were detected.

In respect to the MRS findings, coordination between glutamatergic excitatory neurons and γ-amino butyric acid (GABA) inhibitory interneurons is fundamental to the regulation of neuronal firing rates in the cerebral cortex [91]. Hence, tDCS effects are likely to depend on the regional cortical excitation/inhibition balance (i.e. measured by ratios of glutamate/GABA), which may provide a more meaningful interpretation of the stimulation effects on brain function than looking at Glu and/or Glx alone [92]. This, however, was not possible in the current study due to insufficient data quality for GABA spectra.

Future research should also consider other brain regions when investigating tDCS effects on ERPs. For instance, various regions, such as hippocampus and
temporal-parietal junction, are involved in P3b generation whereas many studies point to the superior temporal gyrus (STG) as a key brain region [93-96], also for MMN generation [97-99]. A topographic recording would also add additional information.

Given the overall small tDCS effects in the current study, non-significant results should also be interpreted with caution due to the relatively small sample size of 16 study participants. Using subjects as their own controls in a cross-over procedures and counterbalancing the order of “sham” and “active” tDCS was intending to control for unwanted biases between treatment groups and potential carry-over effects between sessions. The time between the active and sham tDCS applications before MRS varied between 60 and 90 min. tDCS carry-over effects are unlikely, though can not be completely eliminated. However, order-effects were detected, which could be due to higher arousal levels during the first session and have potentially limited the detection of further tDCS effects. Hence, future studies should consider employing a between-subject study design to control for potential between-session interference.

Similar limitations apply to the patient study where no effect of tDCS on ERPs (including N1) and go/no-go task performance was detected despite confirming smaller N1, MMN and P3 amplitudes in the patient versus control sample. Notable is the significant age difference between the two groups, which is likely to contribute to ERP amplitude differences, although establishing an amplitude difference in the various ERPs between groups was not the primary study aim. It was thought though that smaller ERPs linked to cognitive deficits in
schizophrenia are more likely to respond to tDCS contrary to a potential ceiling effect in healthy subjects.

It is also important to emphasize that the current study only investigated the acute effects of a single tDCS application on two occasions whereas therapeutic effects take place following repeated tDCS over several weeks (e.g. when treating depression [1, 33, 35, 109, 110]). Particularly the repeated application of tDCS is more likely to change neuronal plasticity (e.g. via long-term potentiation), which in turn is thought to facilitate recovery from depression symptoms and supporting re-learning as well as other memory-dependent cognitive processes ([10-13]). Hence, tDCS may be a particularly useful tool when combined with cognitive behaviour therapy.

Future studies should also consider using more complex cognitive tasks when investigating schizophrenia patients and should adjust task difficulty according to patient ability.

Notwithstanding the aforementioned study limitations, the findings such as the N1 amplitude increase are consistent with the notion of increased cortical excitability in response anodal prefrontal tDCS while the correlation of P3b amplitudes with prefrontal cortex glutamate activity may further our understanding of the neurochemical basis of P3b generation. These two novel findings may direct future research which should account for small effect sizes and aim for sufficient sample sizes of >25 study participants. A between-subject design may be more beneficial to control for carry-over effects. Also, stimulating various key generator regions of individual ERPs should be considered together with topographic recordings while tDCS should be employed over repeated
sessions (i.e. consistent with clinical applications of tDCS). More brain metabolites (which are reflecting neuronal activity, such as GABA) should be included in future MRS analyses and potential tDCS-induced changes in cognition should be tested by utilizing more complex tasks which can be adjusted in their degree of difficulty to individual performance levels.
LIST OF ABBREVIATIONS FOR APPENDIX

C = Healthy Control Group
S = Schizophrenia Patient
EEG = Electroencephalography
MMN = Average of Mismatch Negativity calculation
Dur = Duration Deviant
Freq = Frequency Deviant
DEV = Average of Deviant recordings
P3a_MMN = measured P3a for Mismatch Negativity calculated averages
P3a_DEV = measured P3a for averages of Deviant recordings
STD = Average of recordings of Standard stimuli
N1_DEV = measured N1 for averages of Deviant recordings
N1_STD = measured N1 for Averages of Standard stimuli
D = Degree
“-” = Missing Data
Glu = Glutamate
Gln = Glutamine
Cr = Creatine
PCr = Phosphocreatine
GABA = gamma-Aminobutyric acid
Asp = Aspartate
NAA = N-Acetylaspartate
NAAG = N-Acetylaspartylglutamate
Ala = Alanine
Glc = Glucose
GPC = Glycerylphosphorylcholine
Ins = Insuline
Lac = Lactic Acid
### APPENDICES

#### Table 1: Demographics and tDCS Order for Healthy Control Group

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age</th>
<th>Handedness</th>
<th>Order tDCS before EEG</th>
<th>Order tDCS before MRS</th>
</tr>
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<tr>
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<td>23</td>
<td>Right</td>
<td>Active first</td>
<td>Active first</td>
</tr>
<tr>
<td>C2</td>
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<td>19</td>
<td>Right</td>
<td>Active first</td>
<td>Active first</td>
</tr>
<tr>
<td>C3</td>
<td>Male</td>
<td>26</td>
<td>Right</td>
<td>Sham first</td>
<td>Sham first</td>
</tr>
<tr>
<td>C4</td>
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<td>33</td>
<td>Right</td>
<td>Sham first</td>
<td>Active first</td>
</tr>
<tr>
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<td>Left</td>
<td>Sham first</td>
<td>Active first</td>
</tr>
<tr>
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<td>Active first</td>
<td>Active first</td>
</tr>
<tr>
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<td>Sham first</td>
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<td>Sham first</td>
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<td>Sham first</td>
</tr>
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<td>Active first</td>
<td>Active first</td>
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<td>Active first</td>
<td>Sham first</td>
</tr>
<tr>
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Table 2: ERPs of Healthy Control Group after Sham tDCS - MMN and P3a

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<th>P3a_MMN_Freq</th>
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<th>P3a_DEV_Freq</th>
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</tr>
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</tr>
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<td>-1.47</td>
</tr>
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<td>-0.50</td>
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<td>-0.48</td>
</tr>
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</tr>
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</tr>
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Table 3: ERPs of Healthy Control Group after Sham tDCS - N1 and P3b

<table>
<thead>
<tr>
<th>Subject</th>
<th>N1_DEV_Dur</th>
<th>N1_DEV_Freq</th>
<th>N1_STD_Dur</th>
<th>N1_STD_Freq</th>
<th>P3b</th>
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<tbody>
<tr>
<td>C1</td>
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</tr>
<tr>
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<td>-1.29</td>
<td>3.17</td>
</tr>
<tr>
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</tr>
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</tr>
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</tr>
<tr>
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<td>0.05</td>
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</tr>
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</tr>
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<td>-0.69</td>
<td>1.37</td>
</tr>
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<td>5.57</td>
</tr>
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<td>2.15</td>
</tr>
<tr>
<td>C13</td>
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<td>-1.38</td>
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</tr>
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Table 4: ERPs of Healthy Control Group after active tDCS - MMN and P3a
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<th>MMN_Freq</th>
<th>P3a_MMN_Dur</th>
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<th>P3a_DEV_Dur</th>
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<td>-3.10</td>
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*Table 5: ERPs of Healthy Control Group after active tDCS – N1 and P3b*
<table>
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<th>N1_DEV_Freq</th>
<th>N1_STD_Dur</th>
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<tr>
<td>C16</td>
<td>-1.46</td>
<td>-4.56</td>
<td>-1.14</td>
<td>-1.67</td>
<td>3.78</td>
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</table>

Table 6: Demographics and tDCS Order of Schizophrenia Patients
<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age</th>
<th>Handedness</th>
<th>Positive Symptoms</th>
<th>Negative Symptoms</th>
<th>Education</th>
<th>Employment</th>
<th>Living</th>
<th>Order tDCS before EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>Female</td>
<td>54</td>
<td>Right</td>
<td>1</td>
<td>0</td>
<td>Tertiary D.</td>
<td>Unemployed</td>
<td>Parents</td>
<td>Active first</td>
</tr>
<tr>
<td>S2</td>
<td>Male</td>
<td>36</td>
<td>Right</td>
<td>8</td>
<td>2</td>
<td>Tertiary D.</td>
<td>Part time</td>
<td>Alone</td>
<td>Sham first</td>
</tr>
<tr>
<td>S3</td>
<td>Female</td>
<td>48</td>
<td>Right</td>
<td>5</td>
<td>8</td>
<td>Tertiary D.</td>
<td>Unemployed</td>
<td>Alone</td>
<td>Active first</td>
</tr>
<tr>
<td>S4</td>
<td>Female</td>
<td>58</td>
<td>Right</td>
<td>0</td>
<td>0</td>
<td>Tertiary D.</td>
<td>Unemployed</td>
<td>Alone</td>
<td>Active first</td>
</tr>
<tr>
<td>S5</td>
<td>Male</td>
<td>45</td>
<td>Right</td>
<td>1</td>
<td>8</td>
<td>Secondary D.</td>
<td>Unemployed</td>
<td>Alone</td>
<td>Active first</td>
</tr>
<tr>
<td>S6</td>
<td>Male</td>
<td>46</td>
<td>Right</td>
<td>7</td>
<td>14</td>
<td>Secondary D.</td>
<td>Unemployed</td>
<td>Alone</td>
<td>Sham first</td>
</tr>
<tr>
<td>S7</td>
<td>Male</td>
<td>48</td>
<td>Right</td>
<td>1</td>
<td>4</td>
<td>Secondary D.</td>
<td>Unemployed</td>
<td>Alone</td>
<td>Active first</td>
</tr>
<tr>
<td>S8</td>
<td>Male</td>
<td>41</td>
<td>Left</td>
<td>1</td>
<td>7</td>
<td>Tertiary D.</td>
<td>Unemployed</td>
<td>Parents</td>
<td>Sham first</td>
</tr>
<tr>
<td>S9</td>
<td>Female</td>
<td>51</td>
<td>Left</td>
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<td>0</td>
<td>Tertiary D.</td>
<td>Part time</td>
<td>Alone</td>
<td>Sham first</td>
</tr>
<tr>
<td>S10</td>
<td>Male</td>
<td>46</td>
<td>Right</td>
<td>18</td>
<td>14</td>
<td>Secondary D.</td>
<td>Unemployed</td>
<td>Alone</td>
<td>Sham first</td>
</tr>
<tr>
<td>S11</td>
<td>Female</td>
<td>53</td>
<td>Right</td>
<td>3</td>
<td>4</td>
<td>Tertiary D.</td>
<td>Part time</td>
<td>Alone</td>
<td>Sham first</td>
</tr>
<tr>
<td>S12</td>
<td>Male</td>
<td>43</td>
<td>Right</td>
<td>10</td>
<td>2</td>
<td>Tertiary D.</td>
<td>Unemployed</td>
<td>Alone</td>
<td>Active first</td>
</tr>
<tr>
<td>S13</td>
<td>Male</td>
<td>49</td>
<td>Right</td>
<td>0</td>
<td>0</td>
<td>Tertiary D.</td>
<td>Part time</td>
<td>Alone</td>
<td>Active first</td>
</tr>
<tr>
<td>S14</td>
<td>Male</td>
<td>36</td>
<td>Right</td>
<td>1</td>
<td>8</td>
<td>Tertiary D.</td>
<td>Part time</td>
<td>Parents</td>
<td>Sham first</td>
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</table>

Table 7: ERPs of Schizophrenia patients after sham tDCS – MMN and P3
<table>
<thead>
<tr>
<th>Subjects</th>
<th>MMN_Dur</th>
<th>MMN_Freq</th>
<th>P3a_DEV_Dur</th>
<th>P3a_DEV_Freq</th>
<th>P3b</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>0.16</td>
<td>-1.41</td>
<td>-0.12</td>
<td>-1.38</td>
<td>-1.38</td>
</tr>
<tr>
<td>S2</td>
<td>-1.14</td>
<td>-0.23</td>
<td>1.16</td>
<td>-0.93</td>
<td>-0.93</td>
</tr>
<tr>
<td>S3</td>
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<td>-0.61</td>
<td>-2.55</td>
<td>0.55</td>
<td>0.55</td>
</tr>
<tr>
<td>S4</td>
<td>-1.76</td>
<td>0.41</td>
<td>-0.38</td>
<td>2.61</td>
<td>2.61</td>
</tr>
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<td>2.44</td>
</tr>
<tr>
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<td>-0.82</td>
<td>1.32</td>
<td>1.32</td>
</tr>
<tr>
<td>S7</td>
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<td>-3.27</td>
<td>4.45</td>
<td>-3.47</td>
<td>-3.47</td>
</tr>
<tr>
<td>S8</td>
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<td>-6.83</td>
<td>4.29</td>
<td>-4.82</td>
<td>-4.82</td>
</tr>
<tr>
<td>S9</td>
<td>1.19</td>
<td>-2.57</td>
<td>0.97</td>
<td>-1.24</td>
<td>-1.24</td>
</tr>
<tr>
<td>S10</td>
<td>-1.83</td>
<td>0.58</td>
<td>1.44</td>
<td>1.72</td>
<td>1.72</td>
</tr>
<tr>
<td>S11</td>
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<td>3.58</td>
<td>4.35</td>
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<td>3.62</td>
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<td>-1.83</td>
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<td>-0.53</td>
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<tr>
<td>S13</td>
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<td>-2.27</td>
<td>1.50</td>
<td>0.23</td>
<td>0.23</td>
</tr>
<tr>
<td>S14</td>
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<td>-0.99</td>
<td>3.75</td>
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Table 8: ERPs of Schizophrenia patients after sham tDCS – N1
<table>
<thead>
<tr>
<th>Subjects</th>
<th>N1_DEV_Dur</th>
<th>N1_DEV_Freq</th>
<th>N1_STD_Dur</th>
<th>N1_STD_Freq</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>0.18</td>
<td>-0.63</td>
<td>-0.93</td>
<td>-0.29</td>
</tr>
<tr>
<td>S2</td>
<td>-1.30</td>
<td>-0.84</td>
<td>-1.13</td>
<td>-0.21</td>
</tr>
<tr>
<td>S3</td>
<td>-0.01</td>
<td>-0.07</td>
<td>0.41</td>
<td>-0.26</td>
</tr>
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<td>S4</td>
<td>-1.19</td>
<td>-0.36</td>
<td>-0.32</td>
<td>-0.95</td>
</tr>
<tr>
<td>S5</td>
<td>0.92</td>
<td>2.06</td>
<td>1.10</td>
<td>0.52</td>
</tr>
<tr>
<td>S6</td>
<td>0.68</td>
<td>-0.19</td>
<td>-0.48</td>
<td>-0.21</td>
</tr>
<tr>
<td>S7</td>
<td>0.58</td>
<td>-6.45</td>
<td>-2.73</td>
<td>-1.98</td>
</tr>
<tr>
<td>S8</td>
<td>-1.01</td>
<td>-5.50</td>
<td>-0.31</td>
<td>0.00</td>
</tr>
<tr>
<td>S9</td>
<td>1.86</td>
<td>-3.11</td>
<td>-0.42</td>
<td>-0.99</td>
</tr>
<tr>
<td>S10</td>
<td>-1.64</td>
<td>-0.18</td>
<td>-0.82</td>
<td>-1.19</td>
</tr>
<tr>
<td>S11</td>
<td>1.71</td>
<td>0.98</td>
<td>-0.52</td>
<td>-2.12</td>
</tr>
<tr>
<td>S12</td>
<td>-2.75</td>
<td>-1.94</td>
<td>-1.59</td>
<td>-1.00</td>
</tr>
<tr>
<td>S13</td>
<td>-1.45</td>
<td>-3.98</td>
<td>-2.21</td>
<td>-1.93</td>
</tr>
<tr>
<td>S14</td>
<td>1.90</td>
<td>-0.84</td>
<td>1.50</td>
<td>0.88</td>
</tr>
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</table>

Table 9: ERPs of Schizophrenia patients after active tDCS – MMN and P3
<table>
<thead>
<tr>
<th>Subjects</th>
<th>MMN_Dur</th>
<th>MMN_Freq</th>
<th>P3a_DEV_Dur</th>
<th>P3a_DEV_Freq</th>
<th>P3b</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>-0.66</td>
<td>-0.14</td>
<td>0.38</td>
<td>-0.51</td>
<td>3.30</td>
</tr>
<tr>
<td>S2</td>
<td>-1.93</td>
<td>-2.20</td>
<td>0.53</td>
<td>0.76</td>
<td>5.72</td>
</tr>
<tr>
<td>S3</td>
<td>0.91</td>
<td>-0.02</td>
<td>0.06</td>
<td>1.02</td>
<td>0.20</td>
</tr>
<tr>
<td>S4</td>
<td>0.09</td>
<td>-0.82</td>
<td>1.17</td>
<td>-1.09</td>
<td>5.33</td>
</tr>
<tr>
<td>S5</td>
<td>-0.34</td>
<td>-0.92</td>
<td>1.51</td>
<td>-0.13</td>
<td>4.91</td>
</tr>
<tr>
<td>S6</td>
<td>-1.54</td>
<td>0.25</td>
<td>0.43</td>
<td>0.06</td>
<td>1.41</td>
</tr>
<tr>
<td>S7</td>
<td>-1.83</td>
<td>-0.24</td>
<td>0.01</td>
<td>-0.20</td>
<td>5.50</td>
</tr>
<tr>
<td>S8</td>
<td>-3.89</td>
<td>-1.31</td>
<td>5.25</td>
<td>2.33</td>
<td>11.96</td>
</tr>
<tr>
<td>S9</td>
<td>0.22</td>
<td>-0.45</td>
<td>3.79</td>
<td>-0.05</td>
<td>-1.07</td>
</tr>
<tr>
<td>S10</td>
<td>-1.44</td>
<td>-2.64</td>
<td>1.95</td>
<td>-1.40</td>
<td>-0.72</td>
</tr>
<tr>
<td>S11</td>
<td>-2.39</td>
<td>0.52</td>
<td>7.66</td>
<td>-0.21</td>
<td>0.47</td>
</tr>
<tr>
<td>S12</td>
<td>0.51</td>
<td>-0.98</td>
<td>2.55</td>
<td>-0.19</td>
<td>0.25</td>
</tr>
<tr>
<td>S13</td>
<td>-0.76</td>
<td>0.16</td>
<td>3.41</td>
<td>0.95</td>
<td>-0.20</td>
</tr>
<tr>
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<td>0.24</td>
<td>-3.12</td>
<td>0.03</td>
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</table>

Table 10: ERPs of Schizophrenia patients after active tDCS – N1
<table>
<thead>
<tr>
<th>Subjects</th>
<th>N1_DEV_Dur</th>
<th>N1_DEV_Freq</th>
<th>N1_STD_Dur</th>
<th>N1_STD_Freq</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>-0.76</td>
<td>-0.09</td>
<td>-0.07</td>
<td>-0.08</td>
</tr>
<tr>
<td>S2</td>
<td>-3.30</td>
<td>0.57</td>
<td>-0.60</td>
<td>0.52</td>
</tr>
<tr>
<td>S3</td>
<td>3.38</td>
<td>0.77</td>
<td>0.06</td>
<td>0.76</td>
</tr>
<tr>
<td>S4</td>
<td>0.34</td>
<td>-0.88</td>
<td>-0.81</td>
<td>-0.87</td>
</tr>
<tr>
<td>S5</td>
<td>0.63</td>
<td>1.17</td>
<td>0.12</td>
<td>1.18</td>
</tr>
<tr>
<td>S6</td>
<td>-0.66</td>
<td>0.04</td>
<td>-0.20</td>
<td>0.03</td>
</tr>
<tr>
<td>S7</td>
<td>-2.64</td>
<td>-2.12</td>
<td>-2.00</td>
<td>-2.13</td>
</tr>
<tr>
<td>S8</td>
<td>-1.25</td>
<td>-0.86</td>
<td>-0.20</td>
<td>-0.86</td>
</tr>
<tr>
<td>S9</td>
<td>-0.45</td>
<td>-0.82</td>
<td>-0.83</td>
<td>-0.79</td>
</tr>
<tr>
<td>S10</td>
<td>-1.32</td>
<td>0.44</td>
<td>-0.57</td>
<td>0.45</td>
</tr>
<tr>
<td>S11</td>
<td>-1.61</td>
<td>-0.79</td>
<td>-0.81</td>
<td>-0.76</td>
</tr>
<tr>
<td>S12</td>
<td>-0.29</td>
<td>-1.15</td>
<td>-0.96</td>
<td>-1.09</td>
</tr>
<tr>
<td>S13</td>
<td>-1.90</td>
<td>-2.21</td>
<td>-1.59</td>
<td>-2.22</td>
</tr>
<tr>
<td>S14</td>
<td>3.28</td>
<td>-0.32</td>
<td>-0.05</td>
<td>-0.31</td>
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</table>
Table 11: ERP mean data for both groups for sham and active tDCS

<table>
<thead>
<tr>
<th></th>
<th>Healthy Participants</th>
<th>Schizophrenia Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 Duration (SD) Sham tDCS</td>
<td>-0.75 μ V (0.79)</td>
<td>-0.47 μ V (1.11)</td>
</tr>
<tr>
<td>N1 Duration (SD) Active tDCS</td>
<td>-1.15 μ V (1.01)</td>
<td>-0.55 μ V (0.59)</td>
</tr>
<tr>
<td>N1 Frequency (SD) Sham tDCS</td>
<td>-9.2 μ V (0.79)</td>
<td>-0.90 μ V (0.81)</td>
</tr>
<tr>
<td>N1 Frequency (SD) Active tDCS</td>
<td>-1.02 μ V (0.80)</td>
<td>-0.66 μ V (1.44)</td>
</tr>
<tr>
<td>MMN Duration (SD) Sham tDCS</td>
<td>-2.57 μ V (1.97)</td>
<td>-0.64 μ V (2.20)</td>
</tr>
<tr>
<td>MMN Duration (SD) Active tDCS</td>
<td>-2.71 μ V (1.49)</td>
<td>-0.85 μ V (1.34)</td>
</tr>
<tr>
<td>MMN Frequency (SD) Sham tDCS</td>
<td>-1.26 μ V (1.55)</td>
<td>-0.84 μ V (2.31)</td>
</tr>
<tr>
<td>MMN Frequency (SD) Active tDCS</td>
<td>-1.22 μ V (1.27)</td>
<td>-0.50 μ V (0.93)</td>
</tr>
<tr>
<td>P3a Duration (SD) Sham tDCS</td>
<td>0.26 μ V (2.36)</td>
<td>1.91 μ V (3.15)</td>
</tr>
<tr>
<td>P3a Duration (SD) Active tDCS</td>
<td>0.21 μ V (1.88)</td>
<td>2.25 μ V (2.02)</td>
</tr>
<tr>
<td>P3a Frequency (SD) Sham tDCS</td>
<td>0.59 μ V (1.46)</td>
<td>0.76 μ V (2.11)</td>
</tr>
<tr>
<td>P3a Frequency (SD) Active tDCS</td>
<td>0.48 μ V (1.76)</td>
<td>0.76 μ V (0.91)</td>
</tr>
<tr>
<td>P3b (SD) Sham tDCS</td>
<td>6.60 μ V (3.54)</td>
<td>2.38 μ V (3.36)</td>
</tr>
<tr>
<td>P3b (SD) Active tDCS</td>
<td>μ V</td>
<td>2.69 μ V (3.84)</td>
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</table>
Table 12: Behavioural data for both groups

<table>
<thead>
<tr>
<th></th>
<th>Healthy Participants</th>
<th>Schizophrenia Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (SD) EEG</td>
<td>29.9 (6.1)</td>
<td>46.7 (6.4)</td>
</tr>
<tr>
<td>Age mean (SD) MRS</td>
<td>28.6</td>
<td>N/A</td>
</tr>
<tr>
<td>P3b task - Hit Rate (SD)</td>
<td>98.2% (1.4)</td>
<td>96% (10.3)</td>
</tr>
<tr>
<td></td>
<td>Sham tDCS</td>
<td>Active tDCS</td>
</tr>
<tr>
<td>P3b task - False Alarm</td>
<td>&lt;0.01%</td>
<td>&lt;0.01%</td>
</tr>
<tr>
<td></td>
<td>Sham tDCS</td>
<td>Active tDCS</td>
</tr>
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Table 13.1: Metabolites measured by MRS in Healthy Control Group after sham tDCS – Glu, Gln

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Glu</th>
<th>Glu %SD</th>
<th>Glu/Cr+PCr</th>
<th>Gln</th>
<th>Gln %SD</th>
<th>Gln/Cr+PCr</th>
<th>Glu+Gln</th>
<th>Glu+Gln %SD</th>
<th>Glu+Gln/Cr+PCr</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>5.992</td>
<td>6</td>
<td>1.236</td>
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<td>5.992</td>
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<td>1.236</td>
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<td>7.187</td>
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Table 13.2: Metabolites measured by MRS in Healthy Control Group after sham tDCS – GABA, Asp and NAA

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### 13.5: Metabolites measured by MRS in Healthy Control Group after sham tDCS – Ins and Lac

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Table 14.1: Metabolites measured by MRS in Healthy Control Group after active tDCS – Glu, Gln

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Table 14.2: Metabolites measured by MRS in Healthy Control Group after active tDCS – GABA, Asp and NAA
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</thead>
<tbody>
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<td>C1</td>
<td>-</td>
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<td>11</td>
<td>0.577</td>
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<td>1.355</td>
</tr>
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<td>0.35</td>
<td>4.567</td>
<td>16</td>
<td>0.606</td>
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<td>1.036</td>
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<td>45</td>
<td>0.137</td>
<td>3.072</td>
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<td>6.809</td>
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<td>2.188</td>
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<td>1.286</td>
</tr>
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<td>41</td>
<td>0.074</td>
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<td>8</td>
<td>0.519</td>
<td>6.295</td>
<td>2</td>
<td>1.262</td>
</tr>
<tr>
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<td>1.006</td>
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<td>0.217</td>
<td>3.077</td>
<td>12</td>
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<td>0.076</td>
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<td>14</td>
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</tr>
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</tr>
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<td>11</td>
<td>0.566</td>
<td>6.448</td>
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Table 14.3: Metabolites measured by MRS in Healthy Control Group after active tDCS – NAAG, Ala and Glc
<table>
<thead>
<tr>
<th>Subjects</th>
<th>NAAG</th>
<th>NAAG %SD</th>
<th>NAAG/Cr+PCr</th>
<th>Ala</th>
<th>Ala %SD</th>
<th>Ala/Cr+PCr</th>
<th>Glc</th>
<th>Glc %SD</th>
<th>Glc/Cr+PCr</th>
</tr>
</thead>
<tbody>
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<td>53</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>0.741</td>
<td>35</td>
<td>0.151</td>
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<tr>
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<td>95</td>
<td>0.097</td>
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<td>21</td>
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<td>3.416</td>
<td>23</td>
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<tr>
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<td>-</td>
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<td>230</td>
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<td>-</td>
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<td>12</td>
<td>0.153</td>
<td>0.0605</td>
<td>103</td>
<td>0.012</td>
<td>1.233</td>
<td>14</td>
<td>0.247</td>
</tr>
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<td>863</td>
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<td>-</td>
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<td>-</td>
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<td>0.282</td>
<td>69</td>
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</tr>
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<td>-</td>
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<td>0.137</td>
</tr>
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<td>12</td>
<td>0.172</td>
<td>0.0121</td>
<td>583</td>
<td>0.0024</td>
<td>1.1</td>
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<tr>
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<td>341</td>
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<td>-</td>
<td>-</td>
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<td>91</td>
<td>0.051</td>
</tr>
<tr>
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<td>19</td>
<td>0.141</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.441</td>
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Table 14.4: Metabolites measured by MRS in Healthy Control Group after active tDCS – Cr, PCr and GPC
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Cr</th>
<th>Cr %SD</th>
<th>Cr/Cr+PCr</th>
<th>PCr</th>
<th>PCr %SD</th>
<th>PCr/Cr+PCr</th>
<th>GPC</th>
<th>GPC %SD</th>
<th>GPC/Cr+PCr</th>
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<td>8</td>
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<td>1.094</td>
<td>3</td>
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<tr>
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<td>5.339</td>
<td>23</td>
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<td>55</td>
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<td>2.16</td>
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<td>0.287</td>
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<td>12</td>
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<td>0.943</td>
<td>3</td>
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<td>-</td>
<td>-</td>
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<tr>
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<td>8</td>
<td>0.397</td>
<td>1.039</td>
<td>3</td>
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<td>14</td>
<td>0.427</td>
<td>2.662</td>
<td>11</td>
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<td>1.064</td>
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<tr>
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<td>2</td>
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Table 14.5: Metabolites measured by MRS in Healthy Control Group after active tDCS – Ins and Lac
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<tr>
<th>Subjects</th>
<th>Ins</th>
<th>Ins %SD</th>
<th>Ins/Cr+PCr</th>
<th>Lac</th>
<th>Lac %SD</th>
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<tbody>
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<td>C1</td>
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<td>3</td>
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<td>0.044</td>
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