Cortical excitability in adolescents with depression – An investigation of the TMS-evoked potential N100 as a possible biomarker

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ADHD - Attention deficit hyperactivity disorder

AEP - Auditory evoked potentials

AMPA - α-amino-3-hydroxy-5-methy-4-isoxazolepropionic acid

ANOVA - Analyses of variance

BDNF - Brain-derived neurotrophic factor

DLPFC - Dorsolateral prefrontal cortex

DSM-IV - Diagnostic and Statistical Manual of Mental Disorders IV

EEG - Electroencephalography

E/I - Balance between excitation and inhibition

EMG - Electromyography

FDI - First dorsal interosseous

GABA - Gamma-aminobutyric acid

GFP - Global field power

Glx - Combined glutamine and glutamate

ICA - Independent component analysis

ICD - International Classification of Diseases

IPSP - Inhibitory postsynaptic potentials

LatTEP - Lateralized TMS-evoked potential

M1 - Primary motor cortex

MDD - Major depressive disorder

MEP - Motor evoked potentials

NMDA - N-methyl-D-aspartate

RMT - Resting motor threshold

rTMS - Repetitive TMS

SSEP or SEP - Somatosensory evoked potentials

SRI - Serotonin reuptake inhibitor

SSRI - Selective serotonin reuptake inhibitor

TAU - Treatment as usual

TEP - TMS-evoked potentials

TMS - Transcranial magnetic stimulation

TOC - Temporo-occipital cortex

1 Background

1.1 Depression

Depression is a common mental disorder affecting more than 300 million people worldwide, with the number of people affected continuing to rise (World Health Organization, 2017). This mental disorder has far-reaching effects and is globally the largest contributor to non-fatal health loss, with a global total of 50 million Years Lived with Disability in the year 2015 (World Health Organization, 2017). Depressive symptoms interfere with daily and social life and affect performance at work or school. Besides the severe impairments in social and educational spheres, a depressive episode can at times lead to suicide (Thapar et al., 2012). While suicides occur throughout the lifespan, it was the second leading cause of death in young people (15-29 year of age) in the year 2015 (World Health Organization, 2017). Furthermore, depression in adolescence can predict chronification or relapses in adult life and is associated with later challenges, such as mental health problems (e.g., bipolar disorders, substance-related disorders), physical health issues and unemployment (Thapar et al., 2012). It is apparent that an early diagnosis and effective treatment in adolescents is crucial. Despite extensive research, the pathophysiology of depression is not yet fully elucidated, partially due to the heterogeneity of this disorder and various potential aetiologies (Jesulola et al., 2018). The poor understanding of the pathophysiology has implications for the intervention (Zalsman et al., 2006). For example, a comprehensive understanding of the pathophysiology might help to explain the low remission rates of established treatments in youth depression (Kennard et al., 2006). In this context biomarkers could provide complementary information about pathophysiological processes or intervention options and may be identified at any given stage of the process between pathogenesis, onset of first clinical symptoms, diagnosis, treatment outcome or remission (García-Gutiérrez et al., 2020). This work therefore focuses on depression and possible biomarkers in adolescents.

1.1.1 Symptomatology

According to the International Classification of Diseases 10 (ICD-10) a major depressive disorder (MDD) is characterized by a specific set of symptoms such as depressed mood, anhedonia, and decreased energy and at least one or more of the symptoms in Table 1

section c. Depending on the number of symptoms, the depressive episode can be categorized as mild (four to five symptoms from Table 1), moderate (six to seven symptoms) or severe (at least eight symptoms).

Table 1

ICD-10 diagnostic criteria (research criteria)

A)

1. Symptoms persist at least for a 2-week period
2. There has never been a manic or hypomanic episode
3. Symptoms are not attributable to the use of a psychoactive substance or neurocognitive disorder.

B) At least two of the following core symptoms:

1. Depressed mood most of the day, almost every day, which presents a change from previous functioning
2. Loss of interest or enjoyment (anhedonia)
3. Reduced activity or increased fatigue

C) At least one of the following associated symptoms, so that the number of symptoms from categories B and C accumulates to at least four

1. Loss of self-esteem and self-confidence
2. Unreasonable feelings of self-reproach or excessive inappropriate guilt
3. Recurrent thoughts of death or suicide or acts of self-harm
4. Reduced concentration and attention
5. Psychomotor agitation or retardation
6. Sleep disturbance
7. Change in appetite with corresponding change in weight

Note. Adapted and translated from ICD-10 research criteria

While the clinical and diagnostic features of MDD are similar for adolescents and adults, the Diagnostic and Statistical Manual of Mental Disorders IV and 5 (DSM) differentiates between children/adolescents and adults in terms of allowing irritable rather than depressed mood as a core diagnostic symptom (Thapar et al., 2012). Nonetheless, depressions are more often overlooked in adolescents compared to adults, probably due to the symptom fluctuation in adolescents (Thapar et al., 2012). While some authors conclude that adolescent

depression might be an early-onset version of adult depression, as both affected groups show similar clinical characteristics and neuronal activity patterns (Thapar et al., 2012), other authors find differences in symptomatology between adults and adolescents. Vegetative impairments may be more common in adolescents (loss of energy, changes in weight, appetite, and sleep disturbances), while anhedonia/loss of interest and reduced concentration might be more common in adults. These distinctions might indicate different pathophysiological mechanisms (Rice et al., 2019). The question remains whether adolescent depression is similar to adult depression and whether both share common pathophysiological underpinnings.

1.1.2 Prevalence

The World Health Organization (2017) estimated that in 2015 4.4% of the global population was affected by depression. While depression occurs in almost all age groups, the prevalence varies by age. A peak in older adulthood (55-74 years) was described (females: 7.5%, males: 5.5%), whereas prevalence was lower in the age group under 19 (World Health Organization, 2017). A prevalence range from 3-6% was described in adolescents (Bettge et al., 2008; Costello et al., 2006). The prevalence of depression in children is in contrast very low (<1% in most studies) (Thapar et al., 2012).

There is a prevalence difference between sexes, as depression is more common in females (5.1%) than in males (3.6%) (World Health Organization, 2017). Bevor puberty, the prevalence of depression is similar in both sexes, with slightly higher prevalence in boys. During puberty, between the ages 11 and 13, this pattern starts to reverse, and at age 15, females are almost twice as likely to experience a depressive episode (Cyranowski et al., 2000).

1.1.3 Etiology

Depression can have heterogeneous causes, and a monocausal explanation would fall short. Nonetheless, depression often occurs in response to negative environmental circumstances (England et al. 2009). Biopsychosocial approaches, such as the diathesis-stress model, suggest that individuals with a vulnerability are more prone to develop depression when exposed to environmental stressors (Monroe & Simons, 1991). The biopsychosocial perspective recognizes that depression results from the interaction between genetic predispositions, neurochemical and hormonal imbalances, cognitive biases, maladaptive

behaviors, interpersonal stressors, and social context. All of these factors are interrelated and increase the risk of MDD in a probabilistic manner (Thapar et al. 2012). However, it is not always clear whether biopsychosocial factors are risk factors, mediators, or consequences of depression (Thapar et al., 2012). In the following, various stressors and biopsychosocial vulnerabilities are discussed in more detail.

Acute negative life events, particularly bereavement or perceived loss, have been identified as significant stressors and possible triggers for MDD (England et al., 2009). For example, adolescents who have suddenly lost a parent are more prone to depression in the first two years after the loss (Brent et al., 2009). Compared to sudden negative life events, exposure to long-term stressful circumstances is an even stronger predictor of depressive symptoms (McGonagle & Kessler, 1990). For example, chronic stressors include cultural and societal factors such as society expectations, mental health stigma and discrimination, and low socioeconomic status (England et al., 2009). At the micro level, long-term stressors for adolescents include high academic pressure (Jayanthi et al., 2015), lack of adequate financial and other instrumental resources, perceived lack of social support, and low quality of interpersonal relationships, including family dysfunction, conflicts with peers and in romantic relationships (Hammen, 2009; MacPhee & Andrews, 2006). However, it is important to consider that the relationship between chronic stressors and depressive symptoms is bidirectional. Therefore, these chronic stressors can be classified as triggers for depressive symptoms, but also as a social vulnerability in the sense of the biopsychosocial perspective. In addition to acute/chronic stressors, a link has also been established between earlier childhood adversity, such as sexual, physical, or emotional abuse, and the later development of depressive symptoms in adolescence or adulthood (England et al., 2009). However, not everyone who experiences such stressors develops depressive symptoms. In terms of the diathesis-stress model, other individual vulnerabilities, such as psychological and biological factors, can be considered (Monroe & Simons, 1991).

Psychological factors include cognitive, behavioral, and interpersonal factors. According to Beck's (2008) cognitive model, people with depression tend to have negative schemas that involve dysfunctional attitudes toward themselves, the world, and the future. These schemas are developed through past experiences and can be activated by current life events, which in turn can influence the information process toward a negative attentional bias and a distorted interpretation of a current event (e.g., overgeneralization, personalization). This global negative perception of reality leads to rumination and to the development and maintenance

of depressive symptoms (Beck, 2008). Behavioral theories focus on the influence of environmental factors and the reinforcement of maladaptive behavior, such as the learned helplessness theory (Seligman, 1972). When individuals are repeatedly confronted with negative situations perceived as uncontrollable, they may develop a sense of helplessness and reduced response initiation (Seligman, 1972). Other behavioral theories emphasize the role of social withdrawal and inactivity (e.g., due to stressors) and reduced positive reinforcement, and thus a perpetuation of depressive symptoms (Lewinsohn, 1974). The interpersonal view of depression focuses on the role of social skills and interactions that can lead to conflicts and social isolation. Ratings (by self-rating and objective raters) indicate deficits in social skills (e.g., disclosure of negative information about themselves and reduced responsiveness in conversations) and behavioral characteristics (e.g., reduced nonverbal communication) in individuals with MDD (Hames et al., 2013). However, these difficulties tend to correlate with symptoms of depression and are unlikely to represent causal predispositions (Hames et al., 2013). On the other hand, dysfunctional communication behaviors, such as interpersonal feedback-seeking, have been described during depressive episodes in adolescents and adults, but also as a stable communication tendency that may predict depressive symptoms (Hames et al., 2013). One communicative tendency related to interpersonal feedback-seeking behavior is the excessive search for reassurance. This tendency to repeatedly seek reassurance from others that one is lovable and valuable can, over time, cause the initial support to turn into aggravation and rejection. Another interpersonal feedback-seeking behavior is negative feedback-seeking. This tendency to seek negative feedback from others has also been identified as a potential risk factor for interpersonal conflict (Hames et al., 2013). In addition to cognitive and behavioral characteristics and interpersonal feedback-seeking behavior, interpersonal styles such as interpersonal inhibition (e.g., social withdrawal, shyness), interpersonal dependence (i.e., strong need for interpersonal attachment), and insecure attachment (i.e., anxious, avoidant, fearful) have been linked to depression.

In addition to social and psychological vulnerabilities, biological factors are often implicated in the etiology of depression. Several biological factors are implicated, including genetic, immunological, endocrine, and neural aspects (Jesulola et al., 2018). Genetic and familial studies describe higher rates of depression in children/adolescents of parents with MDD compared to children/adolescents of parents without mental disorder diagnoses. Adoption studies suggest that (unrelated) parental depression is an important environmental risk factor

for adolescent depression, but an additional history of MDD in biological parents slightly increases the risk (Rice, 2009; Tully et al., 2008). Twin studies suggest a genetic influence on depression ranging from 30% to 50% depending on age (Rice, 2009). Another biological factor that appears to be important is hormonal inbalance. Hyperactivity of the stress-related hypothalamic-pituitary-adrenal axis has been frequently associated with depression (Palazidou, 2012). Correlations between hormonal changes during life stages (puberty, pre-menstruation, post-pregnancy, and menopause) and increased prevalence of depression in females may be further evidence of the importance of hormonal changes (Albert, 2015). An intergrative biopsychosocial model by Cyranowski et al. (2000) focuses on gender differences in prevalence during puberty. They discuss an interaction between social (e.g., social pressure to conform to stereotypical gender roles) and hormonal (especially oxytocin increases) mechanisms that might stimulate affiliative needs (e.g., a higher preference for emotional communication and interpersonal relationships) in female adolescents during puberty. In conjunction with adolescent transitional difficulties (e.g., insecure parental attachment, anxious temperament), increased affiliative need could lead to depressive diathesis. This vulnerability could increase the likelihood of developing depression when women are confronted with negative life events. This model highlights the importance of considering the complex reality of adolescents in the etiology of this heterogeneous mood disorder.

A variety of biological factors have already been considered in this chapter. Yet, alterations in neurotransmitter systems, neurotrophins, and functional and structural neuronal changes have also been repeatedly associated with depression (Palazidou, 2012). In recent decades, the pathological neurophysiology and possible biomarkers for depression have gained more attention in research. Many questions, however, remain unanswered, especially regarding the pathophysiology in adolescents. Therefore, the focus of this work is on the neural changes associated with depression and can be considered as an important factor in the biopsychosocial approach to depression. This work does not claim to resolve the issue of causal relationship (i.e., neurophysiological changes trigger depressive symptoms or vice versa), but rather represents basic research investigating pathological neurophysiological changes during depressive symptoms in adolescents, with focus on possible biomarker. Most of the neurophysiological research on depression, however, has been conducted in adults, which must be taken into account when studying depression in adolescents. Therefore, general models and research findings on pathological neurophysiological processes in

depression, mainly based on adult subjects, will be presented first before addressing the specifics in adolescents.

1.1.4 Neurobiology

In adults, alterations in several cortical areas are associated with the pathogenesis of depression. Structural imaging studies demonstrated lower gray matter volumes in the prefrontal cortex, amygdala, hippocampus, anterior or paracingulate cortex and parts of the basal ganglia (Drevets et al., 2008; Sacher et al., 2012). Besides structural alterations in various brain regions, functional alterations in the anterior cingulate, dorsolateral, medial and inferior prefrontal cortex, insula, superior temporal gyrus, basal ganglia and cerebellum are consistently reported (Fitzgerald et al., 2008). Increased activity in the amygdala (Siegle et al., 2007) and decreased activity in the dorsolateral prefrontal cortex (DLPFC) (Biver et al., 1994; Siegle et al., 2007) seem to be related to depression as well. The heterogeneous results and the large number of associated brain regions make it difficult to relate the pathogenesis of depression to one specific neuronal circuit. Instead, a complex interaction between cortical circuits was proposed.

1.1.4.1 Neurobiology of emotion regulation in depression.

Phillips et al. (2003a, 2003b) proposed a general neurobiological model of emotion perception and adapted this model to understand pathological neurophysiological processes in depression. Two neural systems have been hypothesized to play a role in general emotion perception. The amygdala, insula, ventral striatum, and ventral parts of the prefrontal cortex and anterior cingulate gyrus were grouped in the ventral system. This system might be responsible for a bottom-up emotional influences, by appraising and identifying the emotional relevance of a stimulus as well as producing a responsive affect and behavior (Phillips et al., 2003a; Rive et al., 2013). The second neural system is referred to as the dorsal system. It has been associated with a top-down regulation of emotion through the control over the affective state and emotional behavior. It includes the hippocampus as well as the dorsal areas of the prefrontal cortex and anterior cingulate gyrus (Phillips et al., 2003a; Rive et al., 2013). This regulatory process might work though inhibition or modulation of the responses of the ventral system, in order to produce an affect, emotional experience and behavior which is appropriate for the context (Phillips et al., 2003a). Phillips et al. (2003b) indicate a dysregulation in these two systems as relevant for the development of depressive symptoms. Volumetric reductions and increased activity in the ventral system, especially the

amygdala, during a depressive episode might be related to a diminished emotional range and a perception bias towards negative emotions. Impaired dorsal system function could lead to dysregulation of executive functions and modulation of affective and behavioral responses of the ventral system. This might lead to a maintenance of the negative emotional bias and diminished emotional range caused by the dysregulation of the ventral system, resulting in anhedonia and depressed mood (Phillips et al., 2003b). Other approaches and adaptions of this model come to a similar conclusion (Ochsner et al., 2004; Palazidou, 2012; Siegle et al., 2007). The common notion is that the prefrontal cortex plays an important role in the cognitive down- and up-regulation of negative emotions. Functional and structural impairments during a depressive episode could lead to a failed regulation of an overactive limbic system (Ochsner et al., 2004; Palazidou, 2012; Siegle et al., 2007), making the prefrontal cortex a promising structure to study the pathogenesis of depression.

1.1.4.2 The role of the DLPFC in depression.

The main function of the prefrontal cortex is executive in nature, which involves working memory, formation of intentions, attentional control and coordination of goal-directed actions as well as abstract reasoning (E. K. Miller & Cohen, 2001). The prefrontal cortex has many projections in areas such as sensory and motor systems, as well as subcortical structures and consists of several interconnected neocortical areas (E. K. Miller & Cohen, 2001). One of these prefrontal areas is the DLPFC. The executive function of the DLPFC seems to pertain to emotion regulation, and a depression associated dysregulation of the DLPFC might be responsible for an impaired top-down cognitive control of negative emotions. The DLPFC seems to be activated during emotion control and regulates reappraisal and suppression of negative emotions (Koenigs & Grafman, 2009). This is, for example, noted in healthy participants, in which the DLPFC is activated when sadness was voluntarily repressed, indicating a role in the voluntary self-regulation (Lévesque et al., 2003). A dysfunction in the DLPFC could therefore contribute to the pathogenesis of depression.

1.1.4.3 Neurotransmitter changes in depression.

The reported alterations in cortical function can be set in relationship with underlying changes in the synaptic transmission. Many years the monoamine hypothesis on depression dominated the neurochemical research in depression. This hypothesis is based on the supposed deficiency of serotonin, norepinephrine, and dopamine levels. The hypothesis is driven by the efficacy of medication that elevate the levels of these neurotransmitters, such

as serotonin reuptake inhibitors (SRIs) in treating depressive symptoms (Delgado, 2000). In recent years, however, this hypothesis has been challenged, as new research findings call into question the consistent and causal relationship between serotonin levels and depression (Moncrieff et al., 2022). Parallel to the monoamine research, the main excitatory neurotransmitter glutamate and the main inhibitory neurotransmitter gamma-aminobutyric acid (GABA) have become the focus of research on the pathogenesis of depression because in combination they control the overall cortical excitation (Duman et al., 2019; Hasler et al., 2007). Cortical excitability therefore reflects a balance between excitation and inhibition.

Glutamate can bind to several types of receptors, such as ionotropic N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methy-4-isoxazolepropionic acid (AMPA) and kainite receptors, as well as three groups of metabotropic receptors (Kew & Kemp, 2005). Glutamate has become of special interest after observing the rapid-acting antidepressant effect of ketamine, an antagonist binding on NMDA receptors (Krystal et al., 2013), leading to the glutamatergic theory of depression. Supportively, studies have found that patients with MDD have lower concentrations of glutamate-related metabolites in the DLPFC, among other cortical areas (Hasler et al., 2007; Yüksel & Öngür, 2010). A meta-analysis of magnetic resonance spectroscopy studies found that combined glutamine and glutamate (Glx) levels are reduced in the prefrontal area in depression and that there is a correlation between Glx levels and depression symptom severity, possibly indicating a dosage effect (Arnone et al., 2015). The extensive glutamate release in the prefrontal cortex after ketamine application might therefore correct aberrant glutamatergic levels/actions in the prefrontal cortex, which could be the key mechanism for the antidepressant effect (Abdallah et al., 2018).

In addition to excitatory glutamate activity, inhibitory neurotransmission and a homoeostasis between inhibition/excitation are also crucial for normal brain function (Duman et al., 2019). GABA is thought to be the main inhibitory neurotransmitter in the central nervous system and binds either on ionotropic (GABA-A and GABA-C) or metabotropic (GABA-B) receptors (Bormann, 2000). Alterations in the GABA system have been implicated in the pathogenesis of depression. A post-mortem study described reduced GABA interneuron density in the DLPFC (Rajkowska et al., 2007). A meta-analysis on studies using transcranial magnetic stimulation with simultaneous electroencephalography (TMS-EEG) in patients with MDD revealed reduced GABAerig functioning. Analysis on TMS-EEG applied to the motor cortex indicate deficits in ionotropic GABA-A and metabotropic GABA-B

receptor functioning (Radhu et al., 2013). GABA concentrations are reduced in the occipital cortex (Sanacora et al., 1999), and antidepressant electroconvulsive therapy and the administration of selective serotonin reuptake inhibitors (SSRI) significantly increased occipital GABA concentrations (Bhagwagar et al., 2004; Sanacora et al., 2003). Similar decreased GABA levels are described for the prefrontal cortex in adults with depression, and a normalization during remission (Hasler et al., 2005, 2007). Therefore, investigating the role of GABA in de prefrontal cortex during depression may be important for a better understanding of the pathogenesis of this mood disorder.

As mentioned before, GABA receptors can be divided in different receptor types, and they might play different roles in the pathophysiology of depression. In rodent models, a specific role of the GABA-B system has been demonstrated in depressive activity (as reviewed in Cryan & Kaupmann, 2005). Antidepressant-like behavior has been displayed by GABA-$B_{(1)}$ subunit knockout mice in behavioral experiments and GABA-B receptor antagonist demonstrated antidepressant effects (Mombereau et al., 2004). A link between antidepressant effects of GABA-B antagonists and the increased levels of nerve growth factor and the brain-derived neurotrophic factor (BDNF) in rat brains after GABA-B antagonist application has been observed (Cryan & Kaupmann, 2005; Heese et al., 2000). BDNF is used as a factor to index neuroplasticity and BDNF levels have been shown to increase significantly after antidepressant treatment, and changes in BDNF level and depression scores correlated significantly (Brunoni et al., 2008).

As described, both glutamate and GABA seem to play a crucial role in depression research. Since glutamate is a precursor for GABA (Yüksel & Öngür, 2010) and a balance between cortical excitation and inhibition is important for normal brain function (Duman et al., 2019), an imbalance between cortical excitation and inhibition (E/I) based on both glutamate and GABA has been proposed as key mechanism in depression pathophysiology (Lener et al., 2017). Aim of this work is therefore, to investigate the E/I balance, with special focus on the GABA-B function, in the prefrontal cortex of patients with depression. However, most of the previously reviewed work is based on adults with depression. A comparative consideration of neurobiological processes in adolescents is needed.

1.1.4.4 Neurophysiology in adolescents with depressive symptoms.

Since the prevalence of depression increases almost linearly from puberty onward, biological changes that occur during this critical developmental period may play a crucial role in the

pathophysiology of depression (Davey et al., 2008; Thapar et al., 2012). Profound structural and functional changes related to brain maturation have been identified (Davey et al., 2008; Gogtay et al., 2004). General maturation studies of adolescents lead to a theory of imbalance in cortical maturation. The limbic systems, associated with emotional reactivity, seems to develop earlier than prefrontal cortical control systems (Casey, 2015; Casey et al., 2008). Gogtay et al. (2004) demonstrated that the DLPFC is one of the latest maturing cortical areas, with maturation observed as late as at the end of adolescence. Considering the theories on emotion regulation in depression, with an overactive limbic system and impaired down- and up-regulation of emotions through an impaired prefrontal cortex (see section 1.1.4.1), a maturational imbalance between prefrontal cortex and the limbic system in adolescents might be a vulnerability for developing depression during adolescents. In addition to structural maturation, developments in the neurotransmitter system are also observed. A normal E/I balance in the prefrontal cortex seems to be driven by extensive maturational changes in the GABA system (Caballero & Tseng, 2016). Indeed, markers for excitation and inhibition, especially the GABA-B system, seem to be age dependent in healthy and depressed adolescents (Croarkin et al., 2014). Nonetheless, it remains unclear whether the neurobiology of adult-onset and adolescent-onset depression is comparable, considering the maturational changes (Zalsman et al., 2006) and described differences in clinical characteristics (Rice et al., 2019). Additionally, rodent models indicate different causes and effects of glutamate and GABA imbalance in adolescents and adults. Adolescent rats develop inhibited GABAergic projections to the amygdala under recurrent stress, indicating impaired regulatory neurocircuitry. Adult rats on the other hand have facilitated glutamate transmission in the amygdala, hippocampus, and frontal cortex under stress conditions, implicating developmental differences in frontolimbic GABA and glutamate systems in depression (Croarkin & MacMaster, 2019; Zhang & Rosenkranz, 2016). Therefore, investigating the E/I balance in adolescents with depression, with focus on the GABA-B system in the prefrontal cortex, is crucial to compare the results to previous findings in adolescents.

1.1.5 Treatment options

There are several treatment options for depression, but the body of evidence foremost supports established treatments with medication, especially the SSRI fluoxetine, cognitive-behavioral therapy, or the combination of both. The latter option was found to be most effective with a remission rate of 37% after 12 weeks (Kennard et al., 2006). However, these

treatment options hold disadvantages such as side effects due to medication, lacking psychotherapy options, long waiting times for psychotherapy and difficulties in everyday life integration. In combination with low rates of remission and often remaining residual symptoms after 12 weeks of treatment as usual (TAU) (e.g., medication, psychotherapy) (Kennard et al., 2006), the demand for alternative treatment approaches is increasing.

Physical activity has been one of the alternative treatment options considered, because it avoids some of the disadvantages of the established treatment options (Cooney et al., 2013). A Cochrane review (Cooney et al., 2013) assessed antidepressant effects of physical activity in adults and found a moderate effect compared to control conditions or no treatment and no superiority of psychotherapy or medication. A metanalysis on young people (12-25 years) supports the positive effects of physical activity on depression symptoms in this age group, with a large effect size compared to controls (Bailey et al., 2018). A pilot study to the here reported project (see Biermann et al., 2022) investigated effects of 6-weeks training on depression symptoms in adolescents during clinical treatment, focusing on the developmental sensitive period between 13-18 years (Wunram et al., 2018). In the pilot study two interventions were performed as add-on to TAU: A less physical and motivational demanding passive muscular training on a whole-body vibration device and a cardiovascular training on an ergometer. Both groups were compared to a control group, which only received TAU. The ergometer and the whole-body vibration trainings lead to significantly reduced depression scores compared to the TAU group after a 26-weeks observation period, with 66% compared to 25% remission rate (Wunram et al., 2018). Limiting the results of this pilot study, however, is the lack of randomization to the control group, as only patients with no motivation to train were included in the control group.

Even though positive effects of physical activity on depressive symptoms have been demonstrated both in adults and adolescents, the causal relation is not fully elucidated. An interaction between psychological and neurobiological processes has been made responsible for the effect. Distraction, strengthening of self-efficiency and sense of independence/success as well as beneficial influence of social interaction have been assumed as relevant psychological mechanisms for the effect (Paluska & Schwenk, 2000). From a neurobiological point of view, effects via increases in levels of monoamines, β-endorphin, vascular endothelial growth factor and/or BDNF were proposed (Ernst et al., 2006; Paluska & Schwenk, 2000). A level increase of these molecules could stimulate adult neurogenesis, which could have an antidepressant effect (Ernst et al., 2006). As described before, a link

between BDNF and GABA-B functioning has been proposed in rodent models (Cryan & Kaupmann, 2005; Heese et al., 2000). Hence, physical activity might influence cortical excitability, which could play an important role in the antidepressant mechanisms. Therefore, we conducted a follow-up randomized control trial, to investigate the therapeutic effects of physical activity in adolescents with depression, focusing on (neuro)biological mechanisms (for more details see Biermann et al., 2022). To examine cortical E/I balance longitudinally while adolescents were completing a 6-week sports intervention in addition to TAU, we used the advanced in vivo technique of TMS-EEG. This technique can be used to examine a potential monitoring biomarker. A monitoring biomarker is analyzed at various time points and can be used to monitor the status of a disorder or as a marker of response to intervention (García-Gutiérrez et al., 2020).

1.2 TMS-EEG

1.2.1 Physical basics

Merton and Morton (1980) developed a technique to investigate the brain through the intact scull by applying brief high-voltage electrical pulses via electrodes on the head surface. With transcranial electrical stimulation it was possible to investigate the primary motor cortex (M1) without invasive operation by eliciting brief muscle responses to the electric stimulation (motor evoked potentials [MEP]) via corticospinal innervation (Merton & Morton, 1980). The main disadvantage of transcranial electrical stimulation, namely the concomitant pain to electric stimulation, was overcome by the development of TMS (Barker et al., 1985; Rossini et al., 2015). TMS is nowadays used in research to study general brain physiology and pathophysiological processes and has been established as a therapeutic tool for various diseases (Hallett, 2007).

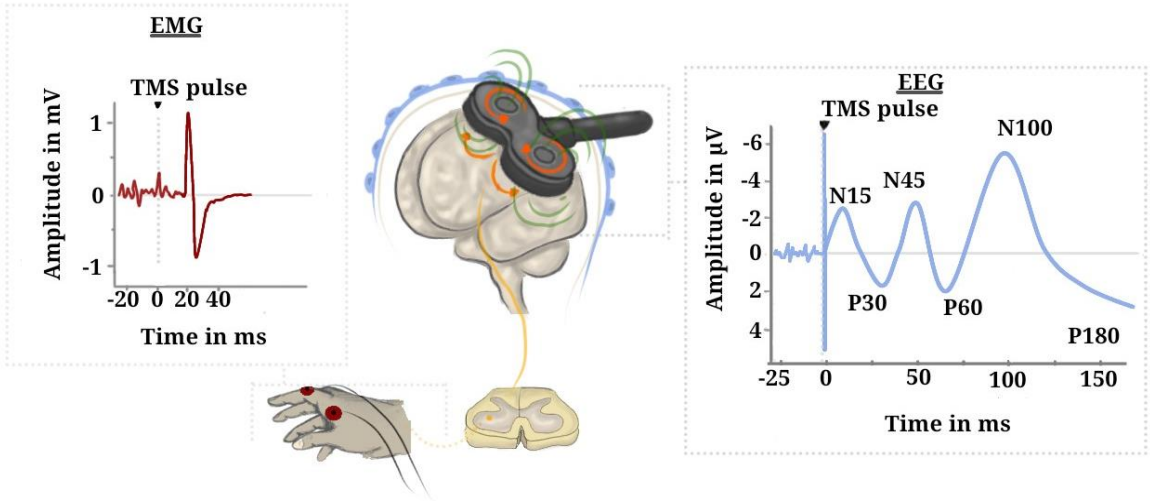
TMS is a non-invasive and painless method to investigate cortical functions in vivo by activating cortical areas via the principle of electromagnetic induction. A TMS device consists of a coil containing circular copper coils, connected to a high-voltage and high-current discharge system. The discharge system can produce a brief current of several thousand Amps, which pass through the coil (Jalinous, 1991). These brief but strong electrical currents result in a less than 1 ms lasting perpendicular magnetic field with a field strength of 1-2.5 Tesla, which can penetrate skin and bone without being significantly attenuated (Groppa et al., 2012; Rothwell, 1997). Rapid time-varying magnetic fields applied

over the brain or peripheral nerves elicit an electric field parallel to the coil, which in turn induces electric currents in the underlining nerve tissue (Tofts, 1990).

The stimulation depth of TMS depends, among other things, on the coil shape. There are several different shapes of TMS coils, such as the circular coil and the figure-of-eight coil. Latter is the most often used coil and consist of two adjoining circular coils with opposing current directions. The electric field produced by figure-of-eight coils is maximal under the intersection of both circles and lowest under the middle of each circle (Cohen et al., 1991). This coil arrangement results in more focal stimulation compared to circular coils but can only produce a suprathreshold field to a depth of 1.5 - 2.5 cm below the central segment of the coil (Roth et al., 2007). Relatively selective stimulation of specific cortical areas is possible with a figure-of-eight coil at low to moderate stimulus intensities and thus preferable for studies in which cortical mapping is required (Groppa et al., 2012) and when distinct superficial cortical areas are targeted.

Figure 1

The basic neurophysiological principle of TMS-EEG



Note. The figure shows the schematic of a TMS application to the motor cortex (M1) and the resulting TMS-induced potentials (TEP) and motor evoked potentials (MEP). The blue waveform (right) shows a schematic TEP wave complex recorded by electroencephalography (EEG). Multiple negative (N) and positive (P) deflections at different latencies (in ms), relative to the TMS pulse application, comprise several TEP components (N15, P30, N45, P60, N100, P180). The schematic of the TMS coil shows that the TMS-induced magnetic field (green lines) is perpendicular to the plane of the TMS coil. The induced electric field in the tissue (orange lines at the cortex) is again perpendicular to the magnetic field. The figure also illustrates the relationship between the direction of the current in the coil (orange lines on the coil) and the direction of the current induced in the brain tissue (orange lines on the cortex), which is antiparallel to the coil current. The red waveform (left) shows an MEP recorded by electromyography (EMG) from the FDI muscle of the hand. Please note that the sizes are not true to scale (own representation, modified and expanded version based on Farzan et al., 2016).

1.2.2 Neurophysiological basics

There is consensus in research on the basic mechanisms of nerve activation by TMS through electromagnetic induction. In short, a suprathreshold TMS pulse causes time-locked depolarization of neurons and results in synchronized neural firing (Barker et al., 1985; Tremblay et al., 2019). However, the exact targets and mechanisms on neuron level are still being investigated. Since many methodical studies focus their investigation on M1, most of the knowledge is based on mechanisms in this cortical area (Siebner & Ziemann, 2007).

Axons are most likely activated by TMS and are the part of the neuron where action potentials are triggered when the depolarization of the membrane potential is above

threshold. More specifically, axon terminals of neurons aligned to the induced electrical field are thought to be activated by TMS (Aberra et al., 2020). To depolarize an axon, the spatial gradient of the induced electrical field in relation to the orientation of the axon is crucial. Axons of these neurons are depolarized when their orientation is not perpendicular or merely parallel to the induced homogeneous electric field, but rather when the axon bends out of the electric field. An axon completely parallel to the electric field will have an equal potential at all points of its length. However, a potential gradient between two points along its length is necessary to depolarize an axon. When an axon bends and cuts the electric field the potential along the axon near the bend differs (Rothwell, 1997). Therefore, axon bends and axon terminals are likely targets for TMS stimulation. When the membrane depolarization induced by the electrical gradient exceeds a threshold, the permeability of voltage-gated ion channels is drastically increased, resulting in an acute influx of sodium ions in the intracellular space, triggering an action potential in the directly stimulated neuron (Siebner & Ziemann, 2007). Action potentials from the area stimulated by TMS can propagate to brain areas connected through cortico-cortical, thalamocortical, and cerebello-cortical pathways by synaptic transmission (Farzan et al., 2016).

Studies focusing on the M1 identified axons of pyramidal neurons (vertical to the cortex surface) and interneurons (horizontal to the cortex surface) as neuronal cell types possibly targeted by TMS (Rogasch & Fitzgerald, 2013). TMS to M1 induces descending volleys in the corticospinal tract, which can be measured with epidural electrodes. So called early D-waves result from direct depolarization of pyramidal corticospinal neurons, while later I-waves are thought to originate from indirect transsynaptic transmission to the corticospinal neurons through interneurons and cortico-cortical axons (Amassian et al., 1989; Di Lazzaro et al., 1998).

While various muscles can be addressed by TMS application over the corresponding cortical area in M1, the motor hot spot for the contralateral hand muscle is a commonly studied target (Hallett, 2007). Neuroimaging studies located M1 and the hand knob: A knoblike structure containing neuronal elements linked to motor hand functioning, in the crown and posterior wall of the precentral gyrus (Yousry et al., 1997). To stimulate M1 optimally, the TMS coil is often positioned in a 45° angel to the sagittal line (perpendicular to the central sulcus) inducing an electrical current in the tissue that runs posterior-lateral to anterior-medial (see Figure 1). This orientation is assumed to be optimal for M1 stimulation as it produces MEPs with smaller stimulus intensities than other positions (Mills et al., 1992;

Thielscher et al., 2011). TMS with the optimal coil orientation targeting M1 produces the strongest electric fields in the crown and lip of the precentral gyrus, thus likely stimulating cortical interneurons in the posterior rim of the gyrus, and maybe interneurons and pyramidal neurons in the lip and/or anterior wall of the central sulcus (Aberra et al., 2020; Bungert et al., 2017; Laakso et al., 2014; Rossini et al., 2015; Thielscher et al., 2011).

Suprathreshold stimulation of M1 results in descending corticospinal volleys. Summation of the excitatory postsynaptic potentials of these volleys can generate action potentials in spinal motor neurons. The action potential is transmitted to the target muscle via the peripheral motor axon. The sum of peripheral motor action potentials causes a muscle contraction in the contralateral extremity, which can be recorded by electromyography (EMG) (see Figure 1). Amplitudes of these MEP allow an assessment of the excitability of the corticospinal tract, which is influenced by properties of the motor cortex, spinal motor neurons and neuromuscular structures (Hallett, 2007; Rogasch & Fitzgerald, 2013; Siebner & Ziemann, 2007).

Over the last decades TMS has been widely used to investigate pathophysiological changes by studying MEP latencies and amplitudes as well as the motor threshold. The motor threshold is defined as the TMS intensity to stimulate the motor cortex and to elicit a reliable MEP of minimal amplitude in the target muscle and is often used to calibrate the TMS stimulus intensity for each individual (Rossini et al., 2015). For this purpose, the resting motor threshold (RMT) is often defined. The RMT was originally defined as the stimulation intensity needed to evoke an MEP with a peak-to-peak amplitudes of at least 50 μV in 5 out of 10 trials in the resting muscle (Rossini et al., 2015). For RMT hunting, one starts with a stimulation intensity below threshold (e.g., 35% of the maximal stimulator output) and increases the intensity in steps of 5% until a sufficient MEP amplitude is elicited. Thereafter, the intensity is gradually reduced in 1% steps, until only 5 out of 10 trials produce a MEP with an amplitude >50 μV (Rossini et al., 2015). Later on, it was suggested to replace the 5 out of 10 procedure with the maximum likelihood method, which takes the success probability into account (Awiszus, 2003).

However, one disadvantage of the sole application of TMS is that MEPs are influenced by cortical, subcortical and spinal cord properties. Hence, MEPs only deliver indirect information about cortical activation, and implications about cortical pathologies or motor

cortex excitability based on MEP analysis alone might be inconclusive (Nikulin et al., 2003). To overcome these limitations, TMS was combined with simultaneous high-density EEG.

EEG allows to co-register direct cortical activation induced by TMS via multiple electrodes on the scalp (Ilmoniemi & Kičić, 2010). Compared to other neuroimaging techniques, EEG has a high time-resolution and can be used to record TMS induced cortical activity with a millisecond time scale, starting a few milliseconds after a TMS pulse while still locating responses with an accuracy of 1–2 cm (Ilmoniemi et al., 1997). The distinguished temporal resolution of EEG allows for mapping TMS-evoked cortical activity (Komssi & Kähkönen, 2006). TMS-EEG is used to quantify and characterize instantaneous cortical responses to TMS, cortical excitation and inhibition as well as the time-resolved spread of activity between cortical areas (Ilmoniemi et al., 1997; Ilmoniemi & Kičić, 2010). Thus, TMS-EEG provides important neurophysiological information on cortical reactivity, connectivity, and neural plasticity, expanding the application possibilities of TMS and makes it possible to probe cortical functioning across a variety of brain areas, no longer limited to the motor cortex (Tremblay et al., 2019).

1.2.3 TMS protocols and EEG outcome variables

TMS-EEG experiments can aim at assessing and quantifying the effect of TMS by considering TMS as an event similar to classical event-related potential paradigm. These designs are often used to study markers of brain health (Farzan et al., 2016). Single-pulse and paired-pulse TMS protocols allow to assess cortical inhibition and excitation in reaction to TMS (Hallett, 2007). The focus in this work is on single-pulse protocols in which the interstimulus interval between consecutive pulses is several seconds long (often with varying intervals) to prevent interaction between pulses (Sandrini et al., 2011). In contrast, paired-pulse TMS protocols involve two interacting pulses with a conditioning stimulus and a subsequent test stimulus. The amplitude of the outcome variable (MEPs or EEG activity) of the paired test stimulus is compared to the amplitude from a test stimulus without prior conditioning stimulus (Daskalakis et al., 2012; Rossini et al., 2015). Longer inter-stimulus intervals of single- and paired-pulse protocols ensure that the TMS stimulation has no long-term effects on cortical activity. In contrast, in repetitive TMS (rTMS) protocols trains of TMS pulses are applied. rTMS can lead to long-lasting changes in cortical activity, thus increasing (high-frequency of 10-20 Hz) or decreasing (low-frequency of <1 Hz) the cortical excitability of the targeted area depending on the stimulation frequency (Chen et al., 2013;

Ferreri & Rossini, 2013). These changes in neuroplasticity are thought to be caused by the modulation of synaptic efficacy through long-term potentiation or long-term depression and can be used therapeutically (Esser et al., 2006; Hallett, 2007).

Each stimulation protocol can be applied to study various research goals and different neurotransmitter systems (Daskalakis et al., 2012), thus allowing for various outcome measures. One research focus is on the cortical reactivity as assessed with single-pulses. On the one hand, TMS effects of single-pulses on MEP amplitudes can yield indirect information about cortical excitability in M1. The motor threshold and the cortical silent period, which is a pause produced by TMS in the current voluntary EMG activity, are two of these outcomes (Hallett, 2007). On the other hand, single-pulse protocols can additionally be used to study cortical reactivity directly by recording regional and global brain responses to TMS. In this respect, EEG signals following TMS pulses can be analyzed according to their temporal, frequency, time-frequency or phase characteristics (Farzan et al., 2016). Temporal analysis examines time domain-specific EEG signal properties such as latency and amplitude of evoked potentials or global mean field amplitudes (Farzan et al., 2016). In the present manuscript, the temporal characteristics of evoked potentials after single-pulse TMS are of particular interest.

1.2.4 TMS-evoked potentials

Many single-pulse TMS studies reported similar TMS time-locked peaks in the EEG after averaging multiple trials, referred to as TMS-evoked potentials (TEPs) (Bonato et al., 2006; Kähkönen et al., 2004; Komssi et al., 2002; Nikulin et al., 2003; Rossini et al., 2015). The TEP is a complex waveform consisting of a series of negative and positive peaks at various latencies which last up to 300 ms after the TMS pulse (see Figure 1). The peaks are named after their polarity (**N**egative or **P**ositive) and the latency at which they occur (Bonato et al., 2006; Hill et al., 2016; Komssi et al., 2004). Even though the exact peak latencies vary slightly between studies, single-pulse TMS applied to M1 yields generally seven reproducible peaks: N15, P30, N45, P55/P60, N100, P180 and N280 (Komssi & Kähkönen, 2006) (see Figure 1).

What TEPs reflect exactly has been widely discussed. A study on patients with different degrees of cortical lesions demonstrated that TEPs can only be evoked in functional portions of the cortex, supporting the notion that TEPs reflect genuine cortical activity and not merely technical artifacts or peripherally evoked responses from nerves or scalp muscles (Gosseries

et al., 2015). Instead, the origin of TEPs is attributed to the time-locked depolarization of neuron populations and synchronized neuronal firing in local and distal networks, through direct stimulation or transsynaptic transmission (Barker et al., 1985; Tremblay et al., 2019). EEG is not sensitive to action potentials due to their symmetrical current distribution and short duration. Therefore, the summation of excitatory and inhibitory postsynaptic potentials (IPSP) of populations of pyramidal neurons is thought to account for the positive and negative deflections in the EEG (Hill et al., 2016; Kirschstein & Köhling, 2009; Rogasch & Fitzgerald, 2013).

Properties of TEPs are linked to the brain state (Komssi et al., 2004), as TEPs are modulated by movement initiation (Nikulin et al., 2003), the vigilance of the participants (Massimini et al., 2005) and experimental changes (Esser et al., 2006; Rogasch & Fitzgerald, 2013). These findings indicate a high sensitivity of TEPs for changes in cortical excitability (Casarotto et al., 2010). Indeed, the latency and amplitude of these TEP components can quantify current cortical excitability within milliseconds time range - changes in both parameters can mirror changes in cortical activity of the stimulated cortical area (Tremblay et al., 2019). While TEPs in general reflect cortical excitability, the distinct TEP components are however related to different cortical processes. It has been assumed that earlier TEPs (N15-P30) are linked to excitatory activity, whereas later peaks, such as N45 and N100, rather reflect inhibitory activity (Tremblay et al., 2019).

Besides cortical excitability, TEP rely on stimulation parameters as well. TEPs are influenced by the TMS coil angle, site of stimulation (Casarotto et al., 2010; Gomez-Tames et al., 2018) and nonlinearly by the stimulation intensity of the TMS pulse (Komssi et al., 2004). When stimulation conditions are comparable, test–retest correlations demonstrate a high reproducibility of TEP peaks nonetheless, indicating consistency over time (Casarotto et al., 2010; Lioumis et al., 2009). The N100 and P200 exhibit the best reliability, with a relatively small number of trials being required to achieve stability, rendering them suitable as outcome measures in biomarker and intervention studies (Kerwin et al., 2018). Thus, the analysis of TEPs is nowadays an established, valid, and reliable method to investigate current cortical activity.

1.2.4.1 N100 origin and function.

The N100 is one of the most replicated and pronounced peaks and represents a promising research tool (Bonato et al., 2006; Kerwin et al., 2018). Many researchers agree on the

underlying neurotransmitter process of this TEP component, as the N100 has often been related to post-synaptic effects of inhibitory interneurons and is thus often used to investigated inhibitory mechanisms (Hill et al., 2016). This assumption is based on several research approaches. Studies focusing on functional aspects demonstrated reductions in N100 amplitudes during movement preparation (Nikulin et al., 2003) and motor response preparation (Bender et al., 2005), but elevation when TMS triggered movement should be resisted (Bonnard et al., 2009). Additionally, the N100 latency coincides with the time characteristics of GABA-B mediated IPSP (Rogasch et al., 2015). Since GABA-B receptors are G-protein coupled, interacting with calcium and potassium channels via second messenger systems, GABA-B mediated IPSP are slower than IPSP mediated by ionotropic receptors (Bormann, 2000; Davies et al., 1990; Ulrich & Bettler, 2007). Pharmacological observations corroborate this association. While the earlier N45 component reflects cortical inhibition mediated by GABA-A activity, the N100 amplitude increase after the intake of the GABA-B receptor agonist baclofen (Premoli et al., 2014). In a recent study by Du et al. (2018) TMS-EEG and magnetic resonance spectroscopy were used to investigate the relationship between neurochemical concentration and TEPs. Their results suggest that the N100 not only reflects cortical inhibition but rather a balance between GABA and the excitatory neurotransmitter glutamate. Thus, the N100 can be utilized to indicate at least cortical inhibition or the balance between inhibition and excitation.

While there is relative consensus among researchers that N100 is an inhibitory component, its cortical origin and function are currently still in dispute. Is it a component that reflects local cortical properties or primarily artifacts, or does it relate to global cortical properties? This fundamental methodological question needs to be answered in order to facilitate the application of the N100 in clinical research, as all three possibilities indicate different N100 functions and implementation options.

The spatiotemporal distribution of the N100 over the head can be illustrated with topographical plots and contains information about local excitability of the stimulated area as well the cortical origin of the TEP and propagation of TMS-evoked activity in other cortical networks (Ilmoniemi & Kičić, 2010; Rossini et al., 2015). Results concerning the topographical distribution of the N100 are however heterogenous. Some studies indicate that the N100 reflects local excitability, specific to the stimulated area (Bender et al., 2005; Bonato et al., 2006). Other researchers argue that the N100 differs from other TEP components and reflects global instead of local cortical reactivity (Du et al., 2017) or that the

N100 is highly influenced by artifacts, and the topography does not adequately reflect transcranially evoked activity (Conde et al., 2019; Freedberg et al., 2020; Leodori et al., 2019). Disentangling transcranially evoked activity from artifacts or peripherally evoked activity is therefore crucial.

1.2.4.2 N100 and artifacts.

Later time windows, especially around 100 ms, are affected by unspecific multisensory stimulation effects. For example, ocular artifacts, auditory evoked potentials (AEPs) and long-latency somatosensory evoked potentials (SEPs) for example have components with a latency around 100 ms after the TMS pulse and therefore overlap with the time range of the transcranially evoked N100 component (ter Braack et al., 2015; Wu et al., 2012).

Prominent physiological artifacts contain spontaneous blinks and eye movements, as well as blink startle response due to TMS over frontal regions. The strong corneo-retinal dipole is responsible for the influence on the EEG signal in frontal electrodes during eye movement and blinks (Plöchl et al., 2012). Eye movement and blinks can be concurrently recorded with an electrooculogram to differentiate these artifacts from genuine transcranially evoked activity. Blink artifacts have a topographical center over anterior electrodes and peak at ~90 ms (Rogasch et al., 2014). To minimize the effect of these artifacts on neuronal data, the blink and eye movement components can be assessed offline with the independent component analysis (ICA). The eye related artifacts have distinct temporal and spatial characteristics and can be subtracted offline from the neuronal activity (Ilmoniemi et al., 2015). The removal of the startle response blinks from the EEG data must be done with caution to avoid deletion of TMS induced neuronal activity. Unlike spontaneous blinks, which are independent from the neuronal activity, startle response blinks have a temporal association with the TMS evoked neuronal activity (Rogasch et al., 2014). Removing blink artifacts is important to assess genuine transcranially evoked activity, and the removal with ICA ensures that the underlying TMS-evoked activity is minimally affected (Rogasch et al., 2014).

Additionally, the direct depolarization of sensory afferents in the scalp or the mechanically activation throughout coil vibration leads to SEP (Ilmoniemi & Kičić, 2010; Rogasch & Fitzgerald, 2013). SEPs have a long-latency component (>100 ms) (Wu et al., 2012) which overlaps with the TEP N100 latency. Additionally, the TMS coil discharge is accompanied by a loud clicking sound, which is conducted via air and bone and can be recorded as

auditory-evoked potentials in the EEG (Nikouline et al., 1999). AEPs consist of a negative deflection at 100 ms and a positive peak at 180-200 ms (ter Braack et al., 2015). To avoid AEPs headphones with white or adapted noise are recommended (ter Braack et al., 2015), but those might be aversive for participants. Instead, the topography of both AEPs and SEPs are helpful to differentiate these components from TMS induced neuronal activity. The AEP-related N100 component either peaks at the vertex (Conde et al., 2019; Rogasch et al., 2014) or in the contralateral hemisphere during monaural acoustic stimulation (Hine & Debener, 2007). The topography of SEPs, especially of the long-latency SEP potentials due to trigeminus stimulation, is bilateral but asymmetric, with the largest amplitudes contralateral to the stimulation site (Hashimoto, 1988; Pokorny et al., 2022). Clearly lateralized TEP components around the stimulation site are unlikely to reflect merely peripherally evoked sensory stimulation, but instead TMS evoked cortical activity (Conde et al., 2019).

1.2.4.3 N100 topography and stimulation location.

Even though artifacts influence the N100 component to some extent, an ipsilateral N100 topography with a maximum at the stimulation site might reflect local cortical activity. This notion fits general assumptions about TMS responses, as they are usually highest in the stimulated hemisphere, specifically in the area under the coil, and diminish with increasing distance to the targeted area, thus indicating local cortical excitability of the stimulated area (Bonato et al., 2006; Rossini et al., 2015). Therefore, TEPs located under/close to the TMS stimulation location might be used to study local effects of TMS (Ilmoniemi & Kičić, 2010). Indeed, topographical distributions with ipsilateral maxima at the stimulation site (at M1) have been described for the N100 component, indicating that the N100, similar to the other TEP components, reflects local cortical properties (Bender et al., 2005; Bonato et al., 2006; Helfrich et al., 2012; Komssi et al., 2004; Nikulin et al., 2003). Contradictory, other studies found N100 topographical maxima in centro-medial regions, while M1 was stimulated (Leodori et al., 2019; Spieser et al., 2010).

As shown, most studies examined the N100 during M1 stimulation. To assess whether the measured N100 component reflects local cortical excitability, mainly artifacts or global inhibitory/excitatory function, the N100 (amplitudes, latencies, and topographies) must be compared at different stimulation sites. A varying topography with a maximum at the stimulation site and differences in amplitudes/latencies between stimulation locations would indicate a dependency on local cortical properties, while stable topographies, amplitudes, and latencies independent from the stimulation location could argue against a reflection of

local functioning. Systematic comparisons of the N100 between stimulation locations are scarce, but in a few studies TEPs in general and the N100 specifically were compared between M1 and prefrontal cortical areas. Smaller N100 amplitudes were reported for prefrontal stimulation compared to M1 stimulation, further indicating a difference in cortical excitability between these cortical areas and its reflection in the N100 (Kähkönen et al., 2005; Lioumis et al., 2009). On the other hand, some studies reported that the N100 topography and amplitude did not change between different stimulation locations (e.g., M1, prefrontal cortex, auditory cortex, vertex, parietal cortex, cerebellum) and stimulation conditions (real TMS vs sham TMS), but remained at central regions (Du et al., 2017; Freedberg et al., 2020). The lack of spatial specificity has been interpreted in the way that the N100 either does not reflect directly induced cortical activation by TMS, but rather sensory artifacts and non-specific processes (Freedberg et al., 2020) or general cortical properties (Du et al., 2017). Du et al. (2017) did not ascribe the stable central topography to peripherally evoked activity such as AEPs, because auditory masking (earplugs) was used. The N100 was instead interpreted as a biomarker to examine global (rather than local) cortical GABA/NMDA receptor functioning (Du et al., 2017). Nevertheless, an influence of bone conducted AEPs and SEPs cannot be ruled out and might be responsible for the central topography of the N100 (Conde et al., 2019).

2 Research questions

The aim of this dissertation was to investigate the possible usage of the N100 as a biomarker in pathophysiological processes in adolescents' depression. To this end, three different studies were conducted (1. Roos & Biermann et al., 2021; 2. Jarczok et al., 202; 3. Biermann et al., 2022). As outlined before, the function of the N100 component needs to be investigated further in order to be useful in clinical research. Specifically, a systematic comparison between stimulation locations is needed. Therefore, two methodological studies were conducted, with focus on the properties of the N100. Exploring whether the N100 reflects mainly artifacts, or rather global or local cortical properties was examined by looking at the effects of coil placements with a small deviation in study 1 (e.g., within one cortical area) and with a large deviation in study 2 (e.g., between distinct cortical areas such as frontal and occipital areas). Both studies had a similar aim but differed in terms of investigating the influence of the specific cortical areas on the N100. In the first study, we focused on M1 as a cortical area to allow motor outputs as another variable to TEPs, so that we were able to contrast both measures and have an indicator in MEPs for motor hotspot

stimulation. In this way, we were able to determine the effects of local cortical properties on the N100. In a second study, we investigated whether this finding is also reliable in other cortical areas. As outlined in the previous chapters, other cortical areas, such as the DLPFC, are more often implicated in the pathophysiological mechanisms of depressive symptoms than motor regions. Therefore, we conducted a second study that considered two different, more distant cortical regions (DLPFC and temporo-occipital cortex) and investigated the effects of the different cortical areas on the N100. These two methodological studies underline the dependency of the N100 on local cortical excitability, as demonstrated in different cortical areas, and suggest that the N100 likely reflects the local E/I balance of the specific cortical area. In this way, we validated the reflection of local cortical properties in general and that of the DLPFC in the N100 before using the N100 to investigate pathophysiological changes in the DLPFC associated with depressive symptoms. Based on this rational, we used the N100 in study 3 to examine E/I balance in the DLPFC of adolescents with depressive symptoms in a longitudinal study. Study 3 represents an interim analysis of the larger "Balancing Vibrations Study". This study examines the effects of 6-weeks of whole-body vibration strength training on depressive symptoms as well as endocrinological and neurobiological parameters in adolescent inpatients with a depressive episode. For the interim analysis, a subsample was analyzed with a focus on TMS-EEG parameters and depression symptoms while data collection for the main study was ongoing. We investigated possible changes in E/I balance during antidepressant therapy, evaluating the N100 as a possible biomarker for pathophysiological changes during depression in adolescents.

3 Overall discussion

The objective of this dissertation was to increase the knowledge on the pathophysiology of depression in adolescents and to establish useful TMS-EEG parameters for clinical research. Even though TMS-EEG is a promising non-invasive method to study mental disorders (Hui et al., 2019), there are knowledge gaps concerning the interpretation of the often-used TMS-EEG parameter N100. The methodological studies 1 (Roos & Biermann et al., 2021) and 2 (Jarczok et al., 2021) helped to further elucidate the properties of the N100 to facilitate interpretation in clinical study 3 (Biermann et al., 2022). The investigation of potential (valid) biomarkers in adolescents with depression is of particular interest as depression has a substantial prevalence of 3-6% in this age group, leading to severe impairment in social and educational domains and predicting later challenges in adulthood (Bettge et al., 2008; Costello et al., 2006; Thapar et al., 2012). Biomarkers have been discussed in recent years as potential tools to improve prevention, diagnosis, and therapy response of mental disorders (García-Gutiérrez et al., 2020). This potential biomarker might be of use as a monitoring biomarker to not only investigate the pathophysiology of depression at one time point, but to further monitor the physiological changes during therapy. In order to facilitate a potential usage of the N100 as a biomarker in the neurophysiological mechanisms in adolescents' depression, the cortical origin and the interpretation of the topography of this parameter had to be evaluated.

3.1 Study 1: Local differences in cortical excitability

In study 1 (Roos & Biermann et al., 2021), we addressed the research question of whether the N100 properties reflect global neural responses, artifacts, or rather site-specific cortical activity. To this end, we systematically compared the N100 during stimulation of distinct sites in a small area around M1. The results indicate a dependency of the N100 amplitude on the cortical excitability of the stimulated cortical area. The N100 amplitudes and the GFP were significantly smaller during anterior-medial stimulation compared to the hot spot, and although not statistically significant, latencies also showed a tendency to be shorter. We concluded that this likely is due to partial stimulation of the less excitable premotor cortex, located anterior to M1. We observed a stable ipsilateral N100 topography slightly posterior to the mean hot spot, independent of the exact stimulation site. This finding was attributed to the anatomical properties of M1 (width/length, location in the crown and posterior wall of

the precentral gyrus) in combination with a partial activation of surrounding cortical areas. The activation of surrounding areas is indicated by source analysis, which revealed a widespread source activation through TMS. The differences in local cortical excitability of these surrounding areas in addition to the created primary motor cortex dipole in each stimulation condition due to the constant activation of the motor cortex, as indicated by MEP occurrences in all conditions, might cause a stable ipsilateral slightly posteriorly located topography near the stimulation site. Even though no significant covariation between N100 topography and the exact stimulation site was detected, descriptively a slight covariation between stimulation site in the small area (4 cm^2) around the motor hot spot and the topography can be observed in the topographical maps.

The initial research question can therefore be answered as follows: The described topography contradicts the assumption, that the N100 only reflects multisensory stimulation effects (such as AEPs or SEPS). AEP topographies are described at the vertex (Conde et al., 2019; Rogasch et al., 2014) or in the contralateral hemisphere during monaural acoustic stimulation (Hine & Debener, 2007) and SEP topographies bilateral but asymmetric, with the largest amplitudes contralateral to the stimulation site (Hashimoto, 1988; Pokorny et al., 2022). The clearly lateralized N100 component around the stimulation site likely reflects genuine TMS evoked cortical activity (Conde et al., 2019). Additionally, these results are in contrast to the described stable N100 topographies medial central near the vertex, independent of the stimulated cortical area (Du et al., 2017; Spieser et al., 2010). Instead of a proposed global neural response (Du et al., 2017), our findings suggest that the N100 might be suitable for illustrating differences in local excitability/inhibition, leading to characteristic differences in amplitude, latency, and possible topography during cortical mapping. These differences in cortical activation likely reflect differences in GABA-B-ergic neurotransmission.

Even though comparison of the N100 characteristics in a small spatial area around the hot spot already indicates a dependency on the local cortical excitability, the topography covaried descriptively but not significantly with the exact stimulation location. As the N100 reflects local GABA and/or the balance between GABA and glutamate, the N100 properties likely reflect characteristics of these neurotransmitter systems of the stimulated cortical area. Since receptor distribution patterns (i.e., receptor fingerprints) differ between functionally distinct cortical areas and differentiate these areas form each other (Zilles et al., 2002), the N100 characteristics should vary between cortical areas. Areas with similar function have

similar receptor fingerprints, while functionally divergent areas differ more in their receptor fingerprints (Zilles et al., 2002). In comparison to the small spatial change in coil positions in study one, a stimulation of functionally distinct cortical areas with larger spatial distance between these areas should yield more information on the N100 characteristics. If the topography does indeed vary with the stimulation site of functionally and spatially divergent cortical areas, the assumed reflection of local differences in GABA and glutamate mediated excitability by the N100 can be supported. Therefore, in study two we focused on the N100 characteristics in two functionally and spatially divergent areas.

3.2 Study 2: Lateralized Long Latency EEG Responses at different stimulation sites

In study 2 (Jarczok et al., 2021), we addressed the question of whether the N100 occurred systematically lateralized and varied with the stimulation site in functionally and spatially divergent areas. Therefore, long-latency TEPs corresponding to the N100 were investigated with TMS stimulation to the DLPFC in one sample and to the temporo-occipital cortex (TOC) in another sample of healthy adults. In order to further disentangle artefacts from site-specific cortical activity, a calculation was carried out to remove evoked components that are not systematically lateralized relative to the stimulated hemisphere. As described and demonstrated before, clearly lateralized ipsilateral potentials are likely to not solely reflect peripherally evoked sensory stimulation (Conde et al., 2019). By stimulating homologous sites in both hemispheres and subtracting invariable evoked activity, lateralized activity at the stimulation site was made accessible (LatTEPs). We found that the N100 associated TEP topography varied with the stimulated site (DLPFC, TOC) and its maxima was systematically lateralized to the stimulated hemisphere. The results of study 2 indicate that N100 associated TEPs can be disentangled from TMS co-occurring components via their topography. These components likely reflect co-activated peripheral sensory afferences, which are invariable across different stimulation sites. Lateralized N100 associated TEP components located at the stimulation site probably reflect activity evoked in the targeted cortex region and can therefore be used to assess local cortical functioning.

Concerning the relationship between stimulated cortical site (with its specific cytoarchitecture) and the other N100 properties, such as latency and amplitude, only descriptive observations can be made in this study. While the latency and amplitude of the long-latency TEP, which is assumed to be associated with the N100, is considerably longer and larger (i.e., more negative) during TOC stimulation than during DLPFC stimulation, no

direct comparison can be drawn due to the different samples. Additionally, a systematic influence of the stimulation site besides cortical excitability on those properties needs to be considered. The scalp-cortex distance varies between different regions of the head, which might have an effect on the level of stimulation in the underlying neural tissue and thereby on the measured TMS-EEG parameters (Stokes et al., 2005). Nonetheless, these findings are in line with the smaller amplitudes and slightly shorter latencies of the N100 during more anteriorly located stimulation sites compared to motor hot spot stimulation in study 1.

Taking together the results of the first two studies in this work, the use of ipsilateral lateralized long-latency TEPs (e.g., N100) might indeed be useful to investigate the local cortical excitability of the stimulated area and not global cortical properties, as Du et al (2017) proposed. When focusing on the lateralized component, an influence of unspecific multisensory stimulation effects is minimized. After these methodologically studies supported the validity of the N100 and its relation to local cortical excitability, we used the N100 to investigate the cortical excitability of the DLPFC in adolescents with depression.

3.3 Study 3: N100 as possible biomarker in adolescents' depression

The third study (Biermann et al., 2022) aimed to investigate the cortical excitability of the left and right DLPFC in adolescents with depression to answer the research question how the N100 is associated with depressive symptoms. Moreover, clinical patients were examined shortly after admission and after six weeks of intervention in order to study potential longitudinal changes. Taking alle results together, the topography of the N100 revealed a clearly lateralized distribution at the stimulation site (left and right DLPFC). Based on the first two studies of this work, the N100 measured in the third study presumably reflects the local DLPFC excitability, more precisely the GABA-B functioning or GABA/Glutamate balance. During the TAU with additional physical exercise, the depressive symptoms decreased significantly, which mirrored the trend observed in the N100 amplitude. This relationship between longitudinal changes in both phenomena is indicated by trend correlation. Similar to study two, the lateralized N100 amplitude was additionally investigated to minimize the effects on co-occurring multisensory stimulation effects. The trend wise decrease in lateralized amplitudes, which is likely not strongly influenced by of co-occurring sensory effects, underlines the alterations in cortical excitability of the DLPFC. This trend towards a longitudinal decrease in lateralized amplitudes supports the hypothesis of a relevant reduction in cortical excitability of the DLPFC during antidepressant therapy

and a reduction in depressive symptoms, while additionally controlling for confounding effects on the N100.

In summary, convincing support was found that higher N100 amplitudes in adolescents with more severe depressive symptoms reflect a considerable E/I imbalance in the DLPFC. Based on previous findings (Dhami et al., 2020; Page & Coutellier, 2019; Voineskos et al., 2019), this imbalance might be caused by an imbalance between inhibition and excitation in favor of inhibition due to an increased postsynaptic GABA turnover. Depression related deficits in GABA neurotransmitter levels (Duman et al., 2019; Hasler et al., 2007) could be over-compensated by altered activity of GABAergic interneurons (Page & Coutellier, 2019). This DLPFC over-inhibition might cause the described hypoactivity of the DLPFC during depression (Biver et al., 1994; Siegle et al., 2007) and might be measured in form of higher N100 amplitudes during a state of more severe depressive symptoms. The reduction in N100 amplitudes after the intervention might reflect the "normalization" of DLPFC over-inhibition in association with reduced depressive symptomatology, indicating severity-dependency.

These findings are not only congruent with several previous TMS-EEG and neurotransmitter studies, as describes in the discussion in study 3, but also fit described theories on the role of the prefrontal cortex in emotion regulation and depression. As a result of the DLPFC hypoactivity in adolescents during greater depression severity, executive functioning in emotion regulation could be diminished. The functioning of the DLPFC and its role in top-down regulation of an overactive limbic system by reappraisal and suppression of negative emotions might be inhibited during an acute depressive episode and might be associated with depressive symptom severity (Koenigs & Grafman, 2009; Phillips et al., 2003b). The clinically observed depressed mood and anhedonia during a depressive episode is therefore consistent with a dysregulation in the DLPFC (Phillips et al., 2003b). The measured aberrant N100 amplitudes before treatment in our study, indicating an E/I imbalance and hypoactivity in the DLPFC, point to an application of the N100 as a biomarker for depression. This biomarker seems to be sensitive to the severity of the depressive state rather than indicating a trait effect/a disposition for depression, as the N100 amplitude changes longitudinally. These alterations indicate a reversibility of the DLPFC dysregulation during antidepressant therapy. This is in line with previously described "normalization" of the GABA level during antidepressant therapies (Bhagwagar et al., 2004; Dubin et al., 2016; Sanacora et al., 2003) and similarity of GABA levels between subjects with a remitted depressive episode and healthy controls (Hasler et al., 2005).

In conclusion, the N100 might be used as a biomarker for the depressive state in adolescents as a function of depression severity. More precisely, the N100 seems to monitor the pathophysiology associated with depressive symptoms longitudinally and might be a monitoring biomarker for therapy response. Furthermore, the question arises whether this could also be true in adults. As described before, similar enhanced N100 amplitudes were found in the DLPFC in adults with depression (Voineskos et al., 2019) and decreased during antidepressant therapy (Voineskos et al., 2021). Moreover, we did not find a correlation in our study between age and N100 amplitudes. Even though the age-range in our study is limited (12-18 years), this finding, in combination with the described results in adults, points in the direction of a generalizability of the N100 as a biomarker for depression, independent of age. However, the sensitivity of the N100 to detect pathophysiological processes connected to depression is to be discussed. The N100 has been widely used to investigate pathophysiology in various disorders. Single-pulse paradigms revealed decreased N100 amplitudes and shorter latencies during M1 stimulation in children with attention deficit hyperactivity disorder (ADHD) compared to healthy controls, indicating inhibitory deficits (Bruckmann et al., 2012). Similar decreased inhibition associated with GABA-B functioning was detected in young adults with specific phobia compared to healthy controls, as reflected in decreased N100 amplitudes during DLPFC stimulation in the specific phobia group (Pokorny et al., 2021). Taken together, the N100 might be used in the future as a biomarker for altered cortical inhibition or an E/I imbalance in general in various mental disorders. However, the direction of the relationship between N100 amplitudes and disorders needs to be considered closely, with an assumed over-inhibition in depression (as reflected by larger N100 amplitudes in a depressive state) and impaired inhibition in ADHD and phobias (as reflected by smaller N100 amplitudes). These findings are in line with observed clinical characteristics of these disorders, with impaired motor regulation in ADHD (Bruckmann et al., 2012) and impaired suppression of amygdala response and therefore an intense fear reaction to specific cues (Pokorny et al., 2021).

3.4 Outlook and further research

Different design approaches may further deepen insights into the cortical excitability in adolescents with depression as indexed by the TEP N100. One promising design would be to investigate the N100 longitudinally in adolescents with depression and a control group

without depressive symptoms. Thus, a comparison between N100 amplitudes in the same age range between a clinical population and a healthy control group could be evaluated to further establish the N100 as a biomarker for depression severity. Additionally, possible order effects that could limit our research (see Biermann et al., 2022, “N100 amplitudes and depression”) could be rejected. In future studies, methodologically limiting factors in our design could be addressed and for example a sham TMS could be applied in randomized order to real TMS. This way, multisensory stimulation effects of TMS could be explicitly researched and contrasted to studies such as the here discussed ones, in which no multisensory stimulation effects were controlled (e.g., auditory masking).

In this work, the difference in depressive symptoms, cortical excitability, and N100 characteristics between adolescents and adults were considered. However, no comparison between age groups was possible. Therefore, a study investigating a larger group of participants, with a broader age range (e.g., from 13 years to 65 years) would be recommendable. The assumed similar N100 characteristics in depression could be tested in different age groups (e.g., adolescents, young adults, middle aged adults, older adults). A longitudinal design with a duration of several years would be useful to study possible aging effects on the N100 characteristics and the relation to depressive symptoms and remission respectively.

4 Declaration of contributions to the publications

Study 1: Shared first authorship

Lea Biermann (shared first and corresponding author) was involved in data analysis and responsible for statistics, interpretation, and visualization of the results. She wrote the statistics, results and discussion of the original manuscript and was involved in editing and critical writing-revision of the introduction and methods.

Roos, D., **Biermann**, L., Jarczok, T. A., & Bender, S. (2021). Local Differences in Cortical Excitability – A Systematic Mapping Study of the TMS-Evoked N100 Component. *Frontiers in Neuroscience, 15,* 623692. https://doi.org/10.3389/fnins.2021.623692

Study 2: Co-authorship

Lea Biermann was involved in data collection, supported the data analysis and proof reading of the manuscript.

Jarczok, T. A., Roebruck, F., Pokorny, L., **Biermann**, L., Roessner, V., Klein, C., & Bender, S. (2021). Single-Pulse TMS to the Temporo-Occipital and Dorsolateral Prefrontal Cortex Evokes Lateralized Long Latency EEG Responses at the Stimulation Site. *Frontiers in Neuroscience, 15,* 616667. https://doi.org/10.3389/fnins.2021.616667

Study 3: First authorship

Lea Biermann (first and corresponding author) was responsible for acquisition, analysis, visualization, and interpretation of the data. She contributed to the design of the study and wrote the original manuscript and was responsible for the revision process.

Biermann, L., Wunram, H. L., Pokorny, L., Breitinger, E., Großheinrich, N., Jarczok, T. A., & Bender, S. (2022). Changes in the TMS-evoked potential N100 in the dorsolateral prefrontal cortex as a function of depression severity in adolescents. *Journal of Neural Transmission, 129,* 1339–1352. https://doi.org/10.1007/s00702-022-02539-9

I hereby confirm that all the information provided by Ms. Lea Biermann is correct.

Cologne, 05.12.23 Prof. Dr. Stephan Bender

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