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Neurobiological correlates of Attention-Deficit/Hyperactivity Disorder (ADHD) and impulsivity – a developmental perspective

Inauguraldissertation

zur Erlangung des Doctor scientiarum humanarum (Dr. sc. hum.)

an der Medizinischen Fakultät Mannheim

der Ruprecht-Karls-Universität zu Heidelberg

vorgelegt von
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aus
Heidelberg
2021

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A true history of human events would show that a far larger proportion of our acts are the result of sudden impulse and accident than of the reason of which we so much boast.
Peter Cooper

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
ADHD	Attention-deficit/hyperactivity disorder
BCI	Brain-computer interface
CANTAB	Cambridge Neuropsychological Test Automated Battery
(C)BT	(Cognitive) Behavior therapy
CD	Conduct disorder
CFA	Confirmatory factor analysis
CGT	Cambridge Guessing Task
CNV	Contingent negative variation
CPT	Continuous Performance Task
CT	Cortical thickness
DC	Direct coupled
dlPFC	Dorso-lateral prefrontal cortex
DMN	Default-mode network
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
EMG	Electromyogram
EOG	Electrooculogram
EPI	Echo-planar imaging
ERN	Error-related negativity
ERP	Event-related potential
ES	Effect size
FA	Fractional anisotropy
FFT	Fast-Fourier transformation
(f)MRI	(Functional) Magnetic-resonance imaging
FRN	Feedback-related negativity
FWHM	Full width at half-maximum
GMD	Grey-matter density
GMV	Grey-matter volume
HKD	Hyperkinetic disorder
ICA	Independent component analysis
ICD	International Classification of Diseases
IQ	Intelligence quotient
ISI	Inter-stimulus interval
MFG	Medial frontal gyrus
MID	Monetary incentive delay
MMN	Mismatch negativity
MNI	Montreal Neurological Institute
NEO-PI-R/NEO-FFI	Neuroticism, Extraversion, Openness Personality Inventory revised/Five-factor inventory

NF	Neurofeedback
n.a.	not available/not applicable
n.s.	not significant
ODD	Oppositional defiant disorder
OFC	Orbitofrontal cortex
Pe	Error positivity
(pre-)SMA	(Pre-)Supplementary motor area
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RDoC	Research Domain Criteria
REML	Restricted maximum likelihood
REX	Region of interest extraction (toolbox)
ROI	Region of interest
SPM	Statistical parametric mapping
SPSS	Statistical analysis toolbox
SST	Stop signal task
SURPS	Substance-use risk-profile scale
tACS	Transcranial alternating current stimulation
TBR	Theta/beta ratio
TCI-R	Temperament and Character Inventory revised version
TE	Echo time
TR	Repetition time
VS	Ventral striatum
wfu	Wake Forest University
WMI	White-matter integrity

1 INTRODUCTION

During the last few decades, a rapidly growing body of literature has addressed the neurobiology of mental disorders in adult as well as child and adolescent psychiatry (Jollans & Whelan, 2018; Sonuga-Barke & Sergeant, 2005). Especially with regard to neurodevelopmental disorders such as Attention-Deficit/Hyperactivity Disorder (ADHD), initial work already acknowledged the role of neurobiological processes in the development and manifestation of mental-health disease (e.g. Friedman & Rapoport, 2015). Basically, neuroscience studies are exploring the brain and aim at understanding the neural structures and processes related to specific patterns of human behavior. New methodological possibilities due to advances in assessment techniques and increasingly sophisticated and powerful analysis tools strengthen neuroscience-based approaches, allowing for more precise studies on underlying neural mechanisms (Stein et al., 2015; Thompson et al., 2020).

The exploration of the neurobiological underpinnings of mental-health disease and dimensions of human behavior may offer great opportunities for diagnosis and therapy in clinical psychology and psychiatry (Charney et al., 2013). A better understanding of the neurobiological pathophysiology will identify relevant diagnostic and predictive biomarkers, facilitate targeted interventions, and enable personalized medicine approaches (Rubia, 2018). In addition, neural markers associated with mental disorders will help in implementing appropriate prevention programs addressing potential early treatment needs. Thereby, the developmental course of mental-health symptoms and associated changes in neural processing are especially relevant (Thapar & Riglin, 2020). However, the major challenge within this approach is to conceptualize the complex and heterogeneous nature of human behavior and, more specifically, psychiatric disorders in a neurobiological plausible and coherent way.

Within the current thesis, studies on the neurobiological underpinnings of ADHD and impulsivity, as one core diagnostic criterion of the latter

neurodevelopmental disorder, are presented (see section 2). Our studies further concentrate on developmental aspects and maturational trajectories from childhood to young adulthood with a special focus on two brain-imaging methods, namely electroencephalography (EEG) to encompass alterations in temporal dynamics and (functional) magnetic-resonance imaging ((f)MRI) to identify regional differences of information processing. Cross-sectional and longitudinal designs are presented that allow for disentangling effects of maturation and effects related to behavioral symptoms and diagnostic status in neurobiological data. In addition, EEG data quality is introduced as an important prerequisite for a valid translation of neurophysiological research findings into successful clinical practice.

In the following sections, a brief introduction into the relevant concepts is given. First, an overview on the highly prevalent neurodevelopmental disorder of ADHD is presented. Second, the symptom dimension of impulsivity and its transdiagnostic significance is introduced. Subsequently, the status quo of research on the neurobiological underpinnings of ADHD and impulsivity is reviewed. Then, the relevance of neuroscientific research in ADHD and impulsivity is presented taking into account the significance of developmental aspects. Finally, the importance of sufficient data quality as an essential prerequisite for clinical application of neuroscientific study results is highlighted.

1.1 ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

Known colloquially in Germany as the *Zappelphilipp-Syndrom* (Heinrich Hoffmann, *The Struwwelpeter*, 1845) for a long time, and first introduced in the Diagnostic and Statistical Manual of Mental Disorders in their 2nd edition (DSM-II) as *hyperkinetic reaction in childhood* in 1978, ADHD nowadays is one of the best known and most common neurodevelopmental disorders. Whereas, the very early focus was primarily on the overt, *socially inacceptable* symptoms of hyperactive and impulsive behavior in affected children, newer classification systems (since the 3rd edition of the DSM) acknowledge three equally relevant main symptom dimensions being

implicated in ADHD. These core symptoms comprise age-inappropriate levels of inattention, hyperactivity, and impulsivity (Biederman & Faraone, 2005). According to the 5th edition of the DSM (American Psychiatric Association, 2013), functional impairment due to six or more aspects related to those core symptoms needs to be present for more than 6 months and in more than one environment (e.g. home and school) already before the age of 12 years. Symptoms of inattention include aspects such as failing to give closer attention to details, being negligent in schoolwork or during other activities, showing difficulties sustaining attention in different tasks or activities, and encompassing difficulties in organizational skills. Further, the diagnostic criterion of impulsivity encompasses symptoms like being impatient with waiting the turn, blurring out answers before questions have been completed, interrupting or intruding on others, and engaging in risky activities. Finally, the symptom dimension of hyperactivity involves excessive energy, acting as if *driven by a motor*, often fidgeting with or taping hands or feet, squirming in seat, or interrupting conversations, for example. The DSM-5 differentiates between the predominantly inattentive, the predominantly hyperactive/impulsive, and the combined subtypes of ADHD. Therefore, within the diagnostic process, symptoms of hyperactivity and impulsivity are grouped and evaluated together along one dimension. Additionally, different levels of severity of the neurodevelopmental disorder are distinguished, namely mild, moderate or severe forms of the disease.

ADHD is associated with a significant social and educational disadvantage of the affected patients (Rowland et al., 2002; Swanson et al., 1998). Furthermore, with a prevalence of approximately 5% (Polanczyk et al., 2015) and a persistence rate of 30-40% into adulthood (Faraone et al., 2006), this externalizing disorder is highly common and has a substantial impact on health care systems worldwide. According to a European survey in 2013, estimated costs related to ADHD range between 9.860 and 14.483 Euros per patient per year (Le et al., 2014).

ADHD is affecting more boys than girls, with a ratio of approximately 3:1 (Wittchen et al., 2011). Further, ADHD patients often suffer from co-occurring

psychiatric conditions with high comorbidity rates of up to 75%. Thereby, the most frequent comorbid conditions are oppositional defiant disorder (ODD), conduct disorder (CD), learning disorders, and autism spectrum disorders (Jensen & Steinhausen, 2015).

In addition, ADHD represents a highly heritable disorder (Bonvicini et al., 2018), with 70% to 80% of variance being associated with genetic factors (Faraone et al., 2005). Neurochemical dysfunctions in dopaminergic, noradrenergic, and serotonergic neurotransmitter systems have been linked to the neurodevelopmental disorder (Banaschewski et al., 2010; Demontis et al., 2019; Franke et al., 2009; Hinney et al., 2011; Mick et al., 2010; Neale, Medland, Ripke, Anney, et al., 2010; Neale, Medland, Ripke, Asherson, et al., 2010). However, psychosocial factors such as the familial context and parenting behavior also play an important role and serve as moderators of those genetic factors (Nigg et al., 2010; Nikolas et al., 2015). Furthermore, pre- and perinatal environmental influences have been related to ADHD such as low birth weight (Franz et al., 2018; Lim et al., 2018), smoking during pregnancy (Holz et al., 2014), low family income, and prematurity (Sciberras et al., 2017). Nevertheless, these findings are rather correlative in nature due to a lack of experimental studies with longitudinal designs in the research field, not (yet) allowing for conclusions on causality in these relationships (for details, see Thapar et al., 2013). To date, consensus exists that multiple factors may contribute to the complex etiology of the externalizing disorder (Nigg et al., 2020).

With regard to the developmental course of ADHD, highly dynamic changes occur in the phenotypical presentation and the profile of ADHD symptoms from childhood to adulthood (for review, see Franke et al., 2018; van Lieshout et al., 2019). Whereas symptoms of inattention seem to persist into adulthood, there is a decline in overt hyperactive/impulsive behavior in patients diagnosed with childhood ADHD (Francx et al., 2015; Willcutt et al., 2012). Furthermore, throughout development comorbidity profiles and treatment responses change over time (e.g. Adler et al., 2017; Faraone et al., 2015; Fayyad et al., 2017). To date, it is not yet clear whether

ADHD should be interpreted as representing a developmental delay or whether it rather reflects a deviation from typical development or both (delay-deviation models for inhibition and attention, see also Doehnert et al., 2010; Shaw et al., 2007; Vaidya, 2012). Conditions of and factors influencing persistence versus remission in ADHD are still not fully understood (Caye et al., 2016; Pingault et al., 2015; Roy et al., 2016). In addition, recent longitudinal data question ADHD to necessarily be a childhood-onset neurodevelopmental disorder (e.g. Agnew-Blais et al., 2016; Moffitt et al., 2015).

Regarding therapy options, current guidelines recommend a multidimensional treatment approach in ADHD, addressing the psychological, behavioral, and occupational or educational needs of the individual patient and his or her family (National Institute for Health and Care Excellence, 2018). Thereby, a variety of pharmacological (e.g. methylphenidate) and non-pharmacological treatment strategies (such as cognitive behavioral therapy (CBT), and neurofeedback (NF)) are available that have previously been proven to be effective and tolerable in ADHD (for review, see De Crescenzo et al., 2017; Drechsler et al., 2020; Sonuga-Barke et al., 2013). Especially, treatment options targeting neuromodulation such as NF have been in the focus of research within the last few years. Results on their effectiveness have been rather mixed, depending on multiple factors that are not yet fully understood (e.g. Bussalb et al., 2019; Riesco-Matías et al., 2021; Van Doren et al., 2019).

Taken together, due to different subtypes and high rates of comorbid conditions ADHD represents a complex and heterogeneous diagnostic category with substantial variability on the phenotypic level (Luo et al., 2019). This heterogeneity subsequently leads to a higher complexity in ADHD diagnosis and treatment. The definition of diagnostic categories such as ADHD within classification systems has prominent clinical utility and a high relevance for health-care systems as well as for the implementation of adequate treatment strategies (First, 2005). However, to better address the complexity and disentangle the heterogeneity of the neurodevelopmental disorder and for a more detailed understanding of the associated neurobiological

underpinnings, a promising future research approach might be to more specifically focus on latent cognitive and behavioral (symptom) dimensions as suggested by the Research Domain criteria (RDoC) approach (Insel et al., 2010).

1.2 IMPULSIVITY – A DIMENSIONAL APPROACH

The above paragraphs focused on the diagnostic category of ADHD as proposed by classification systems with a nosology of mental disorders such as the DSM-5 (American Psychiatric Association, 2013). After having presented ADHD from a categorical perspective, the following section more specifically concentrates on impulsivity as a highly relevant externalizing symptom dimension, representing one of the core diagnostic criteria of ADHD. Adopting a dimensional perspective enables to focus on broad cognitive and behavioral domains (Insel et al., 2010). Those domains might be implicated across a range of different mental diseases, thereby representing potentially relevant transdiagnostic concepts. Consequently, this approach might give new insights that probably help to disentangle the heterogeneity found in previous studies on ADHD but also further impulsivity-related disorders (Robbins et al., 2012).

Broadly defined, impulsivity or impulsive behavior is reflected in actions without foresight that are poorly conceived, prematurely expressed, unnecessarily risky, and inappropriate to the demands of a given situation. Furthermore, long-term consequences of behavior are neglected, often resulting in undesirable outcomes (Bakhshani, 2014; Chamberlain & Sahakian, 2007; Moeller et al., 2001). In addition to detrimental effects on social interactions, interpersonal relationships, and on the overall sense of well-being, impulsivity can also lead to financial harm and legal problems. Individuals with high levels of impulsivity are more likely to engage in behaviors that could be dangerous to themselves or others, including driving recklessly, starting fights, shoplifting, perpetrating domestic violence, and trying to hurt or kill themselves. They are exposed to higher risk of lifetime trauma as well as to substantial physical and psychosocial impairment (Chamorro et al., 2012).

Impulsivity represents a fundamental dimension of healthy as well as clinically relevant, deviant human behavior. Given its involvement in a broad range of psychopathologies such as ADHD, Antisocial and Borderline Personality Disorder, suicidal and aggressive behaviors, pathological gambling, and diverse forms of addiction, impulsivity is as a transdiagnostically relevant symptom dimension (Bari & Robbins, 2013; Beauchaine et al., 2017; Martel et al., 2017).

Impulsivity has been investigated from various perspectives using different assessment methods and several rather heterogeneous definitions have been proposed in the literature (for overview, see Bakhshani, 2014). To date, no single comprehensive theory about impulsivity exists that units all different theoretical approaches (Dalley & Robbins, 2017). Therefore, impulsivity is typically defined as a multifaceted construct encompassing a broad variety of cognitive and behavioral dimensions (Chamberlain et al., 2018; Hasegawa et al., 2019; MacKillop et al., 2016). This broad conceptualization includes impulsive personality traits and further behavioral facets such as decisional components and motoric, action-related aspects. Impulsive personality traits represent the inherent and rather stable self-regulatory capacities of a person, typically assessed via self-reports. For decisional impulsivity, often also referred to as impulsive choice, three further sub-facets could be distinguished (Dalley & Robbins, 2017): temporal discounting, probabilistic discounting, and reflection impulsivity. Thereby, temporal discounting is defined as the preference for small, immediate rewards over later but larger ones. Probabilistic discounting is the preference for smaller but more likely rewards compared to larger but less likely ones. Reflection impulsivity describes the tendency for rapid decision-making without adequately taking into account all available situational evidence. Finally, motoric, action-related forms of impulsivity refer to impulsive behavior and the (in)ability to inhibit a prepotent motor response (inhibitory control). Those behavioral facets of impulsivity are typically measured via neuropsychological testing.

Depending on the facet of impulsivity, *cut-off* criteria assumed, and the specific assessment techniques used, *prevalence* rates of (high) impulsivity vary substantially. In the general population, impulsivity represents a rather common behavioral feature, particularly in males, younger individuals, and especially in adolescence (Chamorro et al., 2012). Furthermore, previous work showed that impulsivity is moderately heritable (Anokhin et al., 2015; Bevilacqua & Goldman, 2013; Coccaro et al., 1993; Niv et al., 2012). This finding is in parallel with the results obtained on heritability indices of impulsivity-related psychiatric disorders, probably due to a shared genetic basis (Hicks et al., 2004; Kendler et al., 2008). Again, depending on the latent facet(s) explored and the specific assessment method used, indices of genetic and (longitudinal) twin studies vary around 50%. In addition, major gender differences need to be taken into account: while in young adolescence heritability of risk-taking is moderate but significant in both sexes, during later adolescence, it increases in males and decreases to non-significant in females. These findings indicate that substantial maturational changes might occur for facets of impulsivity across the lifespan (e.g. Collado et al., 2014; Steinberg et al., 2008). Thereby, previous studies reported on a linear decrease in impulsivity scores from childhood through adolescence into adulthood (Shulman et al., 2016). However, developmental trajectories are still rather unclear, and for measurements of trait impulsivity earlier findings even indicate that they remain relatively stable over time (Amorim Neto & True, 2011). On the level of neurotransmitters, several alterations in monoaminergic signaling have been related to impulsivity with dopaminergic and serotonergic systems being primarily involved (Carver & Miller, 2006; Congdon & Canli, 2008; de Wit & Jentsch, 2020; Grant & Potenza, 2011; Hur & Bouchard, 1997; Kreek et al., 2005; Verdejo-García et al., 2008). Besides a substantial genetic influence, the relevance of further psychosocial factors cannot be neglected.

Regardless of whether a focus is set on ADHD as a diagnostic category or on the concept of impulsivity from a dimensional perspective, it is essential to identify related neurobiological underpinnings for a clearer and more detailed understanding

of typically-developing as well as deviant, clinically relevant human behavior (Jollans & Whelan, 2018). A combination of categorical and dimensional approaches might be very promising, especially with regard to understanding the common neurobiological underpinnings and underlying pathways of ADHD and impulsivity (Kuntsi et al., 2014; Shaw et al., 2011). Exploring the biological basis of psychiatric disorders and latent behavioral dimensions has a crucial relevance for clinical practice (Charney et al., 2013), as will be reviewed in section 1.3.3.

1.3 NEUROBIOLOGICAL CORRELATES OF ADHD AND IMPULSIVITY

Biological correlates or other objective criteria such as markers derived from neuropsychological testing with sufficient sensitivity and specificity could aid in reliably characterizing ADHD and impulsivity as well as identifying adequate treatment targets and (early) treatment needs on an individual basis (Snyder et al., 2015). Further, these objective criteria might be promising potential predictors of treatment outcome within a personalized-medicine framework. However, although various neural correlates have already been identified, objective and robust biomarkers are still lacking, not yet supporting clinical application (e.g. Dalley & Robbins, 2017; Lenartowicz & Loo, 2014; Lozupone et al., 2017). To date, the neurobiological and genetic underpinnings of ADHD and impulsivity are still under debate.

In the following sections, an overview of earlier neurobiological findings in ADHD and the multidimensional, ADHD-related trait of impulsivity is given. However, at first a relevant issue needs to be highlighted: in light of the fact that impulsivity represents a core diagnostic criterion of ADHD and a variety of further mental disorders, there exists an evident overlap between genes, neurotransmitter systems, and brain circuits involved in both, impulsivity and impulsivity-related disorders (Hicks et al., 2004; Kendler et al., 2008). Previous neuroscience studies either addressed the link between impulsivity and neurobiological markers in healthy samples without psychiatric diagnoses or explored neural associations

within patient categories. Conclusions from those latter studies might therefore be substantially influenced by confounding effects of other psychiatric symptom dimensions and further comorbidities. This needs to be taken into account when drawing conclusions from neuroscientific study results.

1.3.1 Neurophysiological correlates

Neurophysiological methods like EEG and event-related potentials (ERPs) are used to explore the neural dynamics and circuits related to human information processing and behavior (Farrens et al., 2020; Luck, 2014; Michel et al., 2009). Those techniques non-invasively assess brain-electric activity at a high time-resolution on the level of milliseconds (ms). They can easily be implemented in various study groups using electrodes that are placed on the scalp to measure summed neural activity from extrapyramidal neurons that are spatially aligned in the brain. Thereby, EEG/ERPs provide(s) unique insights into typical and deviant operations of the human mind. The EEG represents a very promising method, especially with regard to child and adolescent psychiatry, due to its ease of administration, its high tolerability, and the rather low costs associated with the implementation of this method.

During resting-EEG, the brain signal is dominated by oscillations in frequency bands ranging from slow delta (<3.5 Hz) and theta (3.5–7.5 Hz) via alpha (7.5–12.5 Hz) to faster beta (12.5–30 Hz) and gamma (30-100 Hz) band activity (Brandeis & Banaschewski, 2020; Michel et al., 2009). The spectral profile reflects maturational processes as well as arousal states (Drechsler et al., 2020). Typically, slow frequencies dominate during early childhood and slow-wave sleep, while an alpha peak characterizes the mature EEG in adults during a relaxed eyes-closed state (e.g. Chiang et al., 2011). In addition, adequate source models can link scalp topography to neural generators representing the sources of activity and distributed brain networks (Drechsler et al., 2020).

ERPs represent stimulus-locked time epochs in the task-related EEG in response to a sensory, motor or cognitive event (Luck, 2014). They reflect early sensory as well as later higher neurocognitive processes, thereby being able to distinguish between intact and compromised brain functions (Kamarajan & Porjesz, 2012).

1.3.1.1 Resting-EEG

Early resting-EEG studies suggested a robust association between ADHD status and markers of reduced attention, low arousal, and immaturity such as elevated power of slow-wave activity (theta) and decreased power of faster waves (beta), resulting in an increased theta/beta ratio (TBR; Drechsler et al., 2020). However, more recent work, some with substantially larger samples (Clarke et al., 2011; Liechti et al., 2013; Loo et al., 2009) and even review and meta-analytical approaches (Arns et al., 2013; Buyck & Wiersema, 2014; Saad et al., 2018), failed to replicate these findings (also for adult ADHD, see Kiiski et al., 2020). Instead, current studies indicate heterogeneous power deviations (e.g. Clarke et al., 2020; Loo et al., 2013). Even within large cluster analyses, no distinct resting-EEG features characterizing ADHD could be identified. Rather those results reflect the substantial heterogeneity of the ADHD phenotype with its various subgroups possibly diluting a potential diagnostic value of resting-EEG patterns for classification purpose (Loo et al., 2018). Regarding the developmental course of the resting-EEG in ADHD, earlier findings indicate relevant maturational processes from childhood through adolescence into adulthood (Clarke et al., 2019; Doehnert et al., 2010; Koehler et al., 2009; Liechti et al., 2013). When longitudinally compared to non-ADHD groups, ADHD patients show similar maturational effects in the resting-EEG across the lifespan, with a typical non-linear increase in delta and theta power for both groups, respectively (Buyck & Wiersema, 2014; Poil et al., 2014). Furthermore, whereas a significant normalization of child resting-EEG indices might occur in ADHD by young adulthood, other resting-EEG alterations remain persistent throughout the

developmental course. But findings are rather inconsistent, and markers of persistence versus remission are still lacking (Cheung et al., 2016). A recent systematic review in adult ADHD found strong support for elevated levels of absolute and relative theta activity when compared to non-ADHD groups (Adamou et al., 2020), in line with some findings in childhood ADHD. However, results are heterogeneous and besides demographic factors such as age, further methodological factors impact on resting-EEG findings and their value for differentiating between ADHD and non-ADHD groups such as, for example, the time context of the recording (Kitsune et al., 2015). Furthermore, as indicated by more recent results from Zhang and colleagues (Zhang et al., 2019), between-group effects increase over task time showing more elevated differences between ADHD and non-ADHD groups with a longer measurement duration, especially for theta activity. This result highlights the potential value of focusing on temporal profiles and dynamics when exploring spectral power in ADHD and the diagnostic value of the resting-EEG.

Studies on resting-EEG markers of impulsivity also found elevated levels of slow-wave (e.g. theta activity) and reduced fast-wave activity (e.g. beta activity) in normal and subclinical samples (Kamarajan & Porjesz, 2012). Especially, for the TBR robust effects were identified in previous literature (e.g. Lansbergen et al., 2007). Further, earlier work reported a higher anterior asymmetry in the resting-EEG signal related to impulsivity (e.g. Neal & Gable, 2019). However, results are rather inconsistent and other studies also failed to replicate those effects.

1.3.1.2 ERPs

In line with current psychological and neurobiological models of ADHD, results from ERP studies with their high time resolution primarily confirm impairments during preparation, attention, inhibition, action control as well as error, feedback, and reward processing in ADHD (Banaschewski & Brandeis, 2007; Drechsler et al., 2020). In patients with ADHD, the most robust finding is that the later attentional and inhibitory P300 components and the preparatory contingent

negative variation (CNV) are affected. Further, regulatory processes and reward processing are also compromised (Banaschewski et al., 2018; Barry et al., 2003). However, there is a substantial methodological heterogeneity across different ERP studies which hardly use the same tasks and measures making direct comparisons between studies rather difficult (Drechsler et al., 2020). Further, maturational effects on ERPs have been reported when comparing ADHD to non-ADHD groups, highlighting the need for also taking into account changes in developmental patterns across the lifespan. Whereas some ERP-alterations might show remission over time, other ADHD-related ERP-deviations rather persist into adulthood, despite possible alterations of their qualitative aspects (e.g. CNV and NoGo P300, Valko et al., 2009). Consequently, valid conclusions on classification accuracy and effect sizes for ERPs are currently rather limited (Gamma & Kara, 2016). There is an urgent need for a qualitative and quantitative review summarizing the status quo of the research field of ERPs in ADHD (Drechsler et al., 2020). Such an approach would also enable to address the heterogeneity in previous studies by explicitly modeling effects of relevant influence factors such as age and maturation.

For impulsivity, similar findings have been revealed in healthy as well as subclinical samples with ERP studies most prominently reporting on reduced P300 components as well as CNV-alterations (e.g. Brown et al., 1989; Fallgatter & Herrmann, 2001; Harmon-Jones et al., 1997). In addition, more recent studies using a variety of different tasks also found a higher Go/NoGo anteriorization, smaller error-related activity (as reflected by the feedback/error-related negativity component (FRN/ERN) and the error positivity (Pe) components; Onoda et al., 2010; Ruchsow et al., 2005), and a larger mismatch negativity (MMN) activity (Franken et al., 2005). However, further replication is needed addressing impulsivity-related ERPs in non-clinical as well as clinical samples.

1.3.2 Neuroimaging correlates

With its high spatial resolution, MRI provides detailed insights into brain structure such as for example gray matter volume (GMV), gray matter density (GMD), cortical thickness (CT) or white matter integrity (WMI). In addition, fMRI allows insights into human brain functioning and related neural sources (Huettel et al., 2004). Brain structural as well as functional deviations have previously been reported in (f)MRI studies to be implicated in ADHD and impulsivity.

1.3.2.1 Structural MRI

Regarding brain structural alterations in ADHD, a decreased total intracranial volume (Boedhoe et al., 2020; Hoogman et al., 2017) and a reduction of total brain size of around 3-5% (Ambrosino et al., 2017; Castellanos & Tannock, 2002; Durston et al., 2004) have been consistently found in previous studies (Samea et al., 2019). In addition, recent quantitative reviews suggest that this finding might be due to a decrease in the GMV of subcortical structures (Drechsler et al., 2020), especially in the nucleus accumbens, amygdala, caudate, hippocampus, and putamen but also in some cortical areas such as the prefrontal cortex, the parieto-temporal cortex, and the cerebellum (Castellanos & Swanson, 2002; Frodl & Skokauskas, 2012; Greven et al., 2015; Nakao et al., 2011; Valera et al., 2007). Thereby, effect sizes of subcortical reductions were slightly higher in children compared to adults (Hoogman et al., 2017). These brain alterations partly represent delayed developmental trajectories as they are most pronounced in childhood, suggesting a delayed maturation of specific cortical and subcortical areas. However, recent evidence proposes that some of the reported reductions still exist in adulthood (Ambrosino et al., 2017). Especially, some persistent reductions in frontal areas in a subgroup of ADHD patients with enduring symptoms into adulthood have been identified.

For the latent dimension of impulsivity, several brain-structural correlates have been identified in earlier work, distinguishing between different facets of the multidimensional construct. For trait impulsivity, GMV alterations in the anterior

cingulate cortex (ACC), medial frontal gyrus (MFG), dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), and putamen have been reported previously (Korponay et al., 2017; Mitchell & Potenza, 2014). For behavioral forms of impulsivity, structural deviations have been found for the PFC, OFC, ACC, frontal gyri, anterior insula, ventral-striatal areas, and for hippocampal regions. More recent studies also found relevant changes in the white matter microstructure via fractional anisotropy (FA) measures (Alfano et al., 2020), in CT (Miglin et al., 2019), and in cortical folding patterns (Hirjak et al., 2017) being related to facets of impulsivity. Consequently, multiple brain regions and characteristics might be implicated in impulsivity, and for some of those brain regions and indices specific associations with only some facets of impulsivity were found (Mitchell & Potenza, 2014). Therefore, it could be assumed that several cortical structures constitute a brain circuit relevant for impulsivity, with some of those structures being to a larger or minor extend involved in different latent facets of the construct. So far, developmental trajectories are rather unknown.

1.3.2.2 Functional MRI

Several alterations in specific functional networks in ADHD have been identified (Samea et al., 2019). Those neuronal networks are mainly involved in inhibition, attention processes, cognitive control, reward processing, working memory or resting-state. It has been shown that an inverse correlation of the default-mode network (DMN) and the cognitive-control networks is diminished or absent in children and adults with ADHD during rest (Castellanos et al., 2008; Posner et al., 2014; Sun et al., 2012; Sutcubasi et al., 2020). Further, studies found altered processing of attention and inhibition in fronto-basal ganglia circuits in ADHD. Meta-analyses consistently report on a hypo-activation of the fronto-parietal network for executive functions and the ventral attention system for attentional processes in children with ADHD (Cortese et al., 2012; Hart et al., 2013). In addition, as proposed by several models of ADHD, abnormal reward processing seems to be a central characteristic

involved in the etiology of the neurodevelopmental disorder (Sonuga-Barke, 2011; Tripp & Wickens, 2008). An abnormal sensitivity to reward might be due to a hypo-functioning of the dopaminergic system (Scheres et al., 2007). Besides other cortical and subcortical structures, abnormal activation has especially been reported for the ventral striatum (VS) during the early phase of reward anticipation (with a hypo-activation in ADHD; Plichta & Scheres, 2014). Some of the reported alterations in brain responses are rather persistent features of ADHD during the lifespan. However, others are specific to children and adolescents, therefore being characterized as developmentally-delayed (Drechsler et al., 2020).

A variety of functional brain correlates of impulsivity have been identified (Mitchell & Potenza, 2014). For trait impulsivity, the findings are characterized by substantial heterogeneity and studies were primarily conducted on psychiatric patients. Among other findings, previous studies in healthy participants reported on a hyper-activation in the VS during reward anticipation being associated with trait impulsivity (versus a VS-hypo-activation in ADHD; Plichta & Scheres, 2014). Regarding decisional impulsivity, functional deviations were found within the PFC, OFC, ventral-striatal areas, and within hippocampal regions (Dalley et al., 2008). Functional alterations related to behavioral forms of impulsivity were identified in the PFC, OFC, ACC, pre-supplementary motor area (pre-SMA), inferior frontal gyrus (IFG), frontal gyri, the anterior insula, and the striatum (basically the same areas as for structural alterations; Heinrich et al., 2013; Mitchell & Potenza, 2014). Further, differences in connectivity measures related to these brain regions were found (Korponay et al., 2017). Especially, trait impulsivity has been linked to measures of resting-state functional connectivity involving the VS and the OFC (Angelides et al., 2017). Developmental trajectories in the relationship between impulsivity and neurofunctional activity are still unclear.

In the following section, conclusions are drawn from the previously reported neurobiological findings in ADHD and impulsivity. In addition, the clinical relevance of neuroscientific studies for phenotypical characterization and treatment

planning in ADHD is highlighted. Further, the significance of developmental processes is discussed.

1.3.3 Relevance of neurobiological correlates and developmental aspects

A substantial amount of studies has already uncovered the neurobiological underpinnings of ADHD and the multidimensional construct of impulsivity as reviewed above. However, no single biomarker with sufficient sensitivity and specificity has been identified so far (Thome et al., 2012). This might be due to the detrimental heterogeneity and substantial complexity of the ADHD phenotype and the multidimensional nature of the impulsivity-construct (Luo et al., 2019). On the one hand, neurobiological measures have already clarified characteristics of and processes related to human behavior and diagnostic categories (e.g. for EEG, see Chen, Chen, et al., 2019). On the other hand, more replication studies are needed at this stage.

There still exist relevant gaps of knowledge within neuroscience research on ADHD and impulsivity. One highly important aspect that needs to be taken into account in future work is that neuroscientific studies should set a focus on developmental effects when exploring brain-behavior relationships (Franke et al., 2018; Thapar & Riglin, 2020). Especially, with regard to neurodevelopmental disorders, such as ADHD, it is highly warranted to analyse effects of age and maturation for a more detailed understanding of the disorder category (Nigg et al., 2020). So far, for many psychiatric disorders and behavioral (symptom) dimensions typical developmental trajectories across the lifespan are still rather unclear (Thapar & Riglin, 2020). For ADHD, highly dynamic maturational changes have been reported to occur in the phenotypical presentation of the neurodevelopmental disorder as well as on the neural level with regard to brain structure and function (Adler et al., 2017; Franke et al., 2018). More specifically, neural deviations have been linked to both, children and adults with ADHD, with some alterations being rather persistent from childhood into adulthood, in line with models assuming the

psychiatric disorder to represent a deviation from typical development (for an overview, see Franke et al., 2018, and see also section 1.3). However, other neural characteristics of ADHD, such as for example a reduced size of cortico-striatal brain areas, are rather specific to childhood age, in line with models discussing ADHD as representing a developmental delay (Rubia, 2007). Neurodevelopmental trajectories are still unknown and future longitudinal studies need to establish a link between maturational changes that occur on the phenotypical level and on a neural basis, respectively. Further studies are needed that examine age-(in)dependent associations between neurobiological markers with diagnostic status and psychiatric symptom dimensions (Thapar & Riglin, 2020). This would subsequently allow for better understanding the diagnostic value of neurobiological correlates, for identifying predictors of ADHD persistence, and for making use of those markers for clinical practice (Sudre et al., 2020).

So far, due to a lack of sufficient sensitivity and specificity of biomarker-candidates in previous studies, the relevance of neuroscience research on ADHD and impulsivity for daily health-care routine is rather restricted with regard to diagnosis and individualized treatment selection. Nevertheless, promising neuroscientific study results have been reported (Müller et al., 2020), and future work is urgently needed to replicate and expand previous findings. To this end, a developmental perspective is highly warranted to disentangle effects of maturation and diagnostic status or mental-health symptoms, especially with regard to neurodevelopmental disorders such as ADHD. This would enable a more detailed neurobiological description of behavioral symptom dimensions that helps to identify clinical relevance of biomarker-candidates, to implement preventive and tailored treatment strategies, and to evaluate treatment effectiveness (Halperin et al., 2012; Yahata et al., 2017). One essential prerequisite for clinical translation through applying neuroscientific study results in health-care routine is that study results are reliable and valid. Sufficient quality of neurobiological data assures that established research standards are met and results can be validly interpreted and applied for clinical

purpose. Therefore, the following section focuses on (EEG) data quality and its relevance in neuroscientific research.

1.3.4 Significance of neurobiological data quality

For neuroscience studies being applicable for clinical purpose it is essential that implemented brain-based measures reliably and validly reflect the neurobiological construct of interest rather than potential confounds. Contaminations due to noise produced by study-design factors, the specific samples explored, the procedure of recording or the subsequent signal-processing pipeline might negatively impact data quality minimizing and compromising the value of study results for clinical application (e.g. DiStefano et al., 2019). Specifically, data quality - typically defined as the signal-to-noise ratio - might vary substantially between studies, between participants within a study, and for different pre-processing methods (Kappenman & Luck, 2010; Pedroni et al., 2019). Subsequently, data quality probably impacts on results and, consequently, on conclusions derived from neuroscientific studies, with differences in data quality mimicking or diluting *true* effects in datasets. This might then lead to biased interpretations regarding the diagnostic or predictive value of explored biomarker-candidates. Especially, in child and adolescent psychiatry data quality should be taken into account as the study populations of interest are typically prone to substantial signal contaminations during measurements (Kappenman & Luck, 2010).

So far, only a few studies directly addressed the topic of data quality by explicitly analyzing the impact of study-specific variables on data contamination and further consequences with regard to subsequent (biomarker-)analyses (DiStefano et al., 2019). However, a sufficient level of data quality strengthens the basis of neuroscience research and improves interpretability of scientific results. Therefore, factors influencing data quality and subsequent effects on biomarker-analyses are of high interest for a reliable and valid translation of neuroscientific results into clinical routine.

1.4 HYPOTHESES

1.4.1 Earlier versus later ERPs in ADHD across the lifespan (study 1: meta-analysis)

As introduced in the section on neurophysiological correlates (1.3.1.2), a vast amount of neurophysiological studies has already been conducted on ERP differences between ADHD and non-ADHD samples with rather heterogeneous findings. Strikingly up to now, no quantitative synthesis on these studies has been conducted. To summarize the status quo of ERP research in ADHD, we did a meta-analysis with a special focus on differentiating between earlier and later ERP components. In line with previous psychological models of ADHD, we hypothesized that substantial differences between ADHD and non-ADHD groups would occur, especially for later ERPs related to higher cognitive functioning (in line with e.g. Kofler et al., 2019). Based on previous literature, we assumed smaller ERP amplitudes and shorter ERP latencies for most components of interest. A further aim was to explore the heterogeneity in earlier research findings and to address effects of age and maturation.

1.4.2 EEG data quality in ADHD children, adolescents, and adults (study 2: large-scale ADHD multicenter trial)

Further, in section 1.3.4 it was discussed that data quality represents an essential prerequisite for valid conclusions drawn from neuroscientific studies. We therefore explicitly analysed EEG data quality in a large ADHD cohort and a school-age non-ADHD control group, hypothesizing that study-specific variables might influence data quality and that data quality subsequently affects results obtained from spectral power analyses. Thereby, a special focus was on the impact of age and hyperactivity/impulsivity symptoms. We assumed that with decreasing age and increasing symptoms of hyperactivity/impulsivity data quality would decrease due to increased movement activity.

1.4.3 The multifaceted nature of impulsivity, developmental trajectories, and their neurofunctional correlates (study 3: longitudinal population-based cohort study)

Concentrating on trait impulsivity and decisional impulsivity including facets of temporal and probabilistic discounting (see review in paragraph 1.2), we hypothesized that associations between measurements of those dimensions would change across the critical developmental period from adolescence to young adulthood. Additionally, we assumed that measures of impulsivity are associated with neural brain activity during inhibitory control in the pre-SMA and the IFG and reward anticipation in the VS, respectively. Again, we expected developmental changes in those associations from adolescence to young adulthood, mainly driven by substantial changes on the level of neural processing. Specifically, based on previous findings (Plichta & Scheres, 2014), we hypothesized on a VS-hyper-activation being related to higher trait impulsivity in healthy young adult participants. Furthermore, we assumed predictive power of neurofunctional activity in adolescence for later trait and decisional impulsivity in young adulthood.

1.4.4 Developmental effects

In line with Thapar and Riglin (2020), a central aim across all studies was to analyse effects of age and maturation on behavioral symptoms, neurobiological correlates, as well as on data quality. Previous studies mainly relied on cross-sectional designs often exploring only one distinct age group (either children, adolescents or adults). The current work includes studies with cross-sectional designs including participants in childhood, adolescence, and young adulthood as well as a longitudinal design following up participants during the critical developmental period from adolescence into young adulthood. This enables the exploration of maturational trajectories. We thereby assumed distinct developmental effects on human brain maturation in childhood, adolescence, and young adulthood, subsequently affecting the diagnostic and predictive value of neurobiological markers for clinical application. More specifically, within our meta-analysis (study 1),

we expected more pronounced ERP differences between ADHD and non-ADHD groups for children compared to adolescents and adults for most of the ERP components (see also paragraph 1.3.1.2). Regarding our large multicenter trial in ADHD (study 2), we hypothesized on substantial effects of participants age on data quality, with increasing age being related to higher data quality, thereby subsequently affecting (reliability of) regular EEG analyses. For our longitudinal study including a population-based cohort assessed in adolescence and again in young adulthood (study 3), we further expected substantial developmental changes, especially on the neural level, leading to important changes in associations between brain-activity patterns and impulsivity. Specifically, substantial maturational changes were assumed for neural activity during reward processing (see paragraph 1.3.2.2).

2 EMPIRICAL STUDIES

2.1 STUDY 1: Earlier versus later cognitive event-related potentials (ERPs) in attention-deficit/hyperactivity disorder (ADHD): A meta-analysis

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Published as: Kaiser, A., Aggensteiner, P.-M., Baumeister, S., Holz, N. E., Banaschewski, T., & Brandeis, D. (2020). Earlier versus later cognitive event-related potentials (ERPs) in attention-deficit/hyperactivity disorder (ADHD): a meta-analysis. *Neurosci Biobehav Rev, 112*, 117-134. doi: 10.1016/j.neubiorev.2020.01.019

2.1.1 Abstract

The current meta-analysis summarizes relevant literature on earlier (P100, N100, P200, N200, ERN/Ne) versus later (P300, Pe, CNV) cognitive Event-Related Potential (ERP) differences between children, adolescents, and adults with Attention-Deficit/Hyperactivity Disorder (ADHD) and without ADHD (non-ADHD). Furthermore, the heterogeneity in previous research is addressed by analyzing potentially relevant demographic and methodological moderators (age group, IQ, medication, comorbidity, task, cognitive function, modality, inter-stimulus interval, number of electrodes). Via database search 52 relevant articles were identified including n=1576 ADHD and n=1794 non-ADHD. Using multilevel-models, pooled effect sizes were calculated. For earlier components, individuals with ADHD showed shorter Go-P100-latencies than non-ADHD. For later ERPs, individuals with ADHD showed smaller Cue-P300-amplitudes, longer Go-P300-latencies, smaller NoGo-P300-amplitudes, longer NoGo-P300-latencies, smaller CNV-amplitudes, and smaller Pe-amplitudes. The substantial heterogeneity identified for most of the ERP components could be explained by the demographic and methodological moderators of interest. This meta-analysis identified relevant moderate group differences ($-0.32<d<-0.57$), mainly regarding later cognitive ERPs. Nevertheless, results are characterized by substantial heterogeneity and the moderate effect sizes ($d<0.6$) limit the use for clinical application.

2.1.2 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders characterized by core symptoms of age-inappropriate levels of inattention, hyperactivity, and impulsivity (Biederman & Faraone, 2005; Taylor et al., 2004). With a prevalence of approximately 5 % (Polanczyk et al., 2015) and a persistence rate of 30–40 % into adulthood (Faraone et al., 2006), it is considered as a major public health problem due to the significant social and

educational disadvantage of the affected patients (Lesesne et al., 2000; Swanson et al., 1998).

Several findings have already emphasized the biological underpinnings of ADHD (Thome et al., 2012). The study of biological markers in individuals with ADHD represents an important path towards understanding the clinically and etiologically heterogeneous nature of this neurodevelopmental disorder and its therapeutic outcomes (Faraone et al., 2014). While no single reliable biomarker for the diagnosis of ADHD exists to date, some promising candidate brain-based biomarkers have been discussed (Gamma & Kara, 2016). For instance, Event-Related Potentials (ERPs) during response inhibition and response control have been widely examined in ADHD (Gamma & Kara, 2016; Johnstone et al., 2013; see Szuromi et al., 2011 for a quantitative review on adult ADHD P300-differences; Thome et al., 2012).

2.1.2.1 Previous findings on event-related potentials in ADHD

Cognitive ERPs represent stimulus-locked time epochs in the electroencephalogram (EEG). They offer a unique window into the brain and represent promising tools for exploring the biological basis of cognitive functioning in ADHD due to their ease of administration, their functional relevance, and their high time-resolution (Lenartowicz & Loo, 2014). As cognitive ERPs are defined by the time they occur after stimulus presentation in the task-related EEG, they can be divided into earlier (P100, N100, P200, N200, ERN/Ne) and later (P300, CNV, Pe) components reflecting the time course of task-related neural information-processing. For the current meta-analysis and in line with cognitive models of ADHD (e.g. Kofler et al., 2019), cognitive ERPs including sensory components with prominent cognitive modulation are in the focus of interest. Very early components reflecting mainly sensory processing, such as brain stem potentials or the P50 indexing sensory gating (e.g. Micoulaud-Franchi et al., 2015), were excluded. We also excluded the Mismatch Negativity (MMN) component that specifically assesses the integrity of automatic auditory-sensory memory and involuntary attentional switches outside the focus

cognitive tasks. This component had been analysed in a previous meta-analysis in children with ADHD (Cheng et al., 2016), suggesting a reduced MMN amplitude compared to children without ADHD. For a description of relevant ERP components addressed within the current analysis and their neuropsychological equivalent reflecting cognitive activation or modulation, see Table 1.

Several studies have documented robust neurophysiological differences between individuals with ADHD and individuals without ADHD (non-ADHD), especially for later ERPs, including lower NoGo-P300- amplitudes in individuals with ADHD over central regions during auditory and visual response-control tasks compared to non-ADHD children and adolescents, as well as reduced CNV-amplitudes in ADHD (e.g. reviewed in Barry et al., 2003). Regarding earlier ERPs during executive-control tasks, results are less consistent and more depending on potential influence variables: while several studies report on abnormalities of the N200-component (e.g. Albrecht et al., 2005; Pliszka et al., 2000; Tamayo-Orrego et al., 2015), others indicate that these only occur under specific task-conditions (e.g. Yong-Liang et al., 2000). Extensive research has examined ERP differences between individuals with ADHD and individuals without ADHD, but until now there is no quantitative summary of previous literature systematically analyzing ERPs as possible markers of ADHD across the lifespan capitalizing on the high time resolution of ERPs by specifically taking into account differences between effects on earlier and later cognitive ERPs.

2.1.2.2 Potential sources of heterogeneity

The partly inconsistent findings described above might reflect the substantial heterogeneity of patient samples with ADHD (Lenartowicz & Loo, 2014): individual characteristics, such as age, IQ, medication status, symptom severity or the presence of comorbid disorders might influence neurophysiological processing (Bresnahan et al., 1999; Loo et al., 2013). Furthermore, methodological variations between the studies might contribute to the heterogeneity in previous findings. These include the

specific task used to assess cognitive functioning, task-specific variations, such as the modality of stimulus presentation or the Inter-Stimulus-Interval (ISI) as well as technical, EEG-related between-study differences, such as the number of electrodes used to assess neurophysiological processing (e.g. Yong-Liang et al., 2000). To clarify the impact of demographic and methodological between-study differences, a systematic quantitative analysis on these potentially relevant moderator variables is urgently needed.

Based on previous qualitative and quantitative reviews (Gamma & Kara, 2016; Johnstone et al., 2013; Szuromi et al., 2011; Thome et al., 2012), a meta-analysis was conducted summarizing relevant literature on ERP differences in children, adolescents, and adults with ADHD compared to individuals without ADHD. The focus was on identifying group-level differences regarding earlier (P100, N100, P200, N200, ERN/Ne) versus later (P300, CNV, Pe) cognitive ERP components (amplitudes and latencies) during inhibitory control, attention, working memory, and performance monitoring using a quantitative approach. The main aim is to clarify when the most robust neurophysiological deviations occur in individuals with ADHD in the time course of cognitive processing covered by task-related ERPs. Generally, we assume smaller ERP components and longer ERP latencies in individuals with ADHD when compared to individuals without ADHD reflecting inefficient cognitive modulation in neuropsychological processing, especially during later processing-stages. Furthermore, the current work aimed at addressing the heterogeneity found in previous research by defining (based on previous studies) and analyzing (partly in an explorative way) potentially relevant demographic (age group, IQ, medication, comorbidities) and methodological (task, cognitive function assessed by task, modality of stimulus presentation, inter-stimulus-interval, number of electrodes used for analysis) moderators.

Table 1
Overview of ERP components and their mental processing correlates.

ERP component	Mental processing correlates
P100[1]	Spatial attention; gating to stimulus location (Luck et al., 2000)
N100[2]	Spatial attention; orienting response; matching processes with previously experiences stimuli; processing of unexpected stimuli (Luck et al., 1990)
P200[1]	Attention to/processing of visual stimuli; sensation-seeking (Sur & Sinha, 2009)
N200[2]	Processing of deviant stimuli; classification of stimulus (Sur & Sinha, 2009)
P300[1]	Stimulus processing & evaluation of task-relevance (Cortese, 2012); updating of working memory, event categorization, attentional resource allocation, and attentional reorientation (Polich, 2007)
CNV[2]	Stimulus expectation; motor and non-motor preprocessing after cue stimulus (Walter et al., 1964)
ERN/Ne[2]	Error detection; error correction (Coles & Rugg, 1995)
Pe[1]	Error processing (Nieuwenhuis et al., 2001)

Note. [1]positive wave/deflection; [2]negative wave/deflection.

2.1.3 Methods

2.1.3.1 Literature search and selection criteria

The current meta-analysis was registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018098992).

The literature search was performed in line with the PRISMA Statement (Moher et al., 2009), incorporating two different search strategies: An initial search was performed using the databases MEDLINE (via PubMed), PsychINFO, PsychARTICLES, Cochrane Central, and Clinical Trials. The subsequent keywords were entered: ADHD (separately) combined with EEG or ERP (for more detailed information, see Appendix A in Supplemental material 6.1). The literature search was started in January 2018 and originally finished in April 2018. An update of the literature search was done in April 2019, but no new studies were relevant for inclusion. Second, additional records were identified by reviewing the reference lists of the papers included via the database search.

All studies identified were screened and assessed for eligibility according to the following inclusion/exclusion criteria: (a) Reporting of quantitative data to compare ERP-markers of cognitive modulation between children, adolescents, and

adults with and without ADHD. (b) Administration of an EEG while participants engage in tasks involving inhibitory control, (selective) attention, working memory, and error monitoring to assess relevant ERPs. (c) Examination of a group of individuals without ADHD compared to children, adolescents, and/or adults with ADHD. (d) Formal diagnosis of ADHD according to only one of the following criteria: DSM-III-R, DSM-IV, DSM-IV-TR, DSM-V, or ICD-10 (refers to ADHD as hyperkinetic disorder; HKD). (e) Study in one of the following languages: English, German, French, or Spanish. (f) No case studies or review articles. (g) Published study between January 1987 (publication year of DSM-III-R) and April 2018. (h) Sufficient information to calculate the effect size. A total of 984 potentially relevant studies were identified.[1] Fig. 1 provides an overview of the search process and the number of records included through each of the before mentioned search strategies. Finally, the literature search resulted in 52 studies for inclusion (Tamayo-Orrego et al., 2015).[2] An asterisk in the reference list marks the included articles.

[1] After de-duplication.

[2] One further study had to be excluded as the type of ERP indices reported could not be integrated into quantitative analyses.

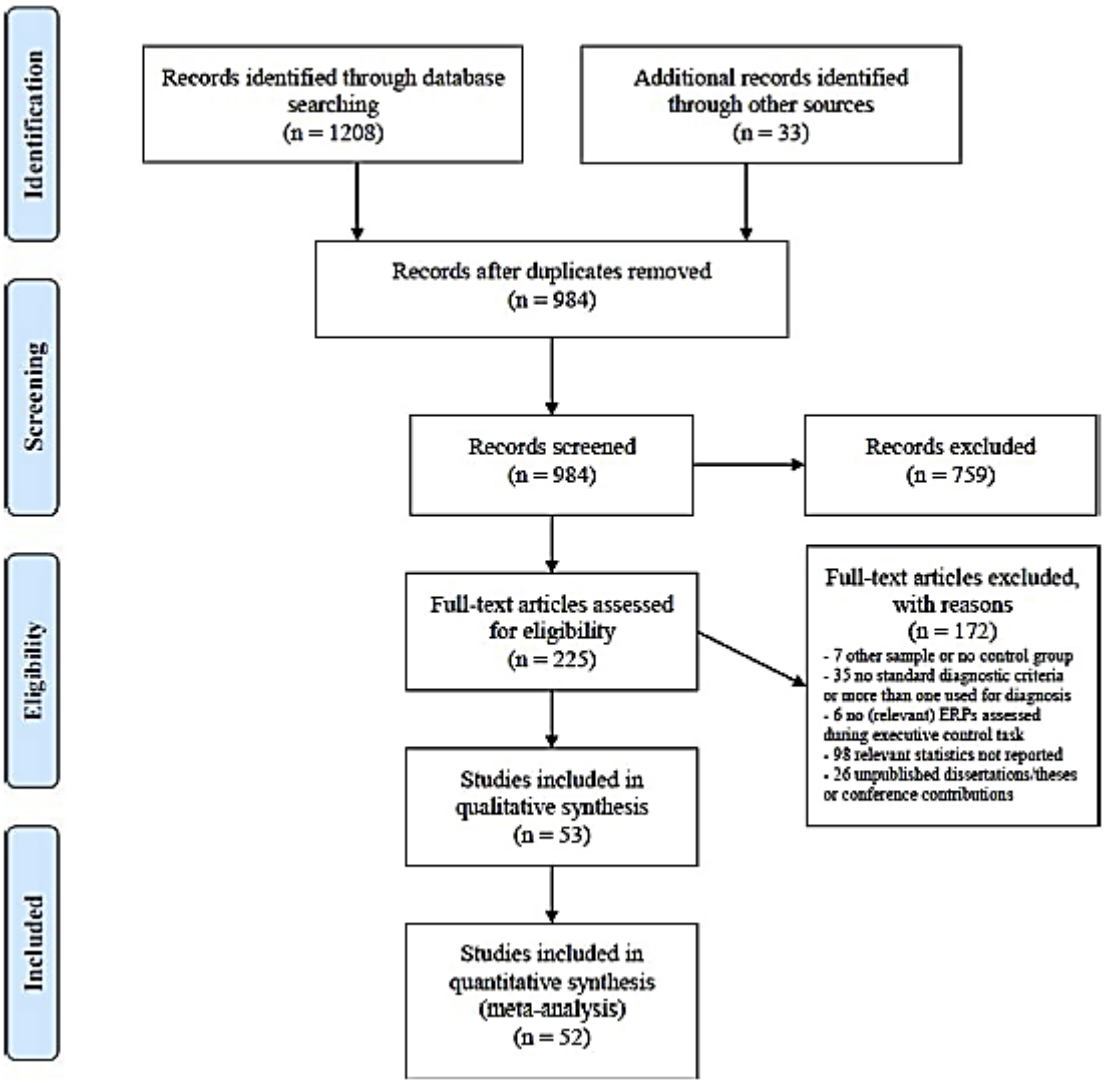

Figure 1. Flow chart displaying the literature selection process according to PRISMA guidelines (Moher et al., 2009).

2.1.3.2 Data coding

A coding sheet was implemented to record all relevant variables (see Appendix B in Supplemental material 6.1). The relevant information was extracted from the articles and coded by the first and second author, independently from each other. Disagreement (< 5 %) was resolved in discussion. The data sheets including the coded information used for subsequent analyses can be found in Appendix C in Supplemental material 6.1.

2.1.3.3 Statistical analyses

For all analyses conducted, the metafor package (Viechtbauer, 2010; metafor Version 2.0.0, released on 22/06/2017) for R (R Development Core Team, 2018; R

Version 3.5.1.) was used. The standardized mean difference (d) in ERP amplitudes[3] and latencies between individuals with and without ADHD was computed as the relevant effect size measure (ADHD minus non-ADHD; Hedges & Olkin, 1985). Effect sizes were not recoded to have all expected effects in the same direction. For amplitudes of positive ERPs, negative effect sizes indicate smaller amplitudes in the ADHD group compared to non-ADHD. For amplitudes of negative ERPs, positive effect sizes indicate smaller amplitudes in the ADHD group. For ERP latencies, positive mean effect sizes are associated with longer latencies in the ADHD group compared to non-ADHD. All effect sizes were calculated using exact statistics reported in the included studies. For each ERP component, a mean effect size was computed for the difference in amplitude and latency. Furthermore, effect sizes were calculated separately for each condition (Cue vs. Go vs. NoGo[4]) for the following ERP components: N100, P100, N200, P200, P300. Multilevel models based on random-effects assumptions were fitted to the data to estimate the true mean effect sizes. Random-effects models were chosen because they allow for unconditional inferences above the specific study implementations (Borenstein et al., 2010). Multilevel models were implemented to address dependencies due to a multilevel structure in the data (more than one ES per study in same analysis e.g. due to more than one age group or neural activity on more than one electrode location assessed; Viechtbauer, 2010). For the estimation of the mean effect sizes, studies were weighted using the heteroscedastic sampling variance. To explore moderator effects, mixed-effects models were fitted to the data.

As an indicator of heterogeneity, the chi-square statistic Q (Cochrane`s Q-test; Hedges & Olkin, 1985) was calculated. The Q_W statistic obtained in the moderator analyses represents the residual heterogeneity after taking into account a moderator

[3] Group mean amplitudes (of individual peak latencies, peak amplitudes or mean amplitudes) are included as dependent variables of interest, as they are commonly reported.

[4] Cue, Go, and NoGo represent different task conditions. Cue – Cue stimulus presented to signal upcoming task, typically before target or NoGo stimulus. Go – Target stimulus presented that requires response (e.g. motor). NoGo – Stimulus presented that requires to inhibit prepared or prepotent response (e.g. motor).

effect. The Q_B statistic refers to the test of a specific moderator. For estimating the amount of heterogeneity in the effect size distribution, the Restricted Maximum Likelihood (REML) estimator was used. Furthermore, sensitivity analyses were conducted to test for the robustness of effects. To address the potential presence of publication bias, trim-and-fill analyses were calculated.

2.1.4 Results

2.1.4.1 Study characteristics

Characteristics of the included studies can be found in Table S1 (Appendix D in Supplemental material 6.1). A summary of demographic study characteristics across all ERP components (P100, N100, P200, N200, P300, CNV, ERN/Ne, Pe), conditions (Cue versus Go versus NoGo), and dependent variables (amplitude versus latency) is presented in Table 2 (a summary of methodological characteristics can be found in Table S2; Appendix E in Supplemental material 6.1). Table S3 (Appendix E in Supplemental material 6.1) displays the relevant demographic characteristics separately for each ERP component, condition, and each dependent variable.

Table 2
Description of included trials: Demographic information (across all ERP components)

	ADHD	**Non-ADHD**	***t***	**df**	***p***
N	1576	1794	-	-	-
$n_{children}$	840	742			
$n_{adolescents}$	275	542			
n_{adults}	461	510			
Age (years), *M* (*SD*)	15.52 (8.53)	15.45 (8.16)	0.04	104	0.96
Male (%), *M* (*SD*)	82.26 (17.12)	74.90 (20.90)	1.91	92	0.06
IQ, *M* (*SD*)	103.06 (7.10)	110.14 (6.37)	-4.23	63	<.0001

Note. Results for Welch-two-sample t-test (between-group comparison)

2.1.4.2 Overall mean effects

Overall mean estimated effect sizes obtained from fitting multilevel models and corresponding heterogeneity estimates are presented in Table 3.

2.1.4.2.1 Cue condition

For the P300-amplitude, the analysis reveals a significant negative mean estimated effect size (*d*=-0.56 [-0.82 – (-0.30)]), indicating a smaller Cue-P300-amplitude in ADHD compared to non-ADHD. The P300-latency analysis resulted in a non-significant negative mean effect size. Fig. 2 displays the forest plot for the Cue-P300-amplitude[5].

2.1.4.2.2 Go condition

Significant mean estimated effect sizes were obtained for the P100-latency (*d*=-0.33 [-0.53 – (-0.13)]), and the P300-latency (*d*=0.52 [0.08 – 0.96]), indicating shorter Go-P100-latencies, and longer Go-P300-latencies in ADHD compared to non-ADHD. Regarding other ERP components, no significant group differences emerged. Figs. 3 and 4 show the forest plots for significant results obtained for the Go condition.

2.1.4.2.3 NoGo condition

The P300-amplitude (*d*= -0.57 [-0.90 – (-0.24)]) and the P300-latency components (*d*=0.35 [0.11 – 0.58]) resulted in significant mean group differences. For the P300-amplitude, the results indicate that individuals with ADHD overall present with smaller P300-amplitudes compared to non-ADHD. The P300-latency results reveal a significantly higher mean latency in ADHD compared to non-ADHD. For other NoGo-ERP components, the results did not reach significance. The forest plots for the significant NoGo condition results can be found in Figs. 5 and 6.

[5] Some studies provide more than one effect size for ERP analyses reflecting distinct demographic (e.g. more than one age group assessed) and methodological aspects (e.g. ERP assessed at several different electrode positions). See Appendix C for a detailed presentation of demographic and methodological characteristics.

Table 3
Overall mean estimated true effects sizes for random-effects models/multilevel linear models

	Amplitude				**Latency**			
ERP component	***k***	***d***	**[*95% CI*]**	***Q*W (*df, p*)**	***k***	***d***	**[*95% CI*]**	***Q*W (*df, p*)**
Cue trials								
P100	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*
N100	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*
P200	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*
N200	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*
P300	18	-0.56***	[-0.82 – (-0.30)]	22.04 (17, .18)	2	-0.35	[-0.80 – 0.10]	2.96 (1, .09)
Go trials								
P100	10	0.41	[-0.69 – 1.50]	61.80 (9, <.0001)	10	-0.33**	[-0.53 – (-0.13)]	8.28 (9, .51)
N100	14	-0.41	[-0.94 – 0.12]	68.41 (13, <.0001)	13	-0.03	[-0.40 – 0.34]	31.16 (12, .002)
P200	16	0.49	[-0.24 – 1.23]	95.68 (15, <.0001)	15	0.01	[-0.83 – 0.86]	106.20 (14, <.0001)
N200	48	0.14	[-0.08 – 0.35]	126.58 (47, <.0001)	31	-0.36	[-1.01 – 0.30]	140.36 (30, <.0001)
P300	76	-0.14	[-0.32 – 0.04]	216.96 (75, <.0001)	38	0.52*	[0.08 – 0.96]	201.33 (37, <.0001)
NoGo trials								
P100	2	-0.19	[-0.58 – 0.19]	0.01 (1, .93)	3	-0.13	[-0.48 – 0.22]	0.35 (2, .84)
N100	5	-0.11	[-0.38 – 0.17]	6.54 (4, .16)	6	0.04	[-0.22 – 0.30]	5.26 (5, .39)
P200	4	0.03	[-0.32 – 0.37]	7.63 (3, 0.05)	5	0.05	[-0.67 – 0.77]	10.65 (4, .03)
N200	16	0.08	[-0.19 – 0.36]	34.76 (15, .00)	5	-0.59	[-2.49 – 1.32]	38.52 (4, <.0001)
P300	37	-0.57***	[-0.90 – (-0.24)]	95.73 (36, <.0001)	9	0.35**	[0.11 – 0.58]	16.85 (8, .03)
CNV	15	0.32*	[0.03 – 0.61]	45.99 (14, <.0001)	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*
ERN/Ne	23	0.21	[-0.06 – 0.47]	69.52 (22, <.0001)	12	0.04	[-0.40 – 0.48]	26.02 (11, .01)
Pe	23	-0.39**	[-0.64 – (-0.13)]	58.33 (22, <.0001)	8	-0.01	[-0.40 – 0.39]	7.37 (7, .39)

Note. *** $p < .001$, ** $p < .01$, * $p < .05$, ° $p < .1$. *n.a. not available.*

2.1.4.2.4 CNV

A significant mean estimated effect size emerged for the CNV-amplitude (*d*=0.32 [0.03 – 0.61]), indicating smaller CNV-amplitudes in ADHD compared to non-ADHD. Fig. 7 shows the forest plot for the CNV amplitude component.

2.1.4.2.5 ERN/Ne, Pe

A significant mean group difference emerged for the Pe-amplitude (*d*=-0.39 [-0.64 – (-0.13)]), indicating smaller Pe-amplitudes in ADHD compared to non-ADHD. No further significant results could be obtained. Fig. 8 shows the forest plot for the Pe-amplitude component. The forest plots for all non-significant results can be found in Appendix F in Supplemental material 6.1. Furthermore, Appendix G in Supplemental material (see 6.1) presents the funnel plots for all ERP components, for amplitude and latency, respectively.

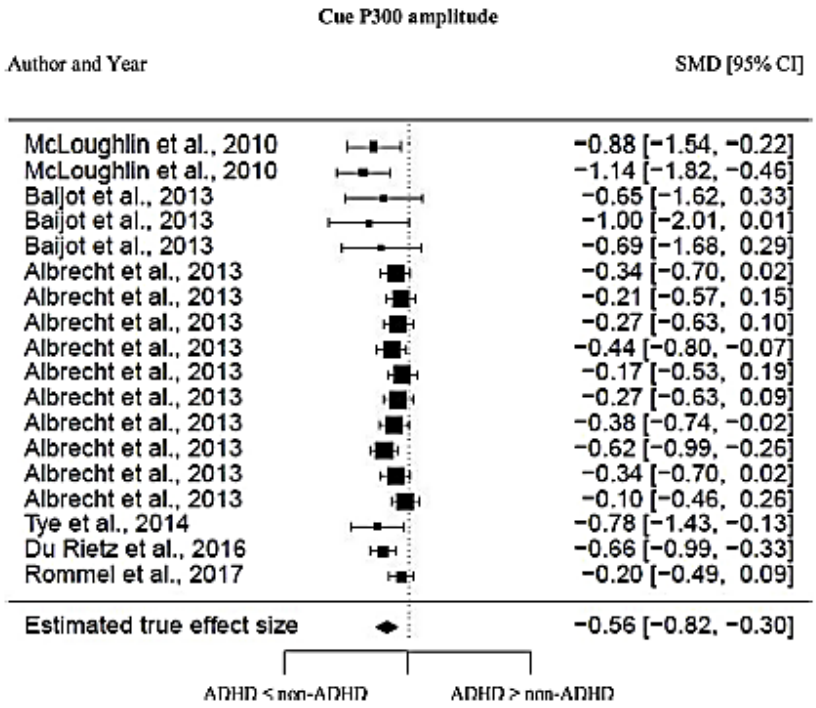

Figure 2. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to Cue P300 amplitude data and addressing multilevel structure. *Note.* Multiple listing of the same study reflect different electrode locations.

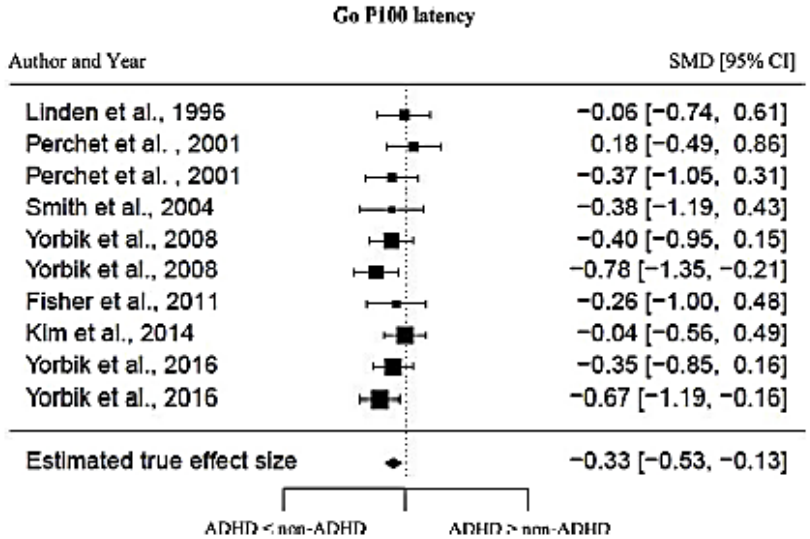

Figure 3. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to Go P100 latency data and addressing multilevel structure. *Note.* Multiple listing of the same study reflect different electrode locations.

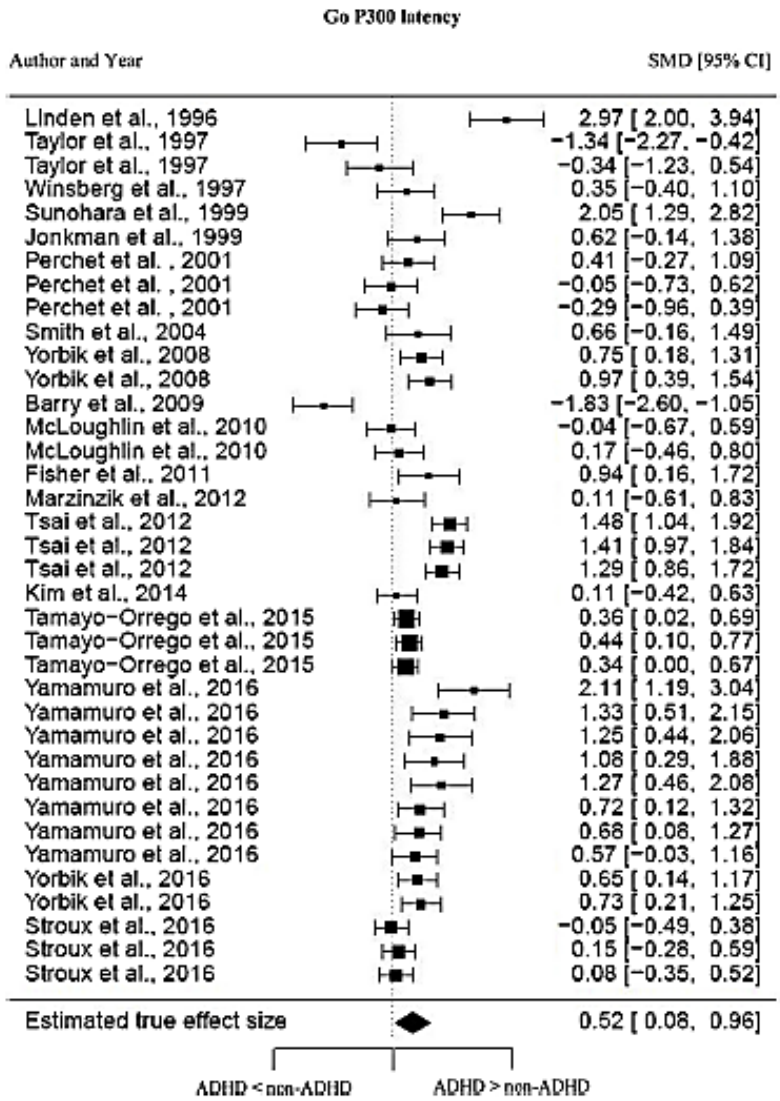

Figure 4. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to Go P300 latency data and addressing multilevel structure. *Note.* Multiple listing of the same study reflect different age groups (Taylor et al., 1997) or electrode locations.

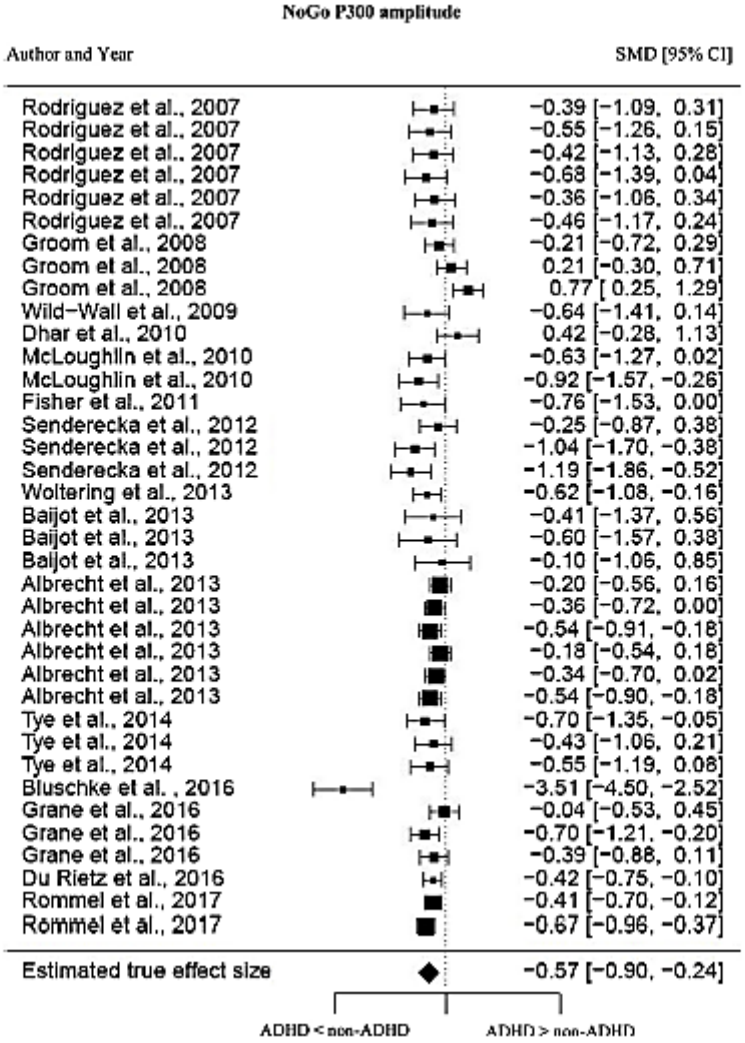

Figure 5. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to NoGo P300 amplitude data and addressing multilevel structure. *Note.* Multiple listing of the same study reflect different ADHD subtypes (Rodriguez & Baylis, 2007) or electrode locations.

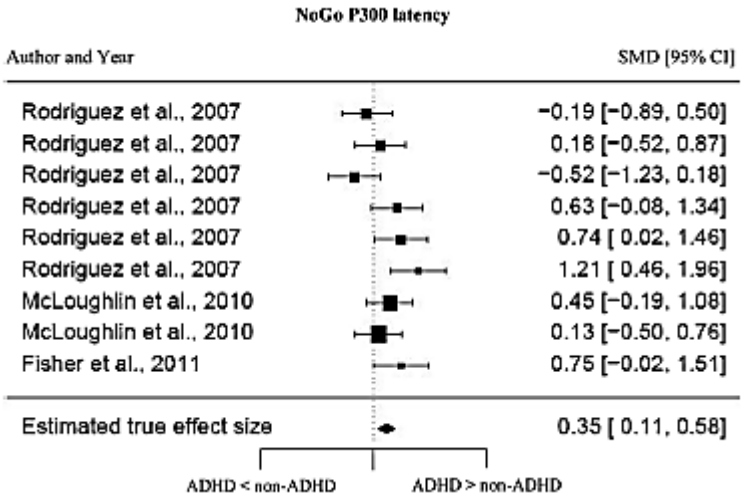

Figure 6. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to NoGo P300 latency data and addressing multilevel structure. *Note.* Multiple listing of the same study reflect different ADHD subtypes (Rodriguez & Baylis, 2007) or electrode locations.

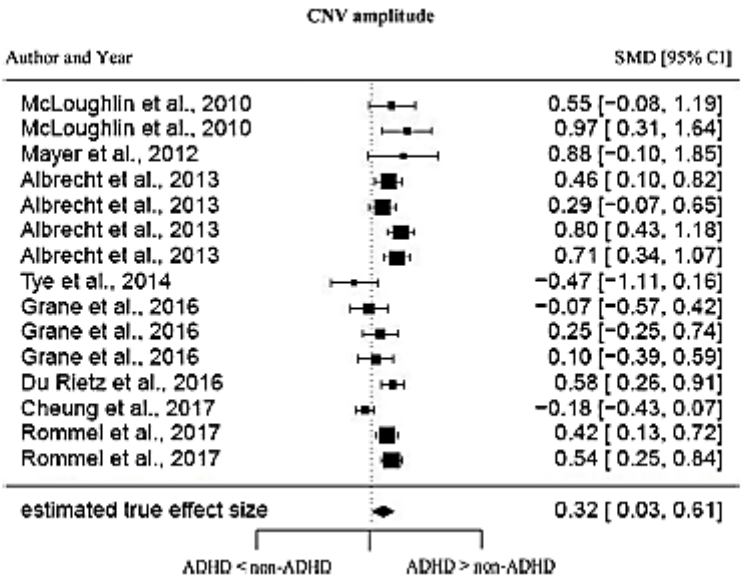

Figure 7. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to CNV amplitude data and addressing multilevel structure. *Note.* Multiple listing of the same study reflect different electrode locations.

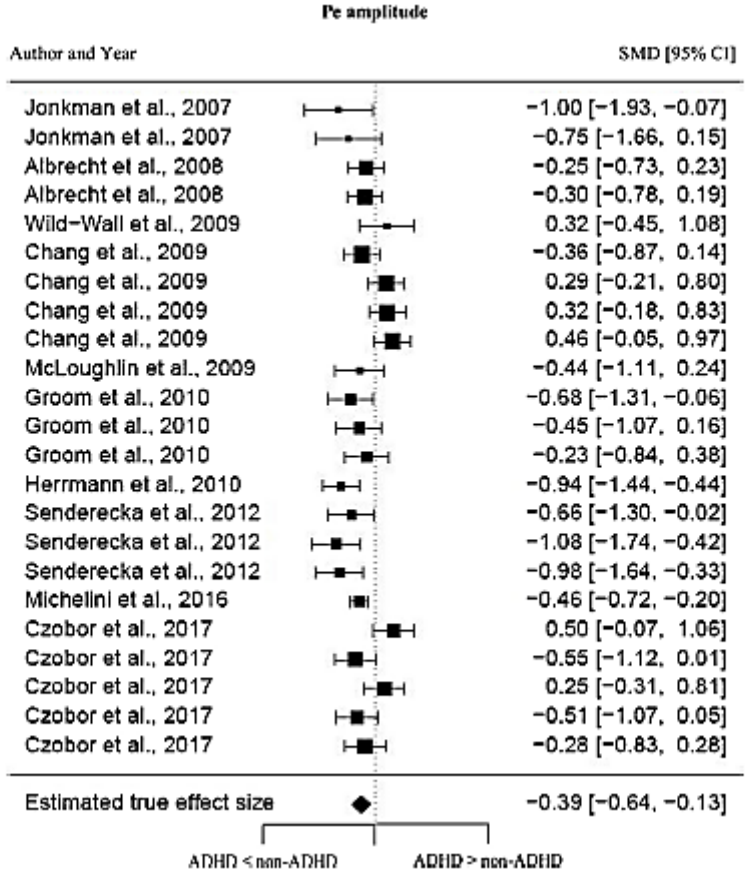

Figure 8. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to Pe amplitude data and addressing multilevel structure. *Note.* Multiple listing of the same study reflect different electrode locations.

2.1.4.3 Moderator effects

As suggested by the Q-statistics obtained in the overall analyses, there is substantial heterogeneity in the distribution of effect sizes. To explore this heterogeneity, moderator analyses were implemented. Due to a lack of reporting and many different scales used to assess ADHD symptom severity, no moderator analysis could be conducted on this potentially relevant influence variable. As can be seen from Tables 4a–4c and Tables 5a–5c, significant moderator results were identified for all moderator variables postulated. For all categorical moderators, subgroup-comparisons are presented within the tables.

2.1.4.3.1 Age

For age moderator analyses, larger mean effect sizes were identified in children compared to adolescents or adults for the NoGo-P300-amplitude ($Q_B(2)=12.84$, $p=.005$), the Pe-amplitude ($Q_B(3)=10.14$, $p=.02$), the Go-P100-latency ($Q_B(2)=13.55$, $p=.001$), the Go-P300- latency ($Q_B(2)=10.49$, $p=.005$), and the NoGo-N200-latency ($Q_B(2)=22.07$, $p < .0001$). For the Cue-P300-amplitude component on the contrary, largest mean effect sizes were obtained in adults ($Q_B(3)=19.62$, $p=.001$).

2.1.4.3.2 IQ

A (marginally) significant positive relationship emerged between IQ and the sizes of the effects for the Go-P200-latency ($Q_B(1)=2.71$, $p=.10$), Go-N200-latency ($Q_B(1)=3.29$, $p=.07$), Go-N100-amplitude ($Q_B(1)=5.48$, $p=.02$), NoGo-P200-latency ($Q_B(1)=7.27$, $p=.007$), Go-N100-latency ($Q_B(1)=9.17$, $p=.003$), NoGo-N200-latency, ($Q_B(1)=32.84$, $p < .0001$).

2.1.4.3.3 Medication status

A significant association between the medication status of the ADHD group and the mean size of the effect was obtained for the following components: NoGo-P300-latency ($Q_B(2)=7.46$, $p=.02$), NoGo-P300-amplitude ($Q_B(4)=13.31$, $p=.01$), Cue-P300-amplitude ($Q_B(4)=14.04$, $p=.003$), Go-P100-latency ($Q_B(2)=11.42$, $p=.003$), Go-N100-amplitude ($Q_B(3)=34.02$, $p < .0001$), and Pe-amplitude ($Q_B(4)=31.03$, $p < .0001$).

2.1.4.3.4 Comorbidity

For comorbidity, a significant influence on mean effect size was obtained for the Go-P300-latency ($Q_B(2)=6.58$, $p=.04$), the Pe-amplitude ($Q_B(2)=6.34$, $p=.04$), the Go-P100-latency ($Q_B(2)=7.69$, $p=.02$), the NoGo-N200-latency ($Q_B(2)=7.64$, $p=.02$), the NoGo-P300-amplitude ($Q_B(2)=41.17$, $p < .0001$), and the CNV-amplitude ($Q_B(2)=46.14$, $p < .0001$) component.

2.1.4.3.5 Task

A significant moderator effect for task was revealed for the following ERPs: NoGo-P300-latency ($Q_B(3)=7.94$, $p=.05$), Go-N100-latency ($Q_B(4)=10.26$, $p=.04$), CNV-amplitude ($Q_B(4)=9.85$, $p=.04$), NoGo-P300-amplitude ($Q_B(4)=10.77$, $p=.03$), Pe-amplitude ($Q_B(2)=8.26$, $p=.02$), Go-P100-latency ($Q_B(5)=17.36$, $p=.004$), and Cue-P300-amplitude ($Q_B(2)=17.11$, $p < .001$), with largest effect sizes for the CPT, the CPT-Flanker version, the Go/NoGo, and the Oddball task.

2.1.4.3.6 Cognitive function

The cognitive function moderator analysis resulted in significant effects for the the Go-N100-amplitude ($Q_B(2)=6.42$, $p=.04$), the NoGo-P300-latency ($Q_B(2)=7.46$, $p=.02$), and the Pe-amplitude ($Q_B(2)=8.24$, $p=.02$), the Go-P100-latency ($Q_B(3)=12.68$, $p=.005$), the NoGo-P300-amplitude ($Q_B(2)=11.12$, $p=.004$), Cue-P300-amplitude ($Q_B(2)=18.05$, $p=.0001$), indicating especially large effect sizes for tasks assessing inhibition.

2.1.4.3.7 Modality

Regarding the modality of stimulus presentation, significant moderator effects were obtained for the following components: NoGo-P300-amplitude ($Q_B(9)=9.57$, $p=.02$), NoGo-P300-latency ($Q_B(2)=9.74$, $p=.008$), Pe-amplitude ($Q_B(2)=12.62$, $p=.002$), Go-P100-latency ($Q_B(2)=15.39$, $p=.001$), Go-P300-latency ($Q_B(3)=15.84$, $p=.0001$), with large effect sizes for auditory stimuli compared to visual stimuli for the Go-P100-latency, the Go-P300-latency, theNoGo-P300-amplitude, and the NoGo-P300-latency.

2.1.4.3.8 ISI

A significant moderator effect of the ISI on mean effect size was revealed for the Go-N200-amplitude ($Q_B(1)=5.86$, $p=.02$), the Pe-latency ($Q_B(1)=6.83$, $p=.009$), the CNV-amplitude ($Q_B(1)=8.30$, $p=.004$), and the Go-N100-latency ($Q_B(1)=14.26$, $p=.0002$), all indicating a small positive relationship between the length of the inter-stimulus-interval in the task and the size of the mean group difference.

2.1.4.3.9 Number of electrodes

For the NoGo-P200-latency ($Q_B(1)=6.600$, $p=.01$), a significant positive moderator effect could be obtained, indicating larger effect sizes with a higher number of electrodes used for the EEG assessment. On the other hand, for the Go-N100-amplitude ($Q_B(1)=7.57$, $p=.006$) a significant negative effect of the moderator was identified: a higher number of electrodes is associated with smaller effect size.

Table 4
Summary of meta-analytic findings for **amplitude** moderator analyses (mixed-effects models fitted) – P100, N100, P200

	Cue				Go				NoGo			
Amplitude	**k**	**Q_B(df, *p*)**	**Q_W(df, *p*)**	**Comparison**	**k**	**Q_B(df, *p*)**	**Q_W(df, *p*)**	**Comparison**	**k**	**Q_B(df, *p*)**	**Q_W(df, *p*)**	**Comparison**
P100												
age	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
IQ	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
medication	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
comorbidity	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
task	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
cogn. function	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
modality	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
ISI	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
electrodes	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
N100												
age	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
IQ	*n.a.*	*n.a.*	*n.a.*	*n.a.*	8	5.48 (1,.02)	30.67 (6, <.0001)	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
medication	*n.a.*	*n.a.*	*n.a.*	*n.a.*	14	34.02 (3, <.0001)	28.67 (11,.003)	2 < 3 < 1*** (neg)	*n.a.*	*n.a.*	*n.a.*	*n.a.*
comorbidity	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
task	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
cogn. function	*n.a.*	*n.a.*	*n.a.*	*n.a.*	14	6.42 (2, .04)	59.13 (12, <.0001)	2 < 1* (neg)	*n.a.*	*n.a.*	*n.a.*	*n.a.*
modality	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
ISI	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
electrodes	*n.a.*	*n.a.*	*n.a.*	*n.a.*	14	7.57 (1, .006)	54.05 (12, <.0001)	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
P200											.	
age	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
IQ	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
medication	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
comorbidity	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
task	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
cogn. function	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
modality	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
ISI	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
electrodes	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*

Note. n.a. not available. *n.s.* not significant. Pos – positive ES. Neg – negative ES. Medication moderator: 1 – medicated; 2 – not medicated; 3 – washout period of 24h; 4 – washout period of 48h. Comorbidity moderator: 1 – yes, comorbid disorder present; 2 – no, no comorbid disorder present. Cognitive function moderator: 1 – Inhibition; 2 – Attention; 3 – Working memory; 4 – Error processing. Modality moderator: 1 – visual; 2 – auditory; 3 – multimodal.

Table 4 (continued)

Summary of meta-analytic findings for **amplitude** moderator analyses (mixed-effects models fitted) –N200, P300

	Cue			Go				NoGo			
Amplitude	**k**	**Q_B(df, *p*)**	**Q_W(df, *p*)**	**Comparison**	**k**	**Q_B(df, *p*)**	**Q_W(df, *p*)**	**Comparison**	**k**	**Q_B(df, *p*)**	**Q_W(df, *p*)**	**Comparison**
N200												
age	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
IQ	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
medication	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
comorbidity	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
task	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
cogn. function	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
modality	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
ISI	*n.a.*	*n.a.*	*n.a.*	*n.a.*	40	5.86 (1, .02)	60.19 (38, .01)	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
electrodes	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
P300												
age	18	19.62 (3, .001)	14.81 (15, 0.47)	Adolescents* < Children** < Adults** (neg)	*n.s.*	*n.s.*	*n.s.*	*n.a.*	37	12.84 (3, .005)	92.85 (34, <.0001)	Adolescents < Adults < Children** (neg)
IQ	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
medication	18	14.04 (3, .003)	16.46 (15, 0.35)	2 < 4** < 1° (neg)	*n.s.*	*n.s.*	*n.s.*	*n.a.*	35	13.31 (4, .01)	80.40 (31, <.0001)	3 < 2 < 4 < 1** (neg)
comorbidity	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	25	41.17 (2, <.0001)	21.54 (23, <0001)	1** < 2*** (neg)
task	18	17.11 (2, <.001)	21.74 (16, 0.15)	2*** > 1*** (neg)	*n.s.*	*n.s.*	*n.s.*	*n.a.*	37	10.77 (4, .03)	93.92 (33, <.0001)	1 < 2 < 13 < 3** (neg)
cogn. function	18	18.05 (2, .0001)	16.99 (16, 0.39)	2*** < 1 (neg)	*n.s.*	*n.s.*	*n.s.*	*n.a.*	37	11.12 (2, .004)	94.49 (35, <.0001)	2 < 1** (neg)
modality	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	37	9.57 (3, .02)	90.92 (34, <.0001)	1** < 2 < 3 (neg)
ISI	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
electrodes	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*

Note. n.a. not available. *n.s.* not significant. Pos – positive ES. Neg – negative ES. Medication moderator: 1 – medicated; 2 – not medicated; 3 – washout period of 24h; 4 – washout period of 48h. Comorbidity moderator: 1 – yes, comorbid disorder present; 2 – no, no comorbid disorder present. Cognitive function moderator: 1 – Inhibition; 2 – Attention; 3 – Working memory; 4 – Error processing. Modality moderator: 1 – visual; 2 – auditory; 3 – multimodal.

Table 4 (continued)

Summary of meta-analytic findings for **amplitude** moderator analyses (mixed-effects models fitted) – CNV, ERN/Ne, Pe

Amplitude	k	Q_B(df, *p*)	Q_W(df, *p*)	Comparison
CNV				
age	*n.s.*	*n.s.*	*n.s.*	*n.a.*
IQ	*n.s.*	*n.s.*	*n.s.*	*n.a.*
medication	*n.s.*	*n.s.*	*n.s.*	*n.a.*
comorbidity	9	46.14 (2, <.0001)	6.96 (7, .43)	2*** < 1 (pos)
task	15	9.85 (4, .04)	18.57 (11, .07)	1 (pos) < 7 (neg) < 3 (pos) < 2*
cogn. function	*n.s.*	*n.s.*	*n.s.*	*n.a.*
modality	15	5.57 (2, .06)	44.87 (13, <.0001)	1° < 2 (pos)
ISI	14	8.30 (1, .004)	17.18 (12, .14)	*n.a.*
electrodes	*n.s.*	*n.s.*	*n.s.*	*n.a.*
ERN/Ne				
age	*n.s.*	*n.s.*	*n.s.*	*n.a.*
IQ	*n.s.*	*n.s.*	*n.s.*	*n.a.*
medication	*n.s.*	*n.s.*	*n.s.*	*n.a.*
comorbidity	*n.s.*	*n.s.*	*n.s.*	*n.a.*
task	*n.s.*	*n.s.*	*n.s.*	*n.a.*
cogn. function	*n.s.*	*n.s.*	*n.s.*	*n.a.*
modality	*n.s.*	*n.s.*	*n.s.*	*n.a.*
ISI	*n.s.*	*n.s.*	*n.s.*	*n.a.*
electrodes	*n.s.*	*n.s.*	*n.s.*	*n.a.*
Pe				
age	23	10.14 (3, .02)	50.16 (20, .0002)	Adolescents < Adults° < Children** (neg)
IQ	*n.s.*	*n.s.*	*n.s.*	*n.a.*
medication	22	31.03 (4, <.0001)	29.01 (18, .05)	1 (pos) < 4** < 3** < 2* (neg)
comorbidity	19	6.34 (2, .04)	44.53 (17, .0003)	1 < 2* (neg)
task	23	8.26 (2, .02)	57.17 (21, <.0001)	13* < 3* (neg)
cogn. function	23	8.24 (2, .02)	53.45 (21, <.0001)	4* < 1 (neg)
modality	23	12.62 (2, .002)	47.73 (21, .0007)	1* < 3* (neg)
ISI	*n.s.*	*n.s.*	*n.s.*	*n.a.*
electrodes	*n.s.*	*n.s.*	*n.s.*	*n.a.*

Note. n.a. not available. *n.s.* not significant. Pos – positive ES. Neg – negative ES. Medication moderator: 1 – medicated; 2 – not medicated; 3 – washout period of 24h; 4 – washout period of 48h. Comorbidity moderator: 1 – yes, comorbid disorder present; 2 – no, no comorbid disorder present. Cognitive function moderator: 1 – Inhibition; 2 – Attention; 3 – Working memory; 4 – Error processing. Modality moderator: 1 – visual; 2 – auditory; 3 – multimodal.

Table 5
Summary of meta-analytic findings for **latency** moderator analyses (mixed-effects models fitted) – P100, N100, P200

	Cue				Go				NoGo			
Latency	**k**	**Q_B(df, *p*)**	**Q_W(df, *p*)**	**Comparison**	**k**	**Q_B(df, *p*)**	**Q_W(df, *p*)**	**Comparison**	**k**	**Q_B(df, *p*)**	**Q_W(df, *p*)**	**Comparison**
P100												
age	*n.a.*	*n.a.*	*n.a.*	*n.a.*	10	13.55 (2, .001)	6.92 (8, 0.55)	Adults < Children*** (neg)	*n.s.*	*n.s.*	*n.s.*	*n.a.*
IQ	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
medication	*n.a.*	*n.a.*	*n.a.*	*n.a.*	8	11.42 (2, .003)	5.70 (6, .46)	3 < 2** (neg)	*n.s.*	*n.s.*	*n.s.*	*n.a..*
comorbidity	*n.a.*	*n.a.*	*n.a.*	*n.a.*	4	7.69 (2, .02)	1.13 (2, .57)	1 < 2** (neg)	*n.s.*	*n.s.*	*n.s.*	*n.a.*
task	*n.a.*	*n.a.*	*n.a.*	*n.a.*	10	17.36 (5, .004)	3.12 (5, .68)	11 < 5 < 10 < 3 < 6*** (neg)	*n.a.*	*n.a.*	*n.a.*	*n.a.*
cogn. function	*n.a.*	*n.a.*	*n.a.*	*n.a.*	10	12.68 (3, .005)	6.73 (7, .46)	3 < 1 < 2*** (neg)	*n.a.*	*n.a.*	*n.a.*	*n.a.*
modality	*n.a.*	*n.a.*	*n.a.*	*n.a.*	10	15.39 (2, .001)	5.09 (8, .75)	1 < 2*** (neg)	*n.s.*	*n.s.*	*n.s.*	*n.a.*
ISI	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
electrodes	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
N100												
age	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
IQ	*n.a.*	*n.a.*	*n.a.*	*n.a.*	8	9.17 (1, .003)	7.90 (6,.25)	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
medication	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a..*
comorbidity	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
task	*n.a.*	*n.a.*	*n.a.*	*n.a.*	13	10.26 (4, .04)	14.26 (9, .11)	5 < 1 < 3 (neg) < 6* (pos)	*n.s.*	*n.s.*	*n.s.*	*n.a.*
cogn. function	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
modality	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	
ISI	*n.a.*	*n.a.*	*n.a.*	*n.a.*	9	14.26 (1, .0002)	7.40 (7, .39)	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
electrodes	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
P200												
age	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a..*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
IQ	*n.a.*	*n.a.*	*n.a.*	*n.a.*	12	2.71 (1, .10)	37.90 (10, < .0001)	*n.a.*	4	7.27 (1, .007)	3.14 (2, 0.21)	*n.a.*
medication	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a..*	*n.s.*	*n.s.*	*n.s.*	*n.a..*
comorbidity	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
task	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
cogn. function	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
modality	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
ISI	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
electrodes	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	5	6.60 (1, .01)	4.06 (3, 0.26)	*n.a.*

Note. n.a. not available. *n.s.* not significant. Pos – positive ES. Neg – negative ES. Medication moderator: 1 – medicated; 2 – not medicated; 3 – washout period of 24h; 4 – washout period of 48h. Comorbidity moderator: 1 – yes, comorbid disorder present; 2 – no, no comorbid disorder present. Cognitive function moderator: 1 – Inhibition; 2 – Attention; 3 – Working memory; 4 – Error processing. Modality moderator: 1 – visual; 2 – auditory; 3 – multimodal.

Table 5 (continued)

Summary of meta-analytic findings for **latency** moderator analyses (mixed-effects models fitted) –N200, P300

	Cue				Go				NoGo			
Latency	**k**	**Q_B(df, *p*)**	**Q_W(df, *p*)**	**Comparison**	**k**	**Q_B(df, *p*)**	**Q_W(df, *p*)**	**Comparison**	**k**	**Q_B(df, *p*)**	**Q_W(df, *p*)**	**Comparison**
N200												
age	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	5	22.07 (2, <.0001)	6.77 (3, .08)	Adults (pos) < Children*** (neg)
IQ	*n.a.*	*n.a.*	*n.a.*	*n.a.*	13	3.29 (1, .07)	14.92 (11, .19)	*n.a.*	3	32.84 (1, <.0001)	0.02 (1, 0.88)	*n.a.*
medication	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a..*	*n.s.*	*n.s.*	*n.s.*	*n.a..*
comorbidity	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	4	7.64 (2, .02)	1.00 (2, 0.61)	1 (neg) < 2** (pos)
task	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
cogn. function	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
modality	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
ISI	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
electrodes	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
P300												
age	*n.a.*	*n.a.*	*n.a.*	*n.a.*	38	10.49 (2, .005)	156.35 (36, <.0001)	Adults (neg) < Children*** (pos)	*n.a.*	*n.a.*	*n.a.*	*n.a.*
IQ	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*
medication	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	9	7.46 (2, .02)	16.75 (7, .02)	4 < 3* (pos)
comorbidity	*n.a.*	*n.a.*	*n.a.*	*n.a.*	15	6.58 (2, .04)	35.71 (13, .0007)	2 < 1* (pos)	*n.a.*	*n.a.*	*n.a.*	*n.a.*
task	2	5.25 (2, .07)	0.00 (0, 1.00)	1 (positive) < 2* (negative)	*n.s.*	*n.s.*	*n.s.*	*n.a.*	9	7.94 (3, .05)	16.26 (6, .01)	2 < 3* < 1 (pos)
cogn. function	*n.a.*	*n.a.*	*n.a.*		*n.s.*	*n.s.*	*n.s.*	*n.a.*	9	7.46 (2, .02)	16.75 (7, .02)	2 < 1* (pos)
modality	*n.a.*	*n.a.*	*n.a.*	*n.a.*	38	15.84 (3, .0001)	113.69 (35, <.0001)	1 (pos) < 3 (neg) < 2*** (pos)	9	9.74(2, .008)	15.69 (7, .03)	1* < 2° (pos)
ISI	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*
electrodes	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*	*n.s.*	*n.s.*	*n.s.*	*n.a.*

Note. n.a. not available. *n.s.* not significant. Pos – positive ES. Neg – negative ES. Medication moderator: 1 – medicated; 2 – not medicated; 3 – washout period of 24h; 4 – washout period of 48h. Comorbidity moderator: 1 – yes, comorbid disorder present; 2 – no, no comorbid disorder present. Cognitive function moderator: 1 – Inhibition; 2 – Attention; 3 – Working memory; 4 – Error processing. Modality moderator: 1 – visual; 2 – auditory; 3 – multimodal.

Table 5 (continued)

Summary of meta-analytic findings for **latency** moderator analyses (mixed-effects models fitted) – CNV, ERN/Ne, Pe

Latency	k	Q_B(df, *p*)	Q_W(df, *p*)	Comparison
CNV				
age	*n.a.*	*n.a.*	*n.a.*	*n.a.*
IQ	*n.a.*	*n.a.*	*n.a.*	*n.a.*
medication	*n.a.*	*n.a.*	*n.a.*	*n.a.*
comorbidity	*n.a.*	*n.a.*	*n.a.*	*n.a.*
task	*n.a.*	*n.a.*	*n.a.*	*n.a.*
cogn. function	*n.a.*	*n.a.*	*n.a.*	*n.a.*
modality	*n.a.*	*n.a.*	*n.a.*	*n.a.*
ISI	*n.a.*	*n.a.*	*n.a.*	*n.a.*
electrodes	*n.a.*	*n.a.*	*n.a.*	*n.a.*
ERN/Ne				
age	*n.s.*	*n.s.*	*n.s.*	*n.a.*
IQ	*n.s.*	*n.s.*	*n.s.*	*n.a.*
medication	*n.s.*	*n.s.*	*n.s.*	*n.a.*
comorbidity	*n.s.*	*n.s.*	*n.s.*	*n.a.*
task	*n.s.*	*n.s.*	*n.s.*	*n.a.*
cogn. function	*n.a.*	*n.a.*	*n.a.*	*n.a.*
modality	*n.a.*	*n.a.*	*n.a.*	*n.a.*
ISI	*n.s.*	*n.s.*	*n.s.*	*n.a.*
electrodes	*n.s.*	*n.s.*	*n.s.*	*n.a.*
Pe				
age	*n.s.*	*n.s.*	*n.s.*	*n.a.*
IQ	*n.s.*	*n.s.*	*n.s.*	*n.a.*
medication	8	7.28 (3, .06)	0.48 (5, 0.99)	4 < 3 (pos) < 1* (neg)
comorbidity	*n.s.*	*n.s.*	*n.s.*	*n.a.*
task	*n.s.*	*n.s.*	*n.s.*	*n.a.*
cogn. function	*n.a.*	*n.a.*	*n.a.*	*n.a.*
modality	*n.a.*	*n.a.*	*n.a.*	*n.a.*
ISI	8	6.83 (1, .009)	0.54 (6, 1.00)	*n.a.*
electrodes	*n.s.*	*n.s.*	*n.s.*	*n.a.*

Note. n.a. not available. *n.s.* not significant. Pos – positive ES. Neg – negative ES. Medication moderator: 1 – medicated; 2 – not medicated; 3 – washout period of 24h; 4 – washout period of 48h. Comorbidity moderator: 1 – yes, comorbid disorder present; 2 – no, no comorbid disorder present. Cognitive function moderator: 1 – Inhibition; 2 – Attention; 3 – Working memory; 4 – Error processing. Modality moderator: 1 – visual; 2 – auditory; 3 – multimodal.

2.1.4.4 Sensitivity analyses

Two sensitivity analyses were conducted to compare meta-analytic results obtained (I) from analyses with and without outlying studies[6] and (II) when there was no separation of different conditions (Cue, Go, NoGo). Results can be found in Tables S4–S9[7] (Appendix E in Supplemental material 6.1). Notably, for the Go-P300-amplitude and the CNV-amplitude, an even larger negative effect size was obtained after excluding outlying studies (d=-0.18 [-0.34 – (-0.02)], d=0.41 [0.16 – 0.67], respectively). Furthermore, significant between-group differences for the overall P300-amplitude (d=-0.25 [-0.43 – (-0.08)]) and latency analyses (d=0.50 [0.09 – 0.91]) emerged when fitting multilevel-models across Cue, Go, and NoGo conditions.

2.1.4.5 Comparison between earlier and later ERPs

For a direct comparison between earlier and later ERPs, a moderator analysis was implemented including data for all ERPs per trial condition (Cue, Go, NoGo[8]). A significant moderator effect for earlier versus later ERP components was obtained for the amplitudes of Cue-ERPs ($Q_M(2)=123.71$, $p < .0001$), the amplitudes and latencies of Go-ERPs ($Q_M(7)=80.65$, $p < .0001$, and $Q_M(7)=113.24$, $p < .0001$), and the amplitudes of NoGo-ERPs ($Q_M(7)=66.03$, $p < .0001$), with significant effects for the following ERPs: Cue-P300-amplitude, CNV-amplitude, Go-N200-amplitude, Go-P100-amplitude, Pe-amplitude, Go-N100-latency, Go-P300-latency, and NoGo-P300-amplitude[9].

2.1.4.6 Publication bias analyses

Trim-and-fill analyses calculated to test for publication bias, revealed significant results for the following ERP components: Cue-P300-amplitude, Go-P200-

[6] To determine statistical outliers, plots of the externally standardized residuals and Cook´s distances provided within the R package were examined.

[7] 1 effect size excluded for: Go-P100-amplitude, N100-amplitude, P200-amplitude, P300 latency, NoGo-N100-amplitude, P300-amplitude, P100-latency. 2 effect sizes excluded for: Go-N200-latency, NoGo-N100-latency, and ERN-amplitude. 3 effect sizes excluded for Go-P300-amplitude.

[8] CNV data were included in the Cue-dataset, while ERN/Ne and Pe data were included in Go- and NoGo-datasets for comparison.

[9] Deviations in results (when compared to overall results, separately conducted for each ERP) are due to a larger number of studies.

latency, NoGo-P100-latency, NoGo-N100-latency, NoGo-P300-amplitude, CNV-amplitude, ERN-amplitude, ERN-latency, Pe-amplitude, and Pe-latency. For the NoGo-P300-amplitude, a smaller but still significant effect size emerged when an estimated number of 10 missing studies was imputed, indicating a potential publication bias (*d*=-0.30 [-0.48 – (-0.11)]). For the other ERP components, no significant results were obtained.

2.1.5 Discussion

2.1.5.1 Summary of effects: cognitive ERPs as brain-based biomarkers for ADHD

The current meta-analysis shows significant group-level ERP differences between ADHD and non-ADHD, most prominently in later components. The results indicate that individuals with ADHD show on average smaller Cue-P300-amplitudes, longer Go-P300-latencies, smaller NoGo-P300-amplitudes, longer NoGo-P300-latencies, smaller CNV-amplitudes, and smaller Pe-amplitudes compared to non-ADHD. In line with current theories on executive functioning deficits in ADHD (Kofler et al., 2019), the moderate to large effects obtained for these later components indicate core deficits in later, higher-order cognitive processing stages and might represent possible biomarkers of ADHD. Although, a potential publication bias might confound the results obtained for the NoGo-P300-amplitude analyses, the findings of both sensitivity analyses further support the idea that P300-components are the most sensitive ADHD-biomarkers. Unexpectedly, individuals with ADHD also had shorter P100-latencies than non-ADHD. A possible explanation may be that in cognitive paradigms, the later part of the P100 includes higher involvement of cognitive modulation-processes. Therefore, shorter P100-latencies might be interpreted as a failure to further engage in such attentional processing necessary for successful cognitive modulation of sensory processing (Leroy et al., 2018). Another unanticipated finding was that the current meta-analysis could not reliably confirm between-group differences for the N200-component. As outlined previously, heterogeneous results have been obtained for N200-alterations in ADHD in primary

studies – a finding also reflected by the significant heterogeneity indices in the current meta-analysis. As can be seen from the moderator analyses, several demographic characteristics such as age, IQ, or comorbid disorders might influence the sensitivity of the N200 as a neurophysiological marker of ADHD. Therefore, the N200-component might indeed be relevant for the characterization of subgroups of individuals with ADHD (e.g. different age groups, IQ levels, with different comorbidities). In addition, non-significant overall results were obtained for the remaining ERP components: Cue-P300-latency, Go-P100-amplitude, Go-N100-amplitude and latency, Go-P200-amplitude and latency, Go-P300-amplitude, NoGo-P100-amplitude and latency, NoGo-N100-amplitude and latency, NoGo-P200-amplitude and latency, ERN-amplitude and latency, as well as the Pe-latency.

Furthermore, the current meta-analyses aimed at addressing sources of heterogeneity and, to this end, investigated several demographic and methodological characteristics. The moderator analysis for age group revealed stronger effects in children compared to adolescents or adults, for the P100, the N200, the P300, and the Pe components in different task conditions. This finding is in line with previous literature (e.g. Johnstone et al., 2007), and might reflect a possible reduction of ADHD symptoms during adolescence and early adulthood, which is reported to occur in approximately 40 %–60 % of individuals with ADHD, primarily for symptoms of hyperactivity (Faraone et al., 2006). However, not all cognitive ERP alterations were reduced in adults. Consistent with results from Doehnert and colleagues (Doehnert et al., 2010), the CNV-amplitude that was reduced in ADHD showed no significant developmental effects, and could therefore be interpreted as a stable neurophysiological marker independent of age. For the Cue-P300-amplitude age-moderator analysis larger group differences were identified for adults compared to children or adolescents, indicating that the Cue-P300-component represents a neuromarker-candidate for adult ADHD. Similar meta-analytic results were obtained from Szuromi and colleagues (Szuromi et al., 2011), who identified the Go-P300-component as a brain-based marker for ADHD in adults. As the obtained moderator

effects might also result from a different number of studies included per age subgroup, they should be interpreted with caution. Nevertheless, age represents an important moderator that helps to understand phenotypic changes in the developmental course of ADHD. Age-related changes might primarily occur for later ERPs due to more efficient higher-order cognitive processing, reflected by a normalization of ERP amplitudes and latencies during the transition from childhood into early adulthood. Further studies need to explore how these results fit with models of prefrontal brain maturation in healthy, as well as ADHD populations. Regarding IQ, the respective moderator analysis indicated larger between-group differences for higher IQ values. Generally, primary studies emphasize the protective role of IQ in the developmental course of psychiatric disorders and for predicting a positive treatment response, suggesting buffering effects of higher intellectual abilities (Handen et al., 1997; Owens et al., 2003). Within the current meta-analysis, larger between-group differences were identified for higher intellectual abilities (mean across groups). One might assume that these larger group differences might be due to a lower ability of individuals with ADHD with higher intellectual abilities to exploit those capacities. Further studies are warranted to explore IQ-effects in more detail. The explorative moderator analysis for ADHD medication-status revealed very heterogeneous results. For some components, larger effects have been obtained in non-medicated ADHD and ADHD after a washout of medication compared to medicated ADHD (e.g. Pe-amplitude) – in line with previous literature reporting on a neurophysiological normalization in individuals with ADHD on appropriate medication (Taylor et al., 1993). Regarding other ERP components (e.g. Cue- and NoGo-P300-amplitude), results are mixed and indicate even more elevated between-group differences between medicated individuals with ADHD and non-ADHD as compared to unmedicated ADHD or ADHD after a medication-washout period and non-ADHD. These ERPs might be unaffected by medication and the medicated ADHD might represent those more severely affected, resulting in larger neurophysiological differences. Furthermore, as shown in previous studies, there are

substantial neurophysiological differences between medication responders and non-responders that might help explaining the current results (Sunohara et al., 1997). However, for most of the included studies the information on the type of medication, dosing, and medication response is lacking and could not be explored. For comorbidity, the results present dilution, as well as elevation effects: the presence of comorbid conditions might result in even smaller or even larger between-group differences – presumably depending on the different types of comorbidities in individuals with ADHD (Rothenberger et al., 2000). Nevertheless, as for most of the studies the explicit type of comorbidity is not reported, no detailed analyses could be conducted. For the task moderator analysis, four tasks revealed large effect sizes, reflecting substantial neurophysiological alterations in individuals with ADHD compared to non-ADHD: the CPT, the CPT-Flanker version, the Go/NoGo, and the Oddball task. This might partly be due to the popularity of these tasks and, consequently, large amount of studies using these tasks. Furthermore, as some of these tasks might also involve vigilance/sustained attention (e.g. Oddball task), the larger effect sizes might be due to further deficits in sustained attention in ADHD (Barkley, 1997). When effect sizes were compared for the different cognitive functions (inhibitory control, (selective) attention, working memory, and error processing), the largest effects emerged for inhibitory control. Inhibitory control has been reported previously in numerous studies as being particularly deficient in ADHD (Albrecht et al., 2005; Barkley, 1997; Oosterlaan et al., 1998; Quay, 1997; Sergeant, 2000; 2005). Future studies are warranted to explore this moderator effect in relation to developmental effects along the lifespan. Further task-related moderators have been explored, such as stimulus modality: results show that largest effect sizes were obtained for auditory stimuli. This finding is somewhat surprising as many studies on ERPs in ADHD use tasks with stimuli being presented visually. A possible explanation might be that visually presented stimuli are more salient and therefore, capture more attention, partly compensating vigilance and state regulation deficits in ADHD. Stimuli presented via different modalities are processed in different brain

regions, thereby activating different neural generators. Depending on the electrode positions used for calculating ERP amplitudes and latencies, some neural generators might have more impact on the neurophysiological signal assessed than others, thereby yielding substantial between-study differences. This points out to the importance of conducting further studies using auditory stimuli compared to visual stimuli to explore the relationship between stimulus modality and neurophysiological deficits in ADHD in more detail taking into account the electrode positions used for calculating ERPs. Regarding the ISI, meta-analytic results show that for a longer time window between the presentation of each stimulus, group differences become more elevated. This result might be interpreted as reflecting difficulties in awaiting the next stimulus presentation in the ADHD group, thereby indicating higher levels of impulsivity symptoms. For the number of electrodes used to assess ERPs, heterogeneous results were obtained in the respective moderator analyses. Further studies are needed to explore if more electrodes might be associated with higher sensitivity in detecting neurophysiological group differences between ADHD and non-ADHD.

2.1.5.2 Practical implications: limited utility of cognitive ERPs for diagnostic purpose, selection of individualized treatment strategies, and tracking of therapy outcomes in ADHD

Although the current meta-analyses identified later ERPs as possible markers of ADHD, results were characterized by substantial heterogeneity, not meeting criteria for clinical application of ERP-markers for diagnostic purpose on an individual level. The heterogeneity in effect sizes, and a number of other factors limit the practical implication of the results. This heterogeneity on a basic neurophysiological level (e.g. Lenartowicz & Loo, 2014) reflects the "inescapable heterogeneity" of the ADHD phenotype (Arns & Gordon, 2014). The substantial amount of variation in the distribution of effect sizes suggests the influence of further relevant moderator variables, such as varying clinical profiles, diversity of

psychiatric comorbidities, varying patterns of neurocognitive impairment, and varying confounds by developmental effects (e.g. Aasen et al., 2018). More studies are needed to understand this heterogeneity, and to validate relevant ERP variables for multimodal classification approaches (Mueller et al., 2011). In addition, to further explore the sensitivity of ERPs as ADHD biomarkers, the question of how specific these neuromarkers are needs to be addressed (Thome et al., 2012): further studies are needed comparing different ADHD (sub-) groups, as well as individuals with ADHD with different types of comorbid symptoms to non-ADHD (Sur & Sinha, 2009). Additionally, machine-learning approaches might use ERPs for identifying ADHD subgroups based on the combination of diagnostic information from different modalities. Beyond that, future studies should try to link ERPs to continuous symptom dimensions adopting the RDoC approach. Prior studies have noted the relationship between neurophysiological processes and therapy response to medication, as well as non-medication therapies (e.g. Banaschewski & Brandeis, 2007; slow-cortical potentials neurofeedback: Heinrich et al., 2004; neurofeedback and methylphenidate: Janssen, Bink, et al., 2016; Janssen, Geladé, et al., 2016; stimulants: Ogrim et al., 2016; atomoxetine: Yamamuro, Ota, Iida, Nakanishi, Matsuura, et al., 2016), indicating that ERPs might be useful as objective diagnostic add-ons that are easy to assess in a non-invasive way to predict and track therapy outcome. The current meta-analysis suggests to (further) explicitly test the predictive value of later ERPs as neuromarkers in a personalized medicine framework (we are aware of a few already published, as well as ongoing studies using EEG/ERPs to predict response to different therapeutic interventions (e.g. ESCAlife trial, Döpfner et al., 2017; Ogrim et al., 2014).

2.1.5.3 Limitations & future directions

A few limitations of the current meta-analysis need to be acknowledged. Generally, because of a small number of studies included for some of the ERP

components[10], the results of the respective analyses should be interpreted with caution. Consequently, there is an urgent need for further studies exploring ERPs in ADHD. Although the current meta-analyses show substantial differences in later cognitive ERP components, further studies are warranted. Within the current work we did not include any unpublished data. The inclusion of unpublished data could possibly itself introduce bias as the unpublished studies located might be an unrepresentative sample of unpublished work and as the studies might be of lower methodological quality (Higgins et al., 2019). Nevertheless, the current results might be slightly biased. To address this issue, publication bias analyses were calculated and reported. For reliably identifying biomarkers we are in clear need of further replication studies. Open science might be a desirable framework promoting such efforts. An open science approach might reduce publication bias, thereby facilitating future meta- and mega-analyses. Due to the low number of studies included for some of the relevant ERPs (especially, for earlier ERPs), moderator variables had to be explored separately. For higher validity of results and exploring the interplay between influence variables, different moderators would have been included in one (full) model. Therefore, the results are explorative and need to be interpreted with caution. For some of the moderators, the number of studies included per subgroup varies substantially, rendering the comparison of categories less stable. As a consequence, future studies are needed to fill the gaps of knowledge on some of the moderator categories: first, there are only a few studies conducted on adolescents with ADHD. Second, most of the studies are conducted in males – a characteristic pattern obtained for studies on (psychiatric) disorders with a higher prevalence in males compared to females (Polanczyk et al., 2007). Most of the studies are conducted on individuals with ADHD of the combined subtype and further studies are warranted on ADHD inattentive and hyperactive/impulsive subtypes (Tamayo-

[10] $1 < k \leq 15$: Cue-P300-latency, Go-P100-amplitude & latency, Go-N100- amplitude & latency, Go-P200-latency, NoGo-P100-amplitude, NoGo-N100- amplitude, NoGo-P200-amplitude, NoGo-P100-latency, NoGo-N100-latency, NoGo-P200-latency, NoGo-N200-latency, NoGo-P300-latency, ERN/Ne-latency, and Pe-latency.

Orrego et al., 2015). Therefore, no moderator analysis could be conducted on ADHD subtype. In addition, there is an urgent need for studies reporting on comorbid symptoms in individuals with ADHD, as well as medication status (possibly, plus adherence and medication response). Furthermore, one important research question remains unanswered at present: how does symptom severity influence effect sizes (Yamamuro, Ota, Iida, Nakanishi, Suehiro, et al., 2016)? This question is highly relevant, especially as the changeability of ERP components according to the clinical phenotype is an important criterion for the validity of biomarkers. Due to a lack of reported information and a variety of different scales used to assess ADHD symptom severity, this highly relevant moderator variable could not be explored. Consequently, there is an urgent need for standardization of ADHD scales in research to compare results obtained from different studies. Many more moderators might be potentially relevant for ERP-differences between individuals with and without ADHD (e.g. child- versus adult-onset ADHD, electrode location/signal generators). Due to the small number of studies for some of the ERPs, a lack of reporting in primary studies, and the many fine differences in the methodological implementation of the primary studies, we need further studies to explore the heterogeneity in effect sizes in more detail.

2.1.5.4 Conclusion

This is the first meta-analysis quantitatively summarizing relevant literature on cognitive event-related potentials (ERPs) in ADHD across the lifespan. In line with current executive functioning-deficit theories of ADHD, the findings confirm that, on a group level, ADHD is associated with specific neurophysiological alterations during cognitive tasks, particularly during later cognitive processing-stages. Compared to non-ADHD, individuals with ADHD show moderate differences, mainly regarding later cognitive ERP components (P300, CNV, Pe). Further studies are needed to fully understand the heterogeneity in effect sizes and the influence of moderator variables to clarify the potential of cognitive ERPs for supporting

objective ADHD diagnosis and neurophysiological subtyping, for selecting individualized treatment strategies, and for tracking therapy outcomes. Clearly, identification of conditions ensuring larger effect sizes are needed before ERPs can become helpful, objective tools supporting diagnostic stratification and precision medicine.

2.2 STUDY 2: EEG Data Quality: Determinants and Impact in a Multicenter Study of Children, Adolescents, and Adults with Attention-Deficit/Hyperactivity Disorder (ADHD)

Published as: Kaiser, A., Aggensteiner, P.-M., Holtmann, M., Fallgatter, A., Romanos, M., Abenova, K., Alm, B., Becker, K., Döpfner, M., Ethofer, T., Freitag, C. M., Geissler, J., Hebebrand, J., Huss, M., Jans, T., Jendreizik, L. T., Ketter, J., Legenbauer, T., Philipsen, A., Poustka, L., Renner, T., Retz, W., Rösler, M., Thome, J., Uebel-von Sandersleben, H., von Wirth, E., Zinnow, T., Hohmann, S, Millenet, S., Holz, N. E., Banaschewski, T., Brandeis, D., on behalf of the ESCAlife-consortium (2021). EEG Data Quality: Determinants and Impact in a Multicenter Study of Children, Adolescents, and Adults with Attention-Deficit/Hyperactivity Disorder (ADHD). *Brain Sci, 11*(2), 214. doi: 10.3390/brainsci11020214

2.2.1 Abstract

Electroencephalography (EEG) represents a widely established method for assessing altered and typically developing brain function. However, systematic studies on EEG data quality, its correlates, and consequences are scarce. To address this research gap, the current study focused on the percentage of artifact-free segments after standard EEG pre-processing as a data quality index. We analyzed participant-related and methodological influences, and validity by replicating landmark EEG effects. Further, effects of data quality on spectral power analyses beyond participant-related characteristics were explored. EEG data from a multicenter ADHD-cohort (age range 6 to 45 years), and a non-ADHD school-age control group were analyzed (n_{total} = 305). Resting-state data during eyes open, and eyes closed conditions, and task-related data during a cued Continuous Performance Task (CPT) were collected. After pre-processing, general linear models, and stepwise regression models were fitted to the data. We found that EEG data quality was strongly related to demographic characteristics, but not to methodological factors. We were able to replicate maturational, task, and ADHD effects reported in the EEG literature, establishing a link with EEG-landmark effects. Furthermore, we showed that poor data quality significantly increases spectral power beyond effects of maturation and symptom severity. Taken together, the current results indicate that with a careful design and systematic quality control, informative large-scale multicenter trials characterizing neurophysiological mechanisms in neurodevelopmental disorders across the lifespan are feasible. Nevertheless, results are restricted to the limitations reported. Future work will clarify predictive value.

2.2.2 Introduction

Electroencephalography (EEG) is a non-invasive method for assessing brain-electrical activity on the scalp using a set number of electrodes (Biasiucci et al., 2019; Mohamed et al., 2017). It has been widely used in the research fields of physiology, psychology, neuroscience, and cognitive science to explore the neural dynamics and

circuits related to typically developing and altered human information processing and behavior (Lau-Zhu et al., 2019). The weak surface EEG signal measured on the scalp is extremely susceptible to interferences during the process of signal collection. Significant signal distortions due to contamination through participant-induced artifacts or experimental factors sometimes lead to unavailability of sufficient EEG data for subsequent analyses, resulting in a lower reliability of study results (Kappenman & Luck, 2010). To this end, a series of offline processing methods exists that are applied to EEG data for extracting uncontaminated signals prior to further analyses. However, there is little standardization, and pre-processing methods vary substantially (Desjardins et al., 2021; Gabard-Durnam et al., 2018).

As the quality of the raw data crucially impacts the validity of analyses and interpretation of scientific results obtained from EEG, assessments of data quality are essential. Evaluating the quality of the raw EEG signals ensures that established standards are met, and results are replicable (Pedroni et al., 2019). Especially, when EEG data are recorded at multiple sites, in developmental populations, and in patient samples prone to EEG artifacts, they are characterized by a high degree of artifact contamination. For example, data from patients with attention-deficit/hyperactivity disorder (ADHD) are often contaminated by movement artifacts due to symptoms of hyperactivity. The assessment of developmental and/or psychiatric populations is typically associated with various challenges, subsequently contributing to lower EEG data quality: Children often have problems following instructions (e.g., not to move during the measurement, to pay attention to task instructions). Further, study protocols typically include far shorter measurement durations for a higher level of tolerance resulting in a lower number of data points available for final evaluations. Additionally, measures to assess physiological artifacts (such as EOG electrodes for ocular movement contamination) are often not implemented. From a data processing perspective, extracting uncontaminated signals from such EEG recordings represents a particular challenge. However, those signal distortions might provide additional useful information characterizing specific developmental and psychiatric

populations. Data quality might be systematically related to age or specific psychiatric symptom dimensions with a potential relevance for classification purpose. This aspect is often neglected and not explicitly addressed in ongoing clinical trials using EEG.

Although the EEG represents an established method for assessing neuronal activity, systematic explorations of signal contamination are rather scarce and existing reports of data quality measures are often inconsistent. Typically, studies only indirectly address data quality by reporting impedance cut-offs (such as < 20 kΩ at each electrode location) or standard cut-off values for the least-acceptable absolute number of sweeps included per participant for subsequent analyses (Fiedler et al., 2010; Fiedler et al., 2013; Tautan et al., 2014). Further studies calculated analytical indices using complex models to explicitly assess EEG data quality (Barthelemy et al., 2019; Liu et al., 2019). However, previous reports were mainly focusing on data quality of wearable dry-electrode devices or when EEG and functional magnetic resonance imaging (fMRI) data were collected simultaneously (Lüchinger et al., 2011). Other recent work focused on online-monitoring of data quality for neurofeedback and brain-computer interface (BCI) applications (Bioulac et al., 2019). Due to this lack of direct assessment and consistent reporting, study quality can often only be indirectly inferred from publications on EEG data. The same refers to study-specific variables potentially influencing it (Artoni et al., 2018; DiStefano et al., 2019).

Identifying and adequately addressing EEG signal distortions ensures reliability of study results. Beyond this, replicating robust landmark effects of the EEG literature in-forms about the validity of analyzed data. However, to date there is little published data on such appropriate validation analyses representing replication analyses of robust landmark effects typically reported in the EEG literature that establish a link with data quality. Only few replication studies have been done so far. Nevertheless, they are urgently needed for consolidation of results in the field of EEG research (Clarke et al., 2020). Thereby, several robust landmark effects have been identified (we do not claim for a comprehensive review of all relevant EEG

landmark effects): (I) For example, in the literature on resting-state EEG activity age effects of increasing fast oscillatory activity and decreasing slow oscillatory activity due to brain maturational processes have been consistently reported (Bresnahan et al., 1999; Clarke et al., 2019; Clarke et al., 2001; Liechti et al., 2013; Poil et al., 2014; Zappasodi et al., 2015). (II) Furthermore, a substantial amount of studies reported on alpha blocking after transition from resting state eyes closed to eyes open or task-related conditions, indicating a decrease in alpha activity primarily in occipital brain regions (Barry et al., 2009; Barry et al., 2007; Barry & De Blasio, 2017; Li, 2010; Liley & Muthukumaraswamy, 2020). (III) For task-related inhibitory control activity assessed via Go/NoGo-paradigms, previous studies showed a substantially higher amplitude of the Go-P3 event-related potential (ERP) compared to the NoGo-P3, especially at posterior brain regions (e.g. Albrecht et al., 2013; Fallgatter et al., 2004). This effect indicates a substantially stronger neurophysiological activity in response to Go- compared to NoGo-trials, with the latter requiring the inhibition of unwanted motor responses. In general, cognitive ERPs represent stimulus-locked time epochs in the EEG that can be related to distinct cognitive processes. (IV) In addition, a recent meta-analysis summarized previous study results on earlier versus later cognitive ERPs in ADHD compared to non-ADHD populations (Kaiser et al., 2020). Results show that for early ERPs ADHD patients present shorter Go-P100-latencies when compared to non-ADHD. For later ERPs, individuals with ADHD showed smaller Cue-P300-amplitudes, longer Go-P300-latencies, smaller NoGo-P300-amplitudes, longer NoGo-P300-latencies, smaller contingent negative variation (CNV-) amplitudes, and smaller Pe-amplitudes. These robust empirical features found in the field of EEG research provide a reliable framework for testing validity of EEG data.

Differences in EEG data quality might exist between different groups assessed within a study due to developmental aspects or psychiatric symptoms. However, these contaminations possibly represent valid, characteristic information of those develop-mental and/or psychiatric populations with a substantial marker value. Those EEG data quality differences between study populations might subsequently

have an impact on between-group differences in classical EEG- and ERP-analyses, and the biomarkers identified. Extensive efforts were made in previous studies to follow standards, control for artifacts, and include sufficient uncontaminated EEG signals for analyses also in clinical contexts: (a) Adequate designs and homogeneous participant groups were selected, and (b) different techniques and pre-processing methods ensured sufficient (largely) artifact-free EEG. Nevertheless, systematic group differences or remaining subtle signal distortions might still affect the analyzed data. Only a few studies so far have explicitly addressed and modelled systematic effects of EEG signal contaminations/data quality on results obtained in subsequent analyses of EEG/ERP data (e.g., on spectral power; e.g., Goncharova et al., 2003) to demonstrate and quantify such effects experimentally. However, these studies are urgently needed to explore the additional explanatory value of data quality besides developmental processes linked to brain maturation and ADHD symptoms, and to establish a link between the quality of assessed EEG data and results from planned EEG/ERP analyses.

Here, we present EEG data quality parameters from a recently conducted multicenter project assessing children, adolescents, and adults with ADHD, as well as non-ADHD children in school-age as control group to give insights into data quality, participant-related and methodological variables influencing data quality, as well as possible validation analyses to link data quality and replication of previous study results. Furthermore, we evaluated the additional influence of data quality on results obtained from spectral power analyses of resting EEG data beyond effects due to maturational processes and symptom severity. We suggest deriving data quality indices after pre-processing of the raw data by defining data quality as how much of the raw data assessed could actually be included in the final analyses. We go beyond the absolute number of acceptable segments after data pre-processing that was often taken as an index of data quality in previous work, and divide it by the total number of segments assessed to get an idea of how much data are useable for subsequent analyses (percentage of artifact-free segments). Within this study we assess how

demographic, participant-related clinical (age, ADHD symptom dimensions, medication status), and methodological (type of measurement, pre-processing method, measurement duration) variables influence EEG data quality. We further conduct validation analyses to replicate robust landmark effects typically reported in the EEG literature. Additionally, we relate data quality to results obtained in spectral power analyses from resting EEG data exploring additional effects of data quality besides maturation and ADHD symptoms on results.

2.2.3 Materials and Methods

2.2.3.1 Participants

Pseudonymized data of children, adolescents, and adults (6–45 years) with ADHD for the present study were obtained from the ESCAlife project (ESCAschool, ESCAadol, and ESCAlate trials), a multicenter study including 14 sites (involving Bochum/Hamm, Bonn, Essen, Frankfurt, Göttingen, Homburg, Köln, Mainz, Mannheim, Marburg, Oldenburg, Rostock, Tübingen, and Würzburg). Details regarding the study protocol, each age-trial, and data acquisition have been published previously (Becker et al., 2020; Döpfner et al., 2017; Geissler et al., 2018; Zinnow et al., 2018). Within ESCApreschool (3–6 years), no EEG data were collected. All studies were previously registered by the German Trial Register (reference numbers: DRKS00008973, DRKS00008974, DRKS00008975, at: https://www.drks.de/drks_web/). Ethics approval was provided by the local ethical committees for each participating center, and written informed consent was obtained from the child, adolescent or adult. Furthermore, written assent was obtained from parents or guardians for participants below the age of 18 years. Exclusion criteria were: IQ < 80, diagnosis of pervasive developmental disorder, schizophrenia, bipolar disorder, severe depressive episode, epilepsy, heart disease, current or planned intensive behavioral therapy for ADHD or oppositional behavior on a weekly basis, for children with severe ADHD known non-response to all standard ADHD medication (methylphenidate, dexamphenidate, and atomoxetine), psychotropic

medication (other than for ADHD) or neuroleptic medication (other than for the treatment of disturbance of impulse control), insufficient German language and reading skills of parents. IQ < 80, and insufficient German language skills were chosen as selection criteria as they were deemed relevant for participation in planned study-assessment (filling out questionnaires or understanding test instructions) and therapeutic interventions. EEG data within the ESCAlife-study were included from participants of the ESCAbrain-trial assessing the neurobiological underpinnings of ADHD, and the potential predictive value of neuronal markers for non-pharmacological treatment options. EEG data were assessed before (pre assessment) and after (post assessment) an intense, non-pharmacological intervention involving behavioral therapy (BT) or neurofeedback (NF) therapy. Finally, data from n = 184 ADHD children (age in years: M = 8.99, SD = 1.59), n = 39 adolescents with ADHD (age in years: M = 14.13, SD = 1.52), and n = 57 ADHD patients in adulthood (age in years: M = 29.39, SD = 6.73) were included in the current analyses. Furthermore, only at Mannheim center, 25 non-ADHD controls without any psychiatric disorder between the age of 6.00 and 11.11 years (non-ADHD controls) were assessed (age in years: M = 8.63, SD = 1.47), and EEG data were collected at two time points. Post assessments were done approximately 6 months after pre assessment. As the focus of the trials was on longitudinal aspects and changes due to different evidence-based ADHD interventions rather than on case-control comparisons, the study protocols did not include non-ADHD controls. Due to limited resources, non-ADHD controls could only be added for children, who form the largest and best studied age group regarding ADHD, although we acknowledge that a fully factorial design with controls in each age group would have been preferable.

2.2.3.2 Assessment of Demographic Information, and Clinical Characterization

Demographic information including age was assessed within an interview prior to any treatment or measurement. For clinical characterization and assessment

of ADHD symptoms, several scales and interviews were used (see Appendix A, Supplemental material 6.2).

2.2.3.3 EEG Data Acquisition

EEG data were acquired at each of the involved sites with NEUROPRAX or THERAPRAX full-band DC-EEG amplifier systems (with a high input impedance >10 GΩ for proprietary impedance control; neuroCare GmbH, Germany). Resting state data were collected with patients first having their eyes open and then eyes closed, four minutes each. The resting-state EEG was recorded using a 22-channel EEG cap (Brain Products, Gilching, Germany), and a sampling rate of 256 Hz (DC–70 Hz). A cued Continuous Performance Task (CPT) was used to probe preparatory and inhibitory neurophysiological activity (see Appendix A in Supplemental material 6.2, for a detailed description). The EEG while performing the cued CPT (in ADHD children from ESCAschool/non-ADHD control children) or the Flanker-version (for adolescents and adults from ESCAadol, and ESCAlate, respectively) was recorded using a higher sampling rate of 512 Hz. Impedances were kept below 20 kΩ.

2.2.3.4 Data Preparation

EEG data were pre-processed using BrainVision Analyzer (Version 2.1) including the following pre-processing steps for the raw EEG signal: Offline filtering using Butterworth Zero Phase filters, a high-pass filter of 0.01 Hz (24 dB/oct), and a low-pass filter of 70 Hz (24 dB/oct). Furthermore, a notch filter of 50 Hz was applied. At first, data were inspected to reject the noisiest segments. Subsequently, for correction of ocular blinks and eye movements, an independent component analysis (ICA) was conducted based on a case-wise visual inspection. Then, data were re-referenced to the average, and segmented (division in equal sized components of 2.048 s for resting-state data). Further, an automatic artifact-detection method was applied using an exclusion criterion of ±150 μV. For later assessing the effects of different ocular correction methods, the same steps were repeated, but instead of

using ICA decomposition, ocular blinks and eye movements were removed by the procedure described by Gratton and colleagues (Gratton et al., 1983).

To assess data quality after implementing all steps of pre-processing, the number of good sweeps (< ±150 μV) was divided by the total number of sweeps assessed (percentage of artifact-free segments).

Regarding the validation analyses, for resting-state data, frequency band analyses using fast-Fourier transformation (FFT) were carried out, with data being divided into beta (12.5–30 Hz), alpha (7.5–12.5 Hz), theta (3.5–7.5 Hz), and delta (0.5–3.5 Hz) frequency bands, focusing on the Fz, Cz, and Pz electrode locations. For task-related data assessed using the cued CPT/Flanker-version of CPT, event-related potentials were extracted, focusing on the P300 component, as well as the CNV. For further analyses of time effects in the resting EEG eyes open and closed data, each dataset was split in two time segments of equal size for the first half and second half of the measurement. Datasets for validation analyses were included with at least 20 segments per participant for resting data, and 10 segments for CPT data per condition, respectively.

For ERP-validation analyses, amplitudes and latencies were calculated for each participant for the Cue-P3 and the CNV components, as well as for Go- and NoGo-P3 components (Albrecht et al., 2013; Cheung et al., 2017; Doehnert et al., 2010; Du Rietz et al., 2016; Rommel et al., 2017). Cue-P3 peaks were identified at electrode Pz within a time window of 300–750 ms after cue onset. The CNV component was quantified at electrode Cz, and the most prominent statistical effects were expected within a time window of 1200–1650 ms after cue onset. Go-P3 and NoGo-P3 were defined as the most positive peaks at around 280–600 ms at electrode Pz and FCz, respectively. Amplitudes for all ERP components, and Cue-P3, Go-P3, and NoGo-P3 latencies were exported for further analysis.

2.2.3.5 Statistical Analyses

All statistical analyses were conducted using SPSS (version 24) and R software version 3.5.1.

To explore the effects of demographic and clinical variables on data quality, stepwise regression models were fitted to the data. To iteratively explore the influence of age, ADHD symptoms (inattention, hyperactivity/impulsivity; z-standardized to compare different scales used for children/adolescents, and adults, respectively), and medication status, those variables were sequentially entered into the model as predictor variables of interest. General linear models were used to analyze effects of condition, directly comparing eyes open versus eyes closed resting conditions, versus CPT. Furthermore, in paired-samples t-tests effects of different pre-processing methods, and measurement duration were explored. For exploring site effects on data quality within the current multicenter trial, again general linear models were fitted.

For validation analyses, correlational analyses (validation analysis I on age effects), paired-samples t-tests (validation analysis II on alpha blocking in transition from eyes closed to eyes open condition, and validation analysis III on CPT effects), as well as in-dependent samples t-tests (validation analysis IV on ERP differences between ADHD and non-ADHD control children) were conducted. Validation analysis III and IV were conducted in children only. As t-tests were conducted for replication purposes or on different or only partly overlapping characteristics and datasets, no corrections for multiple testing were implemented.

To explore the additional effects of data quality on EEG power spectra besides demographic characteristics, stepwise regression models were used.

2.2.4 Results

2.2.4.1 Participant Characteristics

Demographic information on included participants can be found in Table 6.

Table 6
Demographic information

	N	Age, M (SD)	ADHD Symptoms Inattention, M (SD) Hyperactivity/Impulsivity, M (SD)	Medication (%)
Non-attention-deficit/hyperactivity disorder (ADHD) control children	25	8.63 (1.47)	0.20 (0.28) 0.24 (0.23)	0 (0%)
ADHD children from ESCAschool	184	8.99 (1.59)	2.19 (0.40) 1.88 (0.70)	82 (55.78%)
ADHD adolescents from ESCAadol	39	14.13 (1.52)	2.05 (0.39) 1.42 (0.71)	15 (46.88%)
ADHD adults from ESCAlate	57	29.39(6.73)	7.81 (1.14) 5.28 (2.29)	8 (14.81%)

ADHD symptom scale ranges for non-ADHD controls, ADHD children from ESCAschool, and ADHD adolescents from ESCAadol: [0–3], for ADHD adults from ESCAlate: [0–10].

2.2.4.2 Data quality

2.2.4.2.1 Descriptive Statistics

The first research question aimed at exploring data quality in children, adolescents, and adults with a diagnosis of ADHD, and school-age control children, and demographic, patient-related (age, medication, patient status), as well as methodological (type of measurement, pre-processing method, measurement duration) variables influencing data quality. Table 7 shows the descriptive statistics for each condition, and all (age) groups, respectively.

Table 7
Descriptive statistics for data quality index (percentage of artifact-free segments)

Pre Assessment			
	Eyes open, M% (SD)	**Eyes closed, M% (SD)**	**CPT, M% (SD)**
Non-ADHD control children	73.35% (27.33)	75.80% (26.49)	69.92% (26.79)
ADHD children from ESCAschool	41.28% (35.14)	37.27% (36.40)	30.96% (33.19)
ADHD adolescents from ESCAadol	54.84% (38.84)	58.12% (38.29)	49.61% (38.81)
ADHD adults from ESCAlate	57.78% (38.15)	66.61% (38.32)	64.63% (36.42)
Total	48.92% (36.87)	49.04% (38.95)	43.75% (37.42)

The pre assessment was carried out before the intense treatment schedule of the stepped-care treatment program within the ESCAlife study.

2.2.4.2.2 Effects of Demographic and Clinical Information on Data Quality

A stepwise multiple regression was conducted to explore whether age, ADHD symptoms (inattention, hyperactivity/impulsivity), and medication status predict data quality. For pre eyes open, the regression model revealed at step 1, age contributed significantly to the regression model, $F(1, 224) = 5.41$, $p = 0.021$), and accounted for 2.4% of the variation in data quality. Introducing ADHD symptoms explained an additional 6.1%, and this change in R^2 was significant, $F(3, 222) = 6.84$, $p < 0.0001$. This effect was primarily driven by adding hyperactivity/impulsivity to the regression model, $t = -2.62$, $p < 0.01$ (inattention: $p > 0.05$). Finally, the addition of medication explained an additional 0.6% of variation, but the change in R^2 was not significant, $p > 0.05$.

For pre eyes closed, the regression model revealed at step 1, age contributed significantly to the regression model, $F(1, 223) = 15.52$, $p < 0.001$, and accounted for 6.5% of the variation in data quality. Introducing ADHD symptoms explained an additional 7.1%, and this change in R^2 was significant, $F(3, 221) = 11.58$, $p < 0.0001$. This effect was primarily driven by adding hyperactivity/impulsivity to the regression model, $t = -2.40$, $p = 0.017$ (inattention: $p > 0.05$). Finally, the addition of medication explained an additional 2.0% of variation, and this change in R^2 was again significant, $F(4, 220) = 10.18$, $p < 0.0001$. When all independent variables were included at stage 3, a significant effect was revealed for symptoms of inattention additionally, $t = -2.19$, $p = 0.03$.

When exploring pre CPT data quality, at step 1 in the regression model, a significant effect of age was found, $F(1, 223) = 17.27$, $p < 0.001$, accounting for 7.2% of variance. Adding ADHD symptoms explained further 7.1% with a significant change in R^2, $F(3, 221) = 12.29$. $p < 0.001$. Again, this effect was primarily driven by adding hyperactivity/impulsivity to the regression model, $t = -2.60$, $p = 0.010$ (inattention: $p > 0.05$). Finally, the addition of medication explained an additional 0.9% of variation, but the change in R^2 was not significant, $p > 0.05$.

Appendix B (in Supplemental material 6.2, Figure A1-A4) shows the associations between demographic variables of interest and EEG data quality.

2.2.4.2.3 Effects of Condition and Further Methodological Variables on Data Quality

For analyzing the effects of condition (directly comparing eyes open versus eyes closed versus CPT) across all participants, a general linear model was used. No significant effect was obtained, indicating no differences in data quality for different measurement conditions, $p > 0.05$.

Paired-samples t-tests were used to explore differences in data quality for different pre-processing methods (semiautomatic ICA versus automatic correction according to Gratton and Coles). Results show no significant differences for different ocular movement correction methods, $p > 0.05$.

To analyze differences in data quality for measurement duration, paired-samples t-tests were applied. No significant differences emerge for neither eyes open, nor eyes closed condition at pre assessment, $p > 0.05$.

Descriptive statistics and detailed results can be found in Appendix C (in Supplemental material 6.2, Table A1, A2). Results for the effects of study-site on data quality are also presented in Appendix C (in Supplemental material 6.2).

2.2.4.3 Validation Analyses

2.2.4.3.1 Validation Analysis I: Correlation between EEG Power Spectra and Age

Significant small to moderate negative correlations were obtained between age and eyes open alpha activity, eyes open theta activity, and eyes open delta activity at Fz, Cz, and Pz at pre assessment. For eyes closed, significant negative correlations were obtained between age and alpha activity, theta activity, and delta activity at Fz, Cz, and Pz, respectively. In addition, small negative correlations at Fz, and Pz electrode positions were identified for beta activity. These results indicate that with increasing age, power in alpha, theta, and delta bands decreases. Results across all participants are shown in Table 8. Figure 9 presents absolute spectral power (log-transformed values are displayed for illustrative purposes) in all frequency bands of

interest for ADHD children, adolescents, and adults, respectively. Appendix D (in Supplemental material 6.2, Figures A5-A10; Table A3, A4) shows the associations between age and EEG spectral power in resting conditions across all participants. Further, for the purpose of comparison with previous literature (Liechti et al., 2013), Appendix D (in Supplemental material 6.2, Figures A11-A16) presents results from correlational analyses with only children and adolescents included (<16 years of age), separately for ADHD groups and the non-ADHD control children, as typically substantially higher associations are identified for younger age groups and in non-ADHD control groups.

Table 8
Correlations between age and fast-Fourier transformation (FFT) frequency band activity at pre assessment

	Eyes Open			**Eyes Closed**		
Electrode Location	**Fz**	**Cz**	**Pz**	**Fz**	**Cz**	**Pz**
beta[μV] × age[years]	−0.130	−0.088	−0.058	−0.154°	−0.125	−0.151°
alpha[μV] × age[years]	−0.265 ***	−0.297 ***	−0.155°	−0.210 **	−0.299 ***	−0.265 ***
theta[μV] × age[years]	−0.461 ***	−0.452 ***	−0.324 **	−0.521 ***	−0.471 ***	−0.376 ***
delta[μV] × age[years]	−0.387 ***	−0.406 ***	−0.415 ***	−0.404 ***	−0.449 ***	−0.377 ***

Frequency band widths: Beta [12.5 Hz–30 Hz], alpha [7.5 Hz–12.5 Hz], theta [3.5 Hz–7.5 Hz], and delta [0.5 Hz–3.5 Hz]. Pearson product-moment correlations are displayed. *** $p \leq 0.0001$, ** $p \leq 0.001$, * $p \leq 0.01$, ° $p \leq 0.05$.

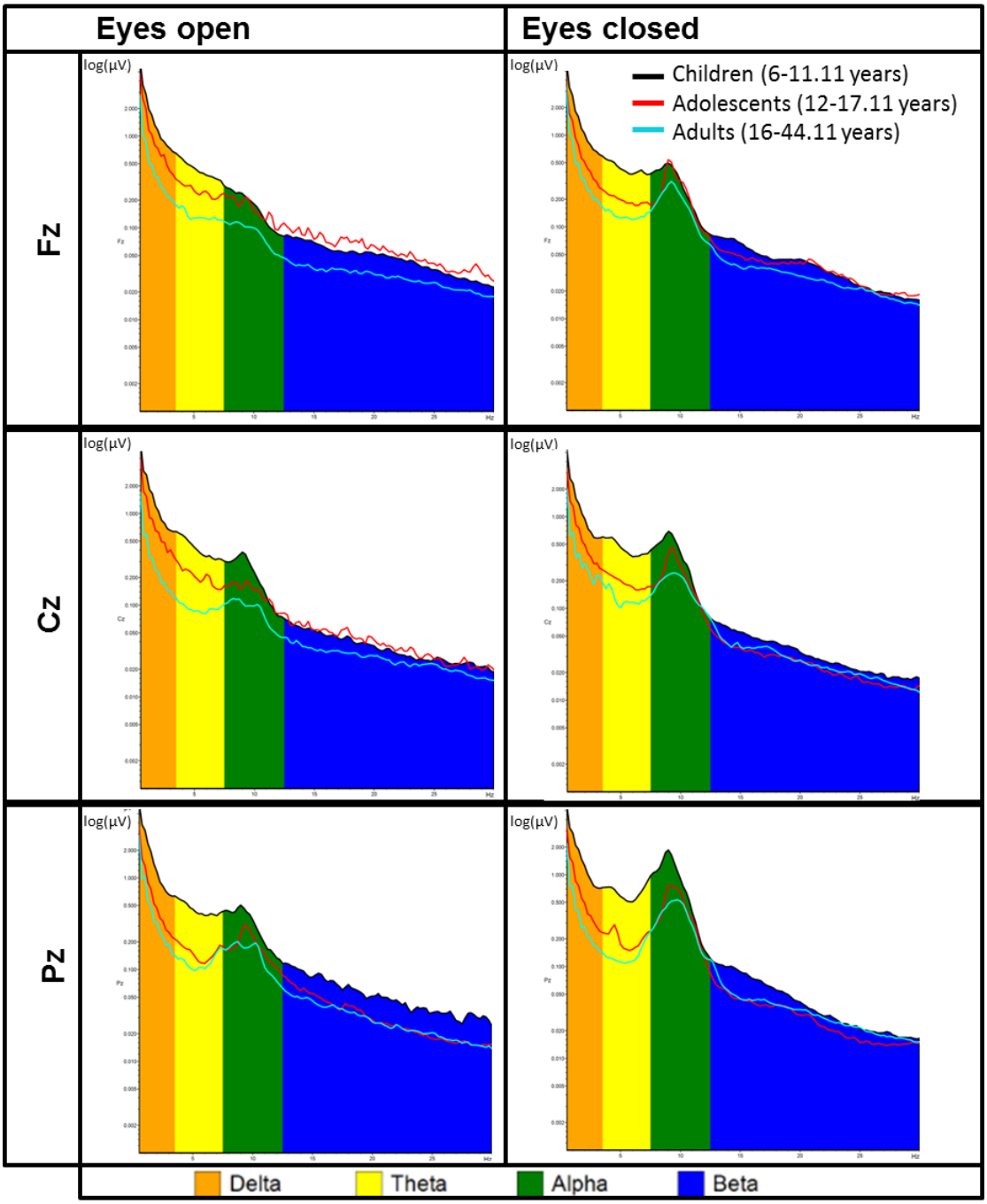

Figure 9. Averaged log10-transformed absolute spectral power in beta [12.5–30 Hz], alpha [7.5–12.5 Hz], theta [3.5–7.5 Hz], and delta [0.5–3.5 Hz] frequency bands for ADHD children (black), adolescents (red), and young adults (blue), respectively.

2.2.4.3.2 Validation Analysis II: Alpha Blocking in Transition from Eyes Closed to Eyes Open Condition (Alpha Reactivity)

Paired samples t-tests were conducted to compare FFT alpha activity in eyes open versus eyes closed conditions at electrode locations Fz, Cz, and Pz, respectively. There was a significant difference in alpha activity at all three electrode positions for eyes open (Fz: M = 0.15, SD = 0.13; Cz: M = 0.19, SD = 0.19; Pz: M = 0.25, SD = 0.26)

and eyes closed (Fz: M = 0.27, SD = 0.22; Cz: M = 0.32, SD = 0.27; Pz: M = 0.68, SD = 0.75), t(208) = −8.549, $p < 0.001$ at Fz, t(208) = −9.168, $p < 0.001$ at Cz, and t(208) = −9.783, $p < 0.0001$ at Pz, respectively. These results indicate an increase in alpha activity at all three electrode locations from eyes open to eyes closed condition (see also Figure 10).

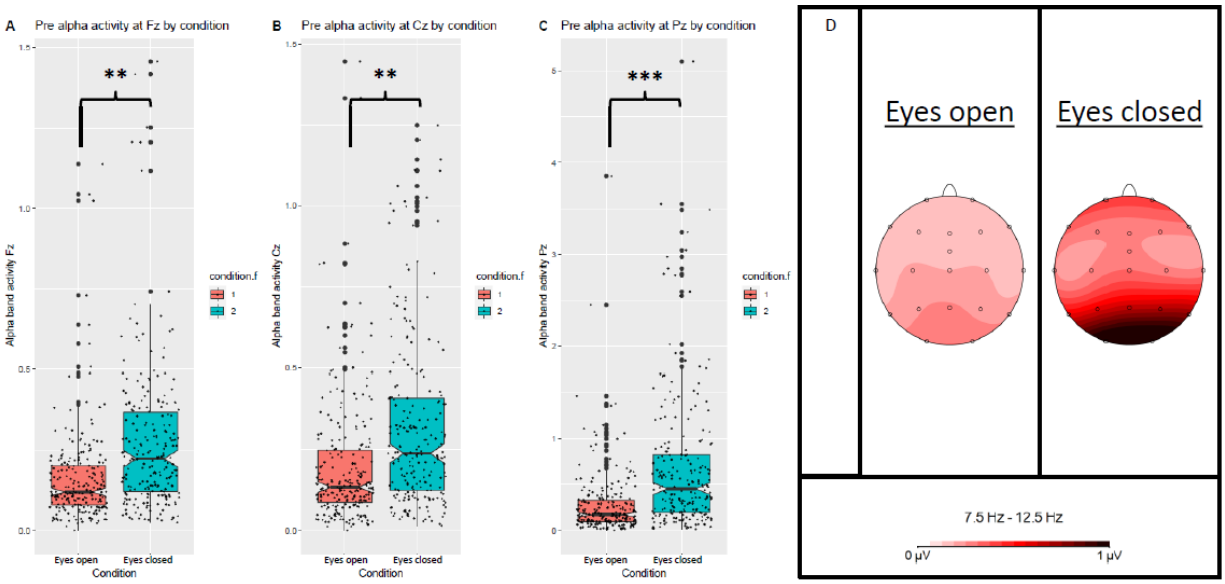

Figure 10. Differences in alpha activity by condition at Fz (**A**), Cz (**B**), and Pz (**C**) electrode locations. Corresponding topographical maps in the alpha frequency range of 7.5–12.5 Hz for eyes open, and eyes closed conditions, respectively (**D**). *** $p \leq 0.0001$, ** $p \leq 0.001$, * $p \leq 0.01$, ° $p \leq 0.05$.

Furthermore, a decrease in frontal beta, an increase in posterior beta, and an increase in central and posterior theta activity from eyes open (M = 0.04, SD = 0.04, M = 0.03, SD = 0.03, M = 0.33, SD = 0.30, M = 0.32, SD = 0.26) to eyes closed condition (M = 0.04, SD = 0.02, M = 0.04, SD = 0.03, M = 0.38, SD = 0.31, M = 0.48, SD = 0.52) was obtained, t(208) = 2.281, $p = 0.024$, t(208) = −4.203, $p < 0.001$, t(208) = −2.784, $p = 0.006$, t(208) = −5.832, $p < 0.001$, respectively.

2.2.4.3.3 Validation Analysis III: CPT Task Effect: Comparison between Go- and Nogo-P3 Amplitude at Pz

Paired-samples t-tests were used to explore mean amplitude differences at Pz electrode for Go- and NoGo-P3. Results show a significant difference between Go- and NoGo-P3 mean activity at posterior regions, with a substantially higher Go-P3

mean amplitude (M = 20.00, SD = 6.65) compared to the NoGo-P3 component (M = 14.64, SD = 7.27), t(128) = 9.402, $p < 0.0001$, see Figure 11.

2.2.4.3.4 Validation Analysis IV: ERP Differences between Children with ADHD and Non-ADHD Controls

Descriptive statistics for ERP amplitudes and latencies of interest can be found in Table 9.

Table 9
Event-related potential (ERP) amplitudes and latencies in ADHD (ESCAschool) and non-ADHD control children

	ADHD Children			**Non-ADHD Control Children**			**Comparison**	
	N	**M**	**SD**	**N**	**M**	**SD**	**t**	***p***
Contingent negative variation (CNV) amplitude	122	−2.43 µV	4.59 µV	25	−3.07 µV	4.00 µV	−0.548	0.585
Cue P3 amplitude	122	13.31 µV	5.43 µV	25	16.11 µV	5.04 µV	2.503	0.013
Cue P3 latency	122	506.9 ms6	118.76 ms	25	531.09 ms	108.26 ms	0.728	0.468
Go P3 amplitude	105	19.79 µV	6.26 µV	25	20.92 µV	7.99 µV	1.006	0.316
Go P3 latency	105	390.12 ms	99.23 ms	25	420.63 ms	102.01 ms	1.024	0.308
NoGo P3 amplitude	109	11.07 µV	8.12 µV	25	11.81 µV	6.76 µV	0.406	0.686
NoGo P3 latency	109	441.10 ms	76.13 ms	25	449.61 ms	69.39 ms	0.608	0.544

Peak definition: Cue-P3 at Pz within a time window of 300–750 ms after cue onset. CNV at Cz, within a time window of 1200–1650 ms after cue onset. Go-P3 and NoGo-P3 at around 280–600 ms at electrode Pz and FCz, respectively.

Comparing children with ADHD to non-ADHD control children in school-age, a significant between-group difference was obtained for the Cue-P3 amplitude, t(145) = 2.37, $p = 0.019$, indicating smaller Cue P3-amplitudes in ADHD children (M = 13.31, SD = 5.43) compared to non-ADHD ESCAschool-controls (M = 16.11, SD = 5.04; see Figure 12). No further differences were obtained for other ERP components.

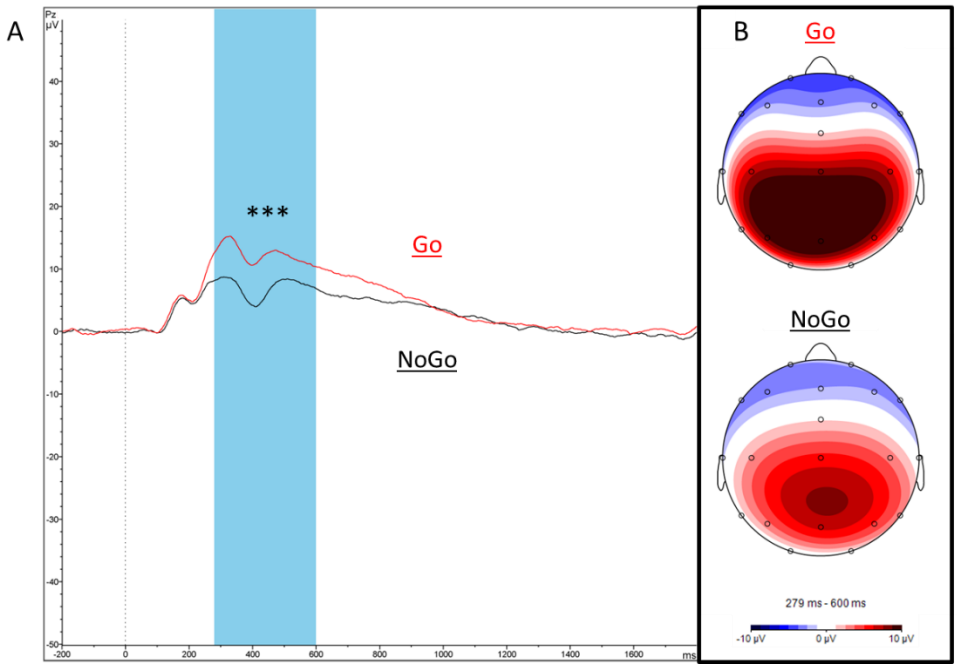

Figure 11. ERP Go- and NoGo-P3 components in children. A Stimulus-locked ERP wave shapes of the Go- (red) and NoGo-P3 (black) components at electrode Pz. B Corresponding maps in the time range of the Go- and NoGo-P3 (280–600 ms). *** $p \leq 0.0001$, ** $p \leq 0.001$, * $p \leq 0.01$, ° $p \leq 0.05$.

2.2.4.4 The Additional Influence of Data Quality on Power Spectra (FFT) Results in Eyes Open and Eyes Closed Resting Conditions

A stepwise multiple regression was conducted to explore whether age, ADHD symptoms (inattention, hyperactivity/impulsivity), and data quality predict FFT power spectra from resting-state measurements.

For pre eyes open data quality, the models revealed an additional significant effect of data quality in step 3 for alpha activity, as well as for beta activity at Fz, and Cz, respectively (alpha: $\Delta R^2 = 0.043$, $p = 0.001$, and $\Delta R^2 = 0.027$, $p = 0.011$; and beta: $\Delta R^2 = 0.035$, $p = 0.005$, and $\Delta R^2 = 0.080$, $p < 0.0001$, respectively). In addition, significant effects were obtained for theta, and delta frequency bands at electrode positions Fz, Cz, and Pz (theta: $\Delta R^2 = 0.035$, $p = 0.001$, $\Delta R^2 = 0.029$, $p = 0.005$, and $\Delta R^2 = 0.016$, $p = 0.047$; delta: $\Delta R^2 = 0.051$, $p < 0.0001$, $\Delta R^2 = 0.059$, $p < 0.0001$, and $\Delta R^2 = 0.063$, $p < 0.0001$, respectively). Furthermore, for pre eyes closed data quality, a significant additional predictive value was obtained for beta, theta, and delta activity at electrode positions Fz, Cz, and Pz (beta: $\Delta R^2 = 0.026$, $p = 0.019$; $\Delta R^2 = 0.074$, $p < 0.0001$; $\Delta R^2 = 0.081$, $p < 0.001$; theta: $\Delta R^2 = 0.052$, $p < 0.001$; $\Delta R^2 = 0.049$, $p < 0.0001$; $\Delta R^2 = 0.039$, $p = 0.002$; and

delta: $\Delta R^2 = 0.082$, $p < 0.001$; $\Delta R^2 = 0.078$, $p < 0.0001$; $\Delta R^2 = 0.082$, $p < 0.001$). Appendix E (in Supplemental material 6.2, Tables A5-A28) shows full details of the results obtained from the stepwise multiple regression models.

To explore the association of data quality and spectral power in more detail, post-hoc correlational analyses were conducted. As revealed by those analyses, data quality is negatively correlated with spectral power for all significant results across all different bands for both conditions, indicating that lower data quality is associated with higher spectral power.

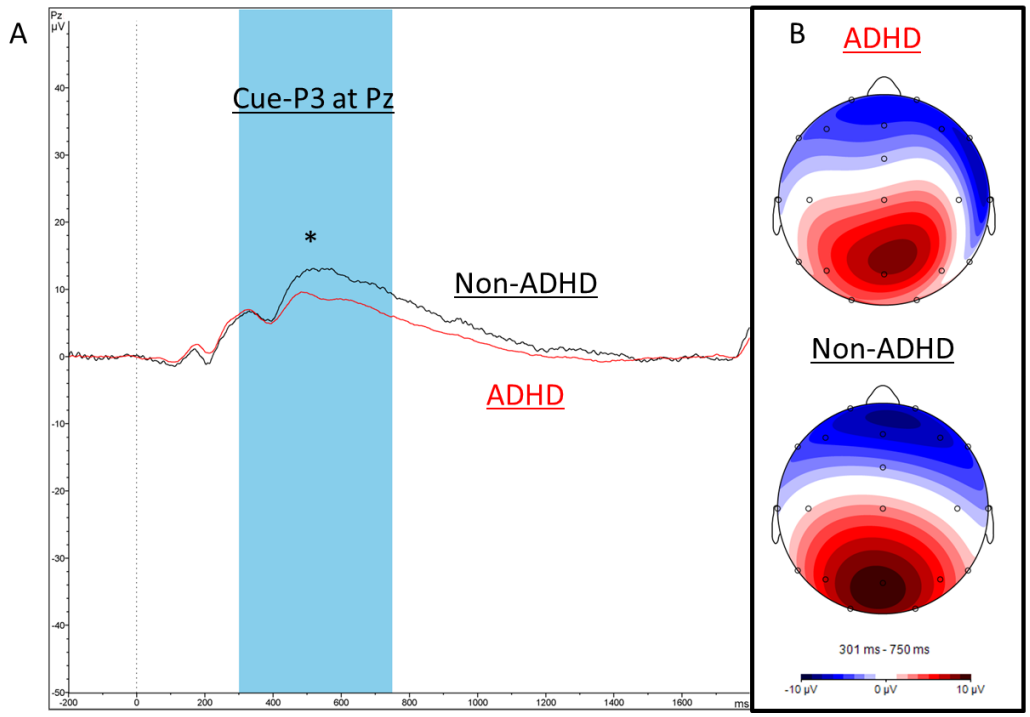

Figure 12. ERP Cue-P3 component for ADHD and non-ADHD control children. A Stimulus-locked ERP wave shapes of the Cue-P3 component for ADHD patients (red), and non-ADHD control children (n=24; black) at electrode Pz. B Corresponding maps in the time range of the Cue-P3 (300–750 ms). *** $p \leq 0.0001$, ** $p \leq 0.001$, * $p \leq 0.01$, ° $p \leq 0.05$.

2.2.5 Discussion

2.2.5.1 Summary of Results and Interpretation

The first aim of this study was to explore EEG data quality parameters in a multi-center study of children, adolescents, and adults with ADHD, and a non-ADHD school-age control sample, and to analyse the potential influence of participant-related and methodological variables. Data quality was defined as the

percentage of artifact-free segments in the EEG after pre-processing. The current study found that across assessments, and most of the measurement conditions, the percentage of artifact-free segments was related to age, and symptoms of hyperactivity/impulsivity. Age is positively associated with data quality, indicating higher data quality with increasing age. For symptoms of hyperactivity/impulsivity, a negative association was obtained, pointing out that with increasing symptoms of hyperactivity/impulsivity the percentage of artifact-free segments decreases. For eyes open data, the association between EEG data quality and ADHD symptoms of hyperactivity/impulsivity was even stronger than for age, whereas for the eyes closed and CPT conditions effects were comparable for those participant-related characteristics. This might possibly be due to sequence effects, with increasing time since the start of the first measurement (resting with eyes open), developmental effects becoming more relevant. Further, for eyes closed data quality, symptoms of inattention seem to play an additional role, with higher symptoms being related to lower data quality. A possible explanation might be that attentional processes are more involved in successfully accomplishing the task of resting with eyes holding closed (e.g., not to move, not to fall asleep). In addition, it is important to note that there are substantial age effects across all task conditions that do not differ between rest-conditions and the CPT, even though a more demanding Flanker-version of the CPT was used for adolescents and adults. Rather than representing a challenge due to task-inherent demands, the 11 min of task completion for the CPT might have caused boredom in children contributing to the reported effect. No significant effect was obtained for condition or any of the methodological influence variables of interest explored within the current trial. No significant data quality differences were obtained for the direct comparison of the three conditions (eyes open versus eyes closed versus CPT, always applied in the same order) across all participants assessed. This indicates that neither task demands nor time effects seem to have a substantial impact on data quality across all participants. From these results it can be suggested that whereas participant-related characteristics have a strong impact on data quality,

the methodological differences regarding study design explored here play a minor role for reliability of EEG study results.

A further objective of this study was to replicate landmark effects typically reported in the EEG literature to prove validity of data. Effects from maturational processes, task demands, and ADHD status have been explored. In line with previous findings, the results of these analyses show that age is negatively associated with EEG spectral power: With increasing age EEG power decreases, especially for slow oscillatory activity (theta and delta bands). However, correlations found here are a bit lower than reported previously (Liechti et al., 2013). This is probably due to a different age range of the assessed ADHD-study population, and symptoms of ADHD with ADHD-patients typically showing lower associations. Furthermore, comparing the alpha reactivity between eyes open and eyes closed conditions, we found an increase in alpha activity in the transition from eyes open to eyes closed replicating previous robust findings on the alpha blocking phenomenon. Additionally, validity analyses addressing robust CPT-effects showed a significantly higher Go-P3 amplitude compared to the NoGo-P3 at posterior regions replicating previous findings on task manipulation effects. Finally, in line with a recent meta-analysis (Kaiser et al., 2020) we found a significant difference in the Cue-P3 amplitude component between children with ADHD and non-ADHD controls, with higher amplitudes in control participants. However, no significant differences were obtained for other ERP components possibly due to different developmental effects. By replicating those landmark effects, we can infer substantial validity of current data allowing for subsequent analyses and valid interpretations, and further, established a link between data quality and replication of previous study results.

Finally, this study aimed to determine the additional effects of data quality on FFT spectral power beyond maturational effects and effects due to symptom severity. As indicated by the stepwise regression models, data quality has a relevant additional impact on spectral power for eyes open, and eyes closed data. As shown by post-hoc correlational analyses, the associations between data quality and FFT

spectral power are negative indicating higher activity in frequency band power with lower data quality. For alpha and beta frequency bands in eyes open datasets, this result might be explained by the fact that those bands include the highest frequency band widths ranging from 7.5 to 12.5 Hz and 12.5 to 30 Hz, respectively. These higher frequency band ranges might be more affected by myogenic activity near the head with a high-frequency activity of >20 Hz (Goncharova et al., 2003). This increased myogenic activity might consequently lead to a lower percentage of artifact-free segments influencing results obtained in FFT analyses, such as diluting or mimicking EEG alpha or beta rhythms.

2.2.5.2 Relevance of Results and Practical Implications

The findings of the current study highlight the relevance of explicit data quality assessments in EEG studies, especially when younger populations are in the focus of interest, and when psychiatric samples are explored prone to EEG artifacts. It is interesting to note, that while participant-related characteristics have a substantial impact on data quality, reliability, and consequently the interpretability of findings, the methodological variables explored here have not. This finding has a highly important impact on the process of study implementation including the planning of data pre-processing strategies. It seems especially relevant that demographic and clinical characteristics of participant samples included in studies are reported explicitly in publications: Effects can be classified more accurately, and addressed in replication studies as well as in reviews and meta-analytic approaches. Nevertheless, future studies should assess further different methodological variables, and efforts on methodological standardization for a higher comparability of study results should moreover be strengthened (Debnath et al., 2020; Kappenman et al., 2021).

By replicating robust landmark effects of the EEG literature, we were able to prove validity of current datasets, and to ensure valid conclusions drawn from subsequent analyses. Ensuring reliability and validity of assessed data has

substantial implications for the status quo of a research field. They allow for valid interpretation of study results, and a higher application value, e.g., for deep-learning approaches (Chen, Song, et al., 2019). This finding further highlights that large-scale multicenter studies on ADHD patients prone to EEG artifacts are feasible. This feasibility is urgently needed for further detailed explorations of the diagnostic and predictive value of EEG/ERP markers for this highly prevalent neurodevelopmental disorder.

The finding of an additional effect of our data quality index on FFT spectral power beyond maturational processes and symptoms of ADHD points out to the need for discussing and challenging EEG results on spectral power as dependent variable, especially for classification purpose. This result might be due to myogenic activity as a potential confounder (diluting or mimicking spectral power effects) contaminating the EEG signal. Nevertheless, those indices might be of value for characterizing psychiatric patients, especially, when motor activity represents a central characteristic of clinical populations explored. They might be of additional value for classification purposes and for differentiating clinical from non-clinical groups, as well as between different clinical groups. In addition, controlling for EEG data quality seems to be urgently needed when spectral power analyses are conducted.

2.2.5.3 Limitations and Future Directions

A few limitations of the current work have to be mentioned. First, in our ADHD sample age was restricted from 6 to 45 years. No older adults were included, and only a few datasets for adolescents. Therefore, effects are primarily driven by data from children and young adults. This has to be taken into account when interpreting current results. Future studies are needed including a sample with a larger age range of included ADHD patients. Furthermore, only a small non-ADHD sample in school-age was recruited. Therefore, as we not have a full-factorial design of ADHD status across all age groups, patient-control comparisons in our validation

analyses could only be conducted on children between 6 and 12 years of age. In future work, larger non-ADHD samples should be included spanning a broader age range.

Within the current study, the focus was set on a few potentially relevant participant-related and methodological variables influencing data quality. Besides those variables addressed within the current work, others might be relevant. Further studies are needed at this stage. In addition, the percentage of artifact-free segments was defined as the relevant index of data quality. There exist many more data quality indices and further replication of current results is needed comparing different data quality indices. Within our analyses, no corrections for multiple testing were applied. However, as our analyses involved replications, and only partial overlap regarding characteristics and datasets within separate tests, this is not necessarily recommended.

Additionally, further EEG measures besides spectral power and ERP amplitudes and latencies might be of relevance for future work on data quality. For example, functional connectivity measures between different electrode locations could be assessed and analyzed in multivariate models in future studies as they might be relevant for a further characterization of ADHD. As we are explicitly interested in data quality effects, the current work focused on peak amplitudes rather than mean amplitudes as peak amplitudes are typically most affected by noise (Boudewyn et al., 2018; Clayson et al., 2013; Clayson & Miller, 2017; Kappenman & Luck, 2016; Luck, 2014). However, future work will also assess other ERP indices. In particular, besides peak amplitude data mean amplitudes of relevant ERP indices will be taken into account for a more robust and unbiased approach.

2.2.5.4 Conclusions

The current study contributes to our understanding of EEG data quality, participant-related and methodological variables influencing EEG data quality, and the additional effects of data quality on results obtained from FFT analyses beyond

demographic and clinical characteristics. To the best of our knowledge, this is the first study explicitly investigating the impact of several study-specific variables on data quality in a large ADHD sample from 6 to 45 years of age. The results of this investigation show that on the one hand demographic variables, especially, age and symptoms of hyperactivity/impulsivity, have a substantial impact on data quality. On the other hand, methodological differences regarding study-design and analytical methods assessed here have not. Furthermore, the current work highlights the importance of replication analyses to prove validity of the assessed data. Additionally, we found that data quality substantially affects spectral power beyond patient-related characteristics pointing out to the need for cautious interpretations of results obtained in EEG analyses on frequency band power. These findings have a high relevance for the implementation of studies, analyzing and publishing EEG data, and for interpreting scientific results obtained from EEG studies. Further, current results show that with a careful design and systematic data quality control, informative large-scale multicenter trials on neurophysiological mechanisms in neurodevelopmental disorders across the lifespan are actually feasible. Nevertheless, results are restricted to the limitations discussed. Future studies are needed to replicate and extend current findings.

2.3 STUDY 3: A developmental perspective on impulsivity-facets and brain-activity correlates from adolescence to adulthood

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In preparation/will be submitted as: Kaiser, A., Holz, N. E., Barker, G. J., Bokde, A. L. W., Quinlan, E.B., Desrivières, S., Flor, H., Grigis, A., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Martinot, J.-L., Paillère Martinot, M.-L./Artiges, L., Papadopoulos Orfanos, D., Paus, T., Poustka, L., Millenet, S., Fröhner, J. H., Smolka, M. N., Walter, H., Whelan, R., Schumann, G., Schwarz, E., Banaschewski, T., Baumeister, S., Brandeis, D., Nees, F., and the IMAGEN consortium (*in preparation*). A developmental perspective on impulsivity-facets and brain-activity correlates from adolescence to adulthood.

2.3.1 Abstract

Impulsivity represents a multidimensional construct including trait components and behavioral facets such as decisional impulsivity. However, so far, changes in associations between measures of impulsivity-facets during adolescence into young adulthood are not fully understood. Further, it is still not clear how measures of trait impulsivity and decisional components relate to neural activity during inhibitory control and reward anticipation, respectively. We used data from the longitudinal multicenter, population-based cohort-study IMAGEN, where 2034 healthy adolescents were investigated at age 14, and 1383 were re-assessed at young adulthood (19 years). We measured trait impulsivity using self-report questionnaires, and decisional impulsivity via temporal- and probabilistic-discounting tasks. With functional magnetic-resonance imaging we assessed brain activity during inhibitory control using the Stop-Signal task and during reward anticipation in the Monetary Incentive-Delay task. Correlations were analysed and mixed-effects models were used to explore developmental and predictive effects. All measures of trait and decisional impulsivity were correlated during adolescence and young adulthood, respectively. Further, pre-supplementary motor-area- and inferior frontal gyrus-activity during inhibitory control was associated with trait impulsivity and probabilistic discounting in adolescents, whereas in young adulthood, reward-anticipation activity in the ventral striatum was associated with trait impulsivity, but not with temporal discounting. No predictive effect of brain responses in adolescence for later trait or decisional impulsivity in young adulthood was found. We identified associations between measures of trait and decisional forms of impulsivity as well as with brain activity during inhibitory control and reward anticipation. Substantial changes occur along the developmental period from adolescence to young adulthood, mainly driven by changes on a neural level. Our findings help to better understand the multidimensional nature of impulsivity and associated patterns of brain activity. Furthermore, current results highlight the need for taking brain-developmental processes into account when exploring neuromarker-candidates.

2.3.2 Introduction

Impulsivity is a multifaceted construct encompassing a broad variety of dimensions, including trait aspects and behavioral components (Dalley & Robbins, 2017). It is still not clear how these different facets of impulsivity are related, and how correlations change over time, particularly during critical developmental periods such as adolescence and young adulthood. Additionally, some previous studies established a link between trait and behavioral forms of impulsivity and brain activity during several different processes such as inhibitory control as a motoric form of impulsivity, and reward processing as a further related concept of motivational control (e.g. Plichta & Scheres, 2014; Wang et al., 2016; Whelan et al., 2012). However, studies are lacking that relate dimensions of impulsivity assessed via different measurement methods to brain-activity patterns and that also address developmental trajectories in these associations. This would enable a deeper characterization and understanding of the multidimensional nature of impulsivity, measures assessing impulsivity, and related developmental changes. Further, it might be relevant for potential clinical application with regard to diagnostic and predictive purposes. The current work addresses these open issues within a large-scale multicentre-study exploring a population-based cohort of adolescents followed longitudinally into young adulthood (Schumann et al., 2010).

Impulsivity or impulsive behavior is a multidimensional concept defined as a predisposition for rapid, but often premature, actions without appropriate foresight (Dalley & Robbins, 2017). The ability to decide and act quickly without hesitation can thus be advantageous in many settings. However, when persistently expressed, it can also have negative consequences in many daily-life situations and can be a risk factor for the development of various mental health disorders (Bari & Robbins, 2013; Beauchaine et al., 2017). The multidimensionality of the concept of impulsivity is reflected by a rather heterogeneous theoretical conceptualization ranging from the definition as a trait assessed via self-report to more behavioral concepts, including decisional components and action-related, motoric aspects, typically measured using

neuropsychological testing (Dalley & Robbins, 2017). While motoric, action-related aspects involve response inhibition, decisional components include temporal and probabilistic discounting of delayed rewards and reflection impulsivity. Temporal discounting is defined as the preference for small, immediate rewards, over later but larger ones; probabilistic discounting is the preference for smaller but more likely rewards compared to larger but less likely ones; reflection impulsivity describes the tendency for rapid decision-making without adequately taking into account all available situational evidence. Some of the component-processes of impulsivity might share common variance, thus suggesting overlapping psychological mechanisms. However, different measures of impulsivity often fail to inter-correlate substantially, indicating that also specific aspects might be involved (MacKillop et al., 2016). Therefore, these low correlations and the earlier heterogeneous findings might be due to a true (at least partial) non-overlap between different impulsivity-facets representing rather distinct psychological component-processes and different measures assessing rather distinct facets of the construct (Dalley & Robbins, 2017; Reynolds et al., 2006; Sharma et al., 2014; Vasconcelos et al., 2014). In addition, another possible reason for the rather inconsistent previous results might be related to characteristics of the included participant samples: earlier studies on impulsivity-facets mainly relied on adult samples in cross-sectional designs, focusing on this later developmental period thereby neglecting longitudinal changes during critical earlier maturational phases (Plichta & Scheres, 2014; Wang et al., 2020). Especially during adolescence, substantial behavioral and brain changes have often been acknowledged (Constantinidis & Luna, 2019; Duka et al., 2017), highlighting the relevance of focusing research on this developmental period (Whelan et al., 2012). Up to now, it is still unclear, how associations between different measures of latent facets of impulsivity change due to developmental processes.

Earlier studies already identified neural correlates of trait and behavioral forms of impulsivity (Mitchell & Potenza, 2014). Thereby, brain responses were assessed as task-related brain activity either during tasks measuring component-

processes of impulsivity inherent in the broad theoretical conceptualization of the construct or during tasks measuring related cognitive processes. For example, brain responses during inhibitory control have been associated with behavioral inhibition during neuropsychological testing (Sakai et al., 2013; Steele et al., 2013) involving the cooperation of the (pre-)frontal cortex such as the inferior frontal gyrus (IFG), the pre-supplementary motor area (pre-SMA), and further subcortical structures (Bartholdy et al., 2019; D'Alberto et al., 2018). Further, reward processing as a form of motivational control has been linked to measures of facets of impulsivity in earlier work: thereby, fronto-striatal deviations during reward anticipation have been associated with e.g. trait impulsivity (Plichta & Scheres, 2014). So far it is not known, how different measures of impulsivity-facets are related with neural activity, and how correlations change across critical developmental periods. Further, it is still rather unclear, if those brain-activity patterns have a predictive value for later changes in impulsivity (Cai et al., 2020).

The current study addressed the associations between trait impulsivity assessed using self-report questionnaires and decisional aspects of impulsive behavior measured via neuropsychological testing. Thereby, two facets of decisional impulsivity, namely temporal and probabilistic discounting, were distinguished. Associations were explored longitudinally during adolescence and young adulthood and linked to brain activity during inhibitory control as a motoric form of impulsivity and reward anticipation as a related construct reflecting aspects of motivational control. Additionally, we aimed at delineating the potential predictive value of neural activity characteristics in adolescence for later trait and decisional impulsivity in young adulthood.

2.3.3 Methods and Materials

2.3.3.1 Participants

Anonymized data for the present study were obtained from the IMAGEN project (Mascarell Maričić et al., 2020), a multicenter study including eight sites (London, Nottingham, Dublin, Mannheim, Dresden, Berlin, Hamburg, Paris).

Healthy participants were longitudinally assessed at baseline during adolescence (at around age 14), and re-assessed at follow-up in young adulthood (at around the age of 19). Ethics approval was provided by the local ethical committees for each participating center and informed consent was obtained from parents or guardians. Furthermore, verbal assent was obtained from the adolescent. As young adults, participants provided written informed consent. Exclusion criteria were: serious medical conditions, previous trauma with loss of consciousness, any MRI contraindications or IQ<70. Details regarding the study protocol and data acquisition have been published previously (Schumann et al., 2010). Participants were included in the current analyses if they had at least one latent facet of either trait impulsivity or decisional impulsivity assessed via self-report questionnaires or neuropsychological testing, respectively, and one functional Magnetic Resonance Imaging (fMRI) task of interest at baseline. Finally, data from n=2034 healthy adolescents (age in years: M=13.96, SD=0.45; IQ: M=108.15, SD=13.53; male in %=49.4), and n=1383 of these participants in young adulthood (age in years: M=19.09, SD=0.77) were included.

2.3.3.2 Assessment of impulsivity-facets: trait & decisional impulsivity

Trait impulsivity was assessed at baseline (adolescence) and follow-up (young adulthood) using the following scales: the extraversion subscale from the NEO-PI-R Personality inventory (Costa & McCrae, 1997), the impulsivity subscale from the Substance Use Risk Profile Scale (SURPS; Conrod & Woicic, 2002), and the Impulsiveness vs. Reflection subscale from the Temperament and Character Inventory revised version (TCI-R; Cloninger et al., 1999). To assess temporal discounting as a form of decisional impulsivity, the Monetary-Choice Questionnaire (KIRBY; Kirby & Maraković, 1996) was used at baseline and follow-up. For measuring probabilistic discounting, as another form of decisional impulsivity, the Cambridge Guessing Task (CGT) from the Cambridge Cognition Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition) was

included at baseline only. For more details on the scales and tasks used, see Supplement A (in Supplemental material 6.3).

2.3.3.3 Assessment of related neural activity – fMRI paradigms

The Stop Signal Task (SST; Duka et al., 2017; Rubia et al., 2001) was implemented to assess neural activity related to inhibitory control as a motoric form of impulsivity in pre-SMA, and IFG (see Supplement B in Supplemental material 6.3 for a detailed description and Figure S1 for an example outline). The Monetary Incentive Delay task (MID; Knutson et al., 2000; Rubia et al., 2001) was used to explore striatal activity during reward anticipation as a related concept reflecting aspects of motivational control (see Supplement B in Supplemental material 6.3 for a detailed description and Figure S2 for an example outline). Both tasks were assessed at baseline and follow-up.

2.3.3.4 Data acquisition

Imaging data were acquired at each of the eight sites with 3T MRI scanners by different manufacturers (Siemens, Philips, General Electric, Bruker). Full details of the MRI acquisition protocols and quality checks have been published previously (Schumann et al., 2010). fMRI images were acquired using an echo-planar imaging (EPI) sequence. For each subject, 444 volumes were acquired for the SST, and 300 volumes were acquired for the MID task. For both tasks, each volume consisted of 40 slices (2.4 mm slice thickness,1 mm gap), and to provide reliable imaging of subcortical areas, echo time was optimized (TE=30 ms; TR=2.2 s). The same scanning protocol was used at all sites.

2.3.3.5 Data preparation

Data were z-standardized and confirmatory factor analyses (CFAs; Chamberlain & Sahakian, 2007) were conducted on the manifest variables assessed for trait impulsivity (NEO-FFI, SURPS, TCI) and temporal discounting (K1-K3 values for the KIRBY resulting in distinct categorical scores), respectively, to form one latent factor using the R software package lavaan version 0.6-6 (Rosseel et al., 2020).

Predicted values were calculated for each participant estimating the factor scores on each latent construct.

fMRI data were analyzed with SPM8 (Wellcome Trust Center, 2009), and Matlab 2011b (MATLAB and Statistics Toolbox Release, 2011). A detailed description of fMRI-data pre-processing has been published previously (Nymberg et al., 2013). In short, data were slice-time corrected. Then, all volumes were aligned to the first volume and non-linear warping was performed to normalize slices to the standard Montreal Neurological Institute (MNI) space. Afterwards, images were smoothed with a Gaussian kernel of 5 mm full width at half-maximum (FWHM). At the first level of analysis for the SST data, for each subject, linear models were created by convolving the canonical hemodynamic response function with the onsets of each trial-type to form regressors of interest. For each subject, movement parameters were added to the design matrix as regressors of no interest. Besides others, the 'stop failure versus stop success' contrast was computed for each participant in order to measure neural activity associated with unsuccessful stopping (Heinrich et al., 2013). In the same way, MID data were pre-processed. Besides others, the contrast 'anticipation hit big win versus anticipation hit no win' was computed for each participant as an index of neural activity associated with anticipation of a large reward (Barker et al., 2019). Region of interest (ROI) masks were derived from the wfu-pickatlas version 3.0.5 (Maldjian et al., 2003): the bilateral IFG, and pre-SMA (separately) for the SST (White et al., 2014), as well as the bilateral VS for the MID task (Oldham et al., 2018; Weiland et al., 2013). Via the Region of Interest Extraction Toolbox version 2.1 (REX; Whitfield-Gabrieli, 2009), mean ROI activity values were exported for each participant. In analogy to the manifest variables assessing trait impulsivity and temporal discounting, values were z-standardized and a CFA was conducted for the SST mean activity values to estimate predicted values for each participant forming one latent factor representing unsuccessful stopping activity related to motoric impulsivity in both ROIs.

Data distribution and the presence of extreme values were explored using Stem-and-Leaf plots in SPSS version 24 (IBM SPSS Statistics, 2016).

2.3.3.6 Statistical analyses

To explore associations between measures of latent facets of trait impulsivity and decisional impulsivity (at baseline and follow-up, respectively) and their relationship with brain-functional measures, linear partial correlation analyses were performed using SPSS version 24 (IBM SPSS Statistics, 2016), controlling for age, sex, IQ, and site. As we explored associations between three or two impulsivity-facets and brain-functional activity at baseline and follow up, respectively, p-values below a Bonferroni-corrected conservative threshold of 0.017 were considered significant. As the CGT was only assessed at baseline, for follow-up data no correlational analyses could be conducted with probabilistic discounting.

To assess changes in relationships from adolescence to young adulthood, linear mixed-effects models were fitted to the data using the *nlme* package in R software version 3.5.1 (R Development Core Team, 2018). Random intercepts and slopes were included. Measures of the latent dimensions of trait impulsivity and decisional impulsivity were entered as dependent variables, separately. Brain-functional measures (during inhibitory control and reward anticipation, respectively) were used as independent variables. Of special interest for exploring developmental changes in associations was the interaction term between visit (baseline vs. follow-up) and brain activity. Furthermore, these models were subsequently used for prediction purpose: again, measures of the latent dimensions of trait impulsivity and decisional impulsivity were entered as dependent variables, separately. Baseline-corrected predictors were additionally entered into the model. Those baseline-corrected predictors were used to explicitly control for confounding effects of previous measurements in longitudinal data.

Age, sex, IQ, and site were included as control variables of no interest for all mixed-effects model analyses. Relevant effects of control variables on latent constructs of interest are presented in Supplement C in Supplemental material 6.3,

S3-S6. As the CGT measuring probabilistic discounting was only assessed at baseline, models could not be fitted for this facet of decisional impulsivity as dependent variable. For linear mixed-effects models, extreme values were not excluded due to the possibility that they represent true random variation that might be of special interest with regards to implications for psychiatric populations.

2.3.4 Results

2.3.4.1 Descriptive statistics

Descriptive statistics for manifest variables at baseline and follow-up can be found in Table 10, respectively. Furthermore, Supplement D in Supplemental material 6.3, Figure S7 shows the distribution of (predicted) values for each of the latent constructs after z-standardization. At first, we explored the linear associations between different measures of facets of impulsivity, namely trait impulsivity and the two forms of decisional impulsivity, namely temporal and probabilistic discounting. During adolescence, there was a significant positive association between all three latent dimensions of trait impulsivity and decisional impulsivity assessed: trait impulsivity and temporal discounting ($r_{partial}$=0.094, p=0.001, df=1315), trait impulsivity and probabilistic discounting ($r_{partial}$=0.113, p<0.001, df=1105), and temporal and probabilistic discounting ($r_{partial}$=0.080, p=0.008, df=1102). During young adulthood, a significant positive linear relationship was observed between trait impulsivity and temporal discounting ($r_{partial}$=0.123, p<0.001, df=917).

Table 10
Descriptive statistics for manifest variables

	Baseline (14 years)			Follow-up (19 years)		
Scale	***N***	***M***	***SD***	***N***	***M***	***SD***
NEO-FFI	2019	30.03	5.60	1448	29.44	5.81
SURPS	2014	2.44	0.45	1428	2.21	0.43
TCI	2011	26.03	4.27	511	25.54	3.35
KIRBY K1	2021	0.04	0.05	1433	0.63	0.11
KIRBY K2	2018	0.03	0.04	1433	0.63	0.10
KIRBY K3	2021	0.03	0.01	1433	0.38	0.07
CANTAB – CGT	1670	0.25	0.14	*n.a.*	*n.a.*	*n.a.*
MID (ROI: VS)	1430	0.26	0.32	749	0.22	0.27
SST (ROI: pre-SMA)	1609	-0.04	0.75	712	-0.05	0.74
SST (ROI: IFG)	1609	-0.03	0.64	712	-0.04	0.64

Note. n.a. not available. Not all data were assessed for each subject included, see selection criteria in methods section (therefore, $N < 2034$).

2.3.4.2 Neural correlates of trait and decisional impulsivity at baseline (age 14)

During adolescence, higher brain activity in pre-SMA and IFG during inhibitory control was related to lower trait impulsivity ($r_{partial}$=-0.075, p=0.015, df=1063), as well as less probabilistic discounting ($r_{partial}$=-0.069, p=0.039, df=884; see Figure 1; see Figures S8 and S9, Supplement E in Supplemental material 6.3 for non-significant associations). Supplement F (in Supplemental material 6.3; Figures S10-S16) presents the results for the relationships in adolescence excluding extreme values, resulting in similar associations.

2.3.4.3 Neural correlates of trait and decisional impulsivity at follow-up (age 19)

During young adulthood, there was a nominally significant positive association between brain activity in the VS during reward anticipation in the VS with trait impulsivity ($r_{partial}$=0.094, p=0.046, df=453; see Figure 13). Again, a similar association was observed when extreme values were removed prior to analysis (Supplement F in Supplemental material 6.3, Figures S17-S21).

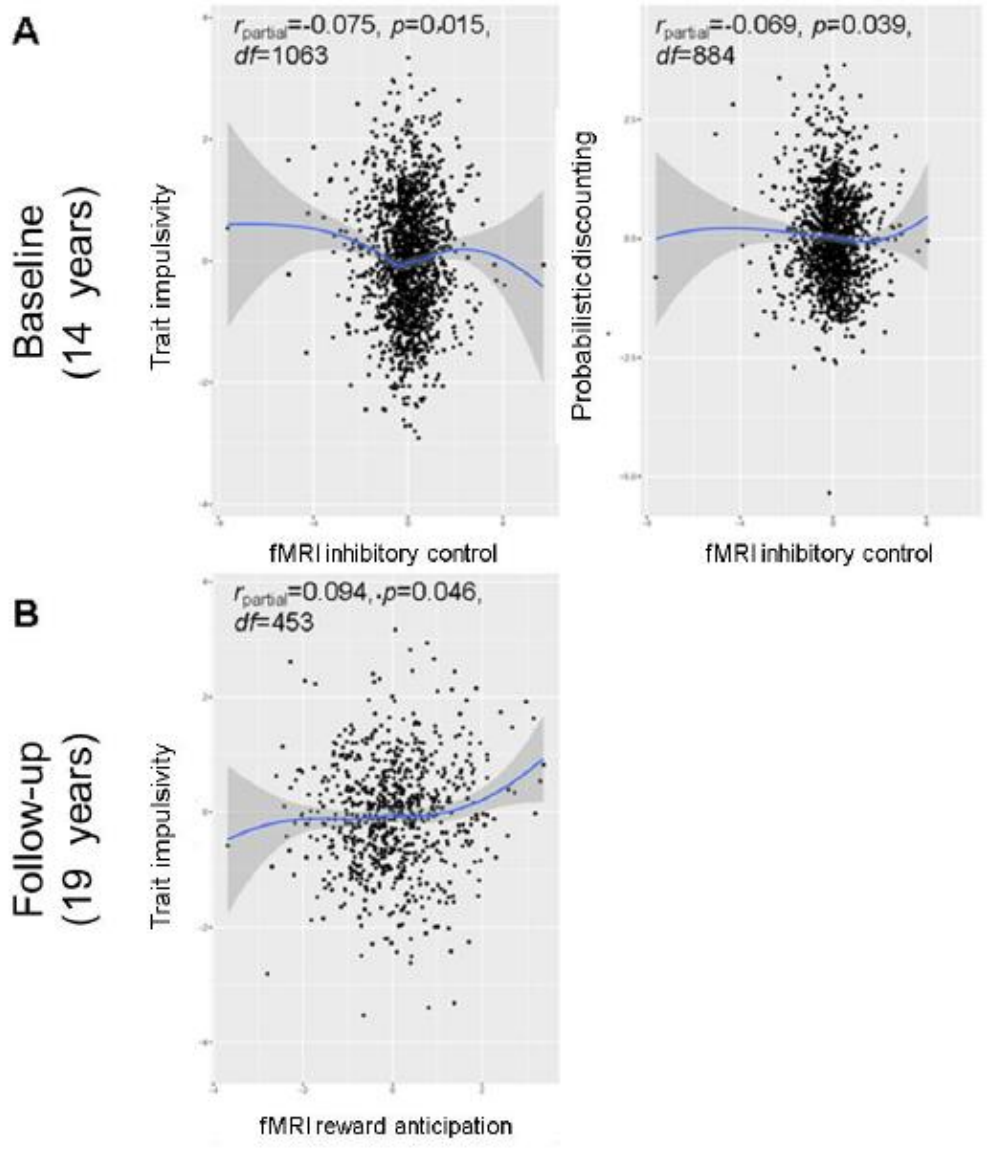

Fig. 13. Significant brain-responsivity impulsivity associations at baseline (A) and follow-up (B), respectively. *Note.* ° $p \leq .10$, * $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$. fMRI reward anticipation represents mean ROI activity in VS. fMRI inhibitory control reflects weighted mean ROI activity (CFA) in pre-SMA and IFG.

2.3.4.4 Changes in associations from baseline (age 14) to follow-up (age 19)

Changes in associations between brain activity and measures of the latent facets of trait impulsivity and decisional impulsivity are displayed in Tables 11 and 12. There was a significant interaction between visit and reward-anticipation activity in the VS for trait impulsivity ($t(281)=2.12$, $\beta=0.12$, $p=0.03$) as well as for temporal discounting ($t(272)=2.32$, $\beta=0.14$, $p=0.02$). During the approximately 5 years from baseline to follow-up, a nominally significant association between striatal activity during reward anticipation and trait impulsivity emerges in young adulthood. No significant changes in association strength were observed for neural activity in pre-SMA and IFG during inhibitory control, neither for trait impulsivity ($p=0.82$) nor for temporal discounting ($p=0.92$).

Figure 14 visually presents the differences in associations at baseline and follow-up, respectively. Plots of residuals and plots of random effects for mixed-effects models can be found in Supplement G (in Supplemental material 6.3; Figures S22-S23).

Table 11
Linear mixed-effects model results for change in association between trait impulsivity/temporal discounting and neural activity during inhibitory control

	Trait impulsivity					**Temporal discounting (decisional impulsivity)**				
Random effects	***SD***	***r***				***SD***	***r***			
Intercept	1.61	-				1.70	-			
visit	0.96	-0.90				1.06	-0.93			
residual	0.54	-				0.55	-			
Fixed effects	**Estimate**	***SE***	***Df***	***t***	***p***	**Estimate**	***SE***	***Df***	***t***	***p***
Intercept	0.02	0.98	1130	0.02	0.99	2.64**	0.93	1126	2.85	<0.01
visit	<0.01	0.05	347	0.18	0.86	0.04	0.06	340	0.73	0.46
fMRI inhibitory control	0.55	1.04	347	0.53	0.60	-0.87	1.02	340	-0.86	0.39
age	<0.001	<0.001	1130	0.33	0.74	<-0.001°	<0.001	1126	-1.95	0.05
sex (as factor)	-0.004	0.06	1130	-0.07	0.95	-0.14**	0.05	1126	-2.70	<0.01
IQ	-0.002	0.002	1130	-0.93	0.35	-0.009***	0.002	1126	-4.15	<0.001
site (as factor)	-	-	-	-	-	-	-	-	-	>0.10[1]
site2	0.09	0.10	1130	0.85	0.39					
site3	0.15	0.13	1130	1.22	0.22					
site4	-0.18	0.12	1130	-1.48	0.14					
site5	-0.18	0.10	1130	-1.81	0.07					
site6	-0.07	0.11	1130	-0.69	0.49					
site7	-0.09	0.10	1130	-0.84	0.40					
site8	-0.34**	0.12	1130	-2.75	<0.01					
visit*fMRI inhibitory control	-0.01	0.06	347	-0.23	0.82	<-0.01	0.06	340	-0.10	0.92
fMRI inhibitory control *age	<-0.001	<0.001	347	-0.71	0.48	<0.001	<0.001	340	0.21	0.83
fMRI inhibitory control *sex	0.03	0.06	347	0.50	0.62	0.11*	0.06	340	2.07	0.04
fMRI inhibitory control *IQ	<0.001	0.002	347	0.29	0.77	0.006**	0.002	340	2.71	<0.01
fMRI inhibitory control *site (as factor)	-	-	-	-	>0.10[1]	-	-	-	-	>0.10[1]

Note. *** $p \leq .001$, ** $p \leq .01$, * $p \leq .05$, ° $p \leq .1$. Sex and site were included as factors with sex 1 and site1 as reference, respectively. [1]all site-effects not significant: p >.10.

Table 12
Linear mixed-effects model results for change in association between trait impulsivity/temporal discounting and neural activity during reward anticipation

	Trait impulsivity					**Temporal discounting (decisional impulsivity)**				
Random effects	***SD***	***r***				***SD***	***r***			
Intercept	1.52	-				1.66	-			
visit	0.92	-0.89				1.03	-0.92			
residual	0.52	-				0.53	-			
Fixed effects	**Estimate**	***SE***	***Df***	***t***	***p***	**Estimate**	***SE***	***Df***	***t***	***p***
Intercept	1.14	0.99	1093	1.15	0.25	2.43*	0.97	1091	2.49	0.01
visit	-0.07	0.05	281	-1.33	0.19	-0.006	0.06	272	-0.10	0.92
fMRI reward anticipation	0.30	0.98	281	0.31	0.76	-1.17	0.99	272	-1.18	0.24
age	<-0.001	<0.001	1093	-0.54	0.59	<-0.001	<0.001	1091	-1.47	0.14
sex (as factor)	-0.04	0.06	1093	-0.66	0.51	-0.17**	0.06	1091	-2.97	<0.01
IQ	-0.004*	0.002	1093	-1.98	<0.05	-0.01***	0.002	1091	-4.58	<0.001
site (as factor)	-	-	-	-	>0.10[1]	-	-	-	-	-
site2						0.10	0.10	1091	0.92	0.36
site3						<0.01	0.13	1091	0.03	0.97
site4						0.18	0.12	1091	1.44	0.15
site5						0.12	0.10	1091	1.23	0.22
site6						0.19	0.11	1091	1.71	0.09
site7						0.23*	0.10	1091	2.24	0.03
site8						0.02	0.11	1091	0.23	0.83
visit*fMRI reward anticipation	0.12*	0.06	281	2.12	0.03	0.14*	0.06	272	2.32	0.02
fMRI reward anticipation *age	<-0.001	<0.001	281	-0.59	0.55	<0.001	<0.001	272	0.88	0.38
fMRI reward anticipation *sex	-0.07	0.05	281	-1.26	0.21	<0.01	0.05	272	0.13	0.89
fMRI reward anticipation *IQ	0.001	0.002	281	0.65	0.52	<0.001	0.002	272	0.46	0.65
fMRI reward anticipation *site (as factor)	-	-	-	-	>0.10[1]	-	-	-	-	>0.10[1]

Note. *** $p \leq .001$, ** $p \leq .01$, * $p \leq .05$, ° $p \leq .1$. Sex and site were included as factors with sex 1 and site1 as reference, respectively. [1]all site-effects not significant: p >.10.

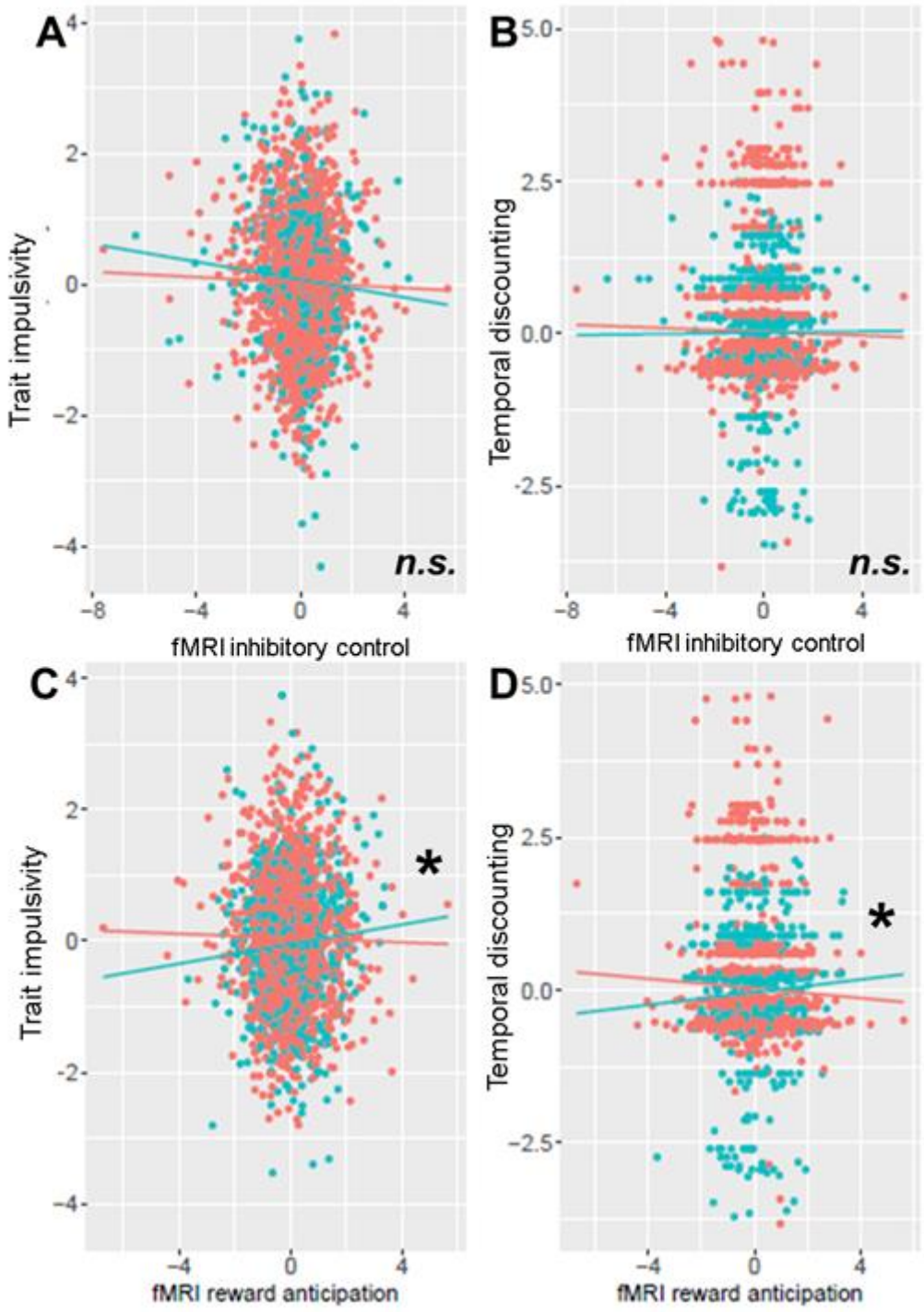

Fig. 14. Plots of changes of brain-responsivity impulsivity relationships from adolescence to young adulthood. *Note.* A - association between trait impulsivity and fMRI inhibitory control; B - association between temporal discounting and fMRI inhibitory control; C - association between trait impulsivity and fMRI reward anticipation; D - association between temporal discounting and fMRI reward anticipation. Red dots and lines represent data in adolescence (Baseline). Turquoise dots and lines show data in young adulthood (Follow-up). * $p \leq .05$, ° $p \leq .1$, *n.s.* not significant (significance value refers to change in association).

2.3.4.5 Predictive value of neural activation patterns at baseline (age 14) for impulsivity at follow-up (age 19)

Using mixed-effects models, we explored whether brain activity during adolescence predicted either trait impulsivity or temporal discounting during young adulthood, but found no significant associations. Tables 13 and 14 present the results from the mixed-effects model analyses including baseline-corrected predictors.

2.3.4.6 Post-hoc analyses

In post-hoc analyses, partial correlations between baseline and follow-up measurements were calculated to explore associations across time controlling for age, IQ, and sex. Results are presented in Supplement H (in Supplemental material 6.3). Especially, we found low and non-significant correlations for neural activity measures between baseline and follow-up, indicating substantial changes on a neural level during the 5-year time period from adolescence to young adulthood.

Table 13
Linear mixed-effects model results for predicting trait impulsivity based on neural activity

	Trait impulsivity				
Random effects	***SD***	***r***			
Intercept	0.64	-			
visit	0.32	0			
residual	0.24	-			
Fixed effects	**Estimate**	***SE***	***Df***	***t***	***p***
Intercept	3.35°	1.46	500	2.29	0.02
trait impulsivity (*baseline*)	0.25***	0.04	500	5.93	<0.001
fMRI reward anticipation (*baseline*)	-0.04	0.04	500	-0.86	0.39
fMRI inhibitory control (*baseline*)	-0.07	0.05	500	-1.60	0.11
age	<-0.001*	<0.001	500	-1.98	<0.05
sex (as factor)	-0.07	0.08	500	-0.83	0.41
IQ	-0.006°	0.003	500	-1.68	0.09
site (as factor)	-	-	500	-	<0.10

Note. *** $p \leq .001$, ** $p \leq .01$, * $p \leq .05$, ° $p \leq .1$. Sex and site were included as factors with sex 1 and site 1 as reference, respectively.

Table 14
Linear mixed-effects model results for predicting temporal discounting based on neural activity

	Temporal discounting (decisional impulsivity)				
Random effects	***SD***	***r***			
Intercept	0.72	-			
visit	0.36	0			
residual	0.27	-			
Fixed effects	**Estimate**	***SE***	***Df***	***t***	***p***
Intercept	2.73	1.66	488	1.40	0.16
Temporal discounting (*baseline*)	0.14**	0.05	488	2.84	<0.01
fMRI reward anticipation (*baseline*)	-0.03	0.05	488	-0.51	0.61
fMRI inhibitory control (*baseline*)	0.07	0.05	488	1.42	0.16
age	<-0.001	<0.001	488	-1.05	0.29
sex (as factor)	-0.09	0.10	488	-0.93	0.35
IQ	-0.01°	0.004	488	-1.82	0.07
site (as factor)	-	-	-	-	-
site2	0.41*	0.18	488	2.30	0.02
site3	0.14	0.23	488	0.60	0.55
site4	-0.03	0.23	488	-0.11	0.91
site5	0.26	0.16	488	1.56	0.12
site6	0.32	0.18	488	1.81	0.07
site7	0.13	0.17	488	0.74	0.46
site8	0.52**	0.19	488	2.68	<0.01

Note. *** $p \leq .001$, ** $p \leq .01$, * $p \leq .05$, ° $p \leq .1$. Sex and site were included as factors with sex 1 and site 1 as reference, respectively.

2.3.5 Discussion

2.3.5.1 Summary of results and interpretation

Within our large population-based sample of adolescents assessed longitudinally at age 14 and again as young adults at age 19, we found significant associations between all measures of trait impulsivity, temporal discounting, and probabilistic discounting in adolescence. For young adulthood, a significant correlation was identified for trait impulsivity and temporal discounting as probabilistic discounting was not assessed at follow-up. In line with previous results (Cyders & Coskunpinar, 2011; Hasegawa et al., 2019; Sharma et al., 2014), correlations between measures of impulsivity-facets were rather small indicating that although different measures of component processes of impulsivity share common variance, they are also characterized by requiring distinct psychological processes. This conclusion is further supported by the finding that measures of different facets of impulsivity distinguished within the current work show distinct patterns of

associated brain activity. During adolescence, the exploration of the relation between trait impulsivity and two forms of decisional impulsivity with neural activity resulted in a significant, but weak negative association between neural activity in pre-SMA and IFG during inhibitory control and trait impulsivity. Further, a nominally significant negative correlation with probabilistic discounting was identified. During young adulthood, we found a nominally significant positive association between neural activity in VS during reward anticipation and trait impulsivity. As indicated by these results, brain activity in pre-SMA and IFG during inhibitory control might represent a possible candidate-network for trait impulsivity and probabilistic discounting in adolescence. However, neural correlates of motoric forms of impulsivity are not associated with temporal discounting as another aspect of decisional impulsivity. This might be due to stronger associations of motoric forms of impulsivity with trait-related aspects of impulsivity, as well as probabilistic discounting assessed via the CGT task that also requires an impulsive-action component. Further replication is needed establishing relevant biomarker-criteria such as sufficient sensitivity and specificity of those relationships (Thome et al., 2012). Our findings indicate no relationship between facets of trait impulsivity and decisional forms of impulsivity with VS activity during reward anticipation in adolescence. However, we found a nominally significant positive association between VS activity and trait impulsivity in young adulthood, indicating a striatal hyper-activation with higher trait-impulsivity scores. This finding is in line with previous meta-analytical results for healthy young adult populations that showed higher activation in striatal brain areas with increasing trait impulsivity (Plichta & Scheres, 2014). Consequently, reward anticipation-related activity in the VS might represent a potentially relevant neurobiological candidate for characterizing adult trait impulsivity. Especially, the facet of trait impulsivity is broadly associated with different brain-activity patterns. Current results indicate that trait impulsivity seems to represent a core construct within the broad and rather heterogeneous impulsivity-concept. An important objective of this study was to explore developmental

trajectories in the associations of interest. We found that relationships between neural activity and measures of impulsivity-facets change substantially across the developmental period from adolescence to young adulthood. Specifically, a potentially relevant change emerged for the association between reward-anticipation activity in the VS with distinct impulsivity-facets from adolescence to young adulthood. These developmental effects are primarily driven by changes on a neural level, whereas latent dimensions of trait impulsivity and decisional impulsivity remain relatively stable during the developmental period of interest as also shown by post-hoc correlational analyses. This finding is in line with results from previous studies that reported on ongoing critical developmental changes, especially with regard to neural reward processing, during the sensitive period of adolescence and into young adulthood (Dhingra et al., 2020).

Finally, this study aimed to address whether brain activity during inhibitory control or reward anticipation in adolescence might have a predictive value for later trait or decisional impulsivity in young adulthood. Unfortunately, we found no such predictive effect.

2.3.5.2 Relevance of results and potential clinical implications

Impulsivity is a highly prevalent characteristic of normal as well as altered, deviant human behavior being implicated in a broad range of psychiatric disorders (Bari & Robbins, 2013; Beauchaine et al., 2017). Therefore, current findings are of high practical relevance. Our results have substantial implications for the conceptualization of the multidimensional nature of impulsivity, its developmental course, and associated neural activity patterns. Further, current findings are of relevance for our understanding of the aetiology, diagnosis, and treatment of impulsivity-related behavioral problems and mental-health disorders.

First, on a theoretical level, current results strengthen previous findings that impulsivity represents a rather heterogeneous construct including trait-related and behavioral facets that on the one hand share common variance but nevertheless represent distinct psychological aspects that could be assessed via a broad variety of

different measures available (Dalley & Robbins, 2017; Reynolds et al., 2006; Sharma et al., 2014; Vasconcelos et al., 2014). These findings underline the need for an informed, theoretically-driven fragmentation of the construct in future research and clinical practice including detailed and direct assessments, analyses, and comparisons of component processes. Further, our study identified that brain activity in pre-SMA and IFG during inhibitory control as a motoric form of impulsivity might be one candidate biomarker-network characterizing the facets of trait impulsivity and probabilistic discounting in adolescents. Consequently, brain activity related to inhibitory-control processing might be a potential aid in characterizing trait impulsivity and probabilistic discounting in adolescent age. Furthermore, reward-anticipated activity in the VS might be an additional useful characteristic for characterizing adult trait impulsivity. Current results underline the non-unitary of the concept of impulsivity and highlight that distinct facets of impulsivity are differentially related to distinct neural activity patterns. Further, relationships change substantially during the critical developmental period from adolescence to young adulthood, resulting in distinct patterns of associations at baseline and follow-up, respectively. The identified emergence of associations between reward-anticipation activity in the VS and impulsivity in young adulthood is consistent with previous findings that report on ongoing dramatic changes with regard to neural processing until early adulthood (Dhingra et al., 2020). These findings highlight the need for taking maturational processes into account when assessing impulsivity within and across different developmental periods, especially on a neural level (in line with Thapar & Riglin, 2020).

Previous literature categorized (neuro-)psychological processes based on their socio-emotional valence by distinguishing between cold and hot processing. Thereby, the latter involves additional social and emotional internal and external influence factors (MacKenzie et al., 2017). Within this framework, inhibitory control as a motoric form of impulsivity represents cold processing, whereas reward processing including aspects of motivational control has been defined as reflecting

cold as well as hot processes. Our results show that brain activity during cold processing seems to be implicated in adolescent impulsivity. However, during young adulthood impulsivity is related to neural processing during reward processing including both, cold and hot functioning. These findings further support the definition of impulsivity as a rather heterogeneous, multidimensional concept (MacKillop et al., 2016), including various component processes related to and involving components of both, cold as well as hot functioning, to a varying extent, depending on maturational stage. By young adulthood, impulsivity seems to depend rather more on socio-emotional internal and external influence factors.

Given the small effect sizes identified, current results suggest a rather restricted value for clinical application with regard to (clinical) characterization and classification. Nevertheless, the neural correlates identified within the current work might already be relevant for inclusion in machine-learning approaches aiming at the integration of different kinds of data for a deeper characterization of human behavior for subsequent practical application (Bzdok & Meyer-Lindenberg, 2018). The identified neural correlates are not yet ready to be solely used for diagnostic purpose. With regard to the predictive value of neural activity for later impulsivity, results are rather disappointing, not yet allowing for further recommendations for clinical application.

2.3.5.3 Limitations and future directions

A few limitations of the current work have to be mentioned. First, a healthy populations-based sample was recruited excluding clinical patients diagnosed with impulsivity-related disorders. Therefore, variance within the latent facets of trait and decisional impulsivity might be restricted. Associations might change in extremer ranges of the impulsivity dimensions. Future studies are needed including larger samples with individuals having more extreme and clinically-relevant scores on impulsivity measures for broader conclusions that additionally explore non-linearity in those relationships. Further, effect sizes identified within current analyses are rather small and results obtained within mixed-effects model analyses do not explain

a substantial amount of variance, questioning the relevance of the biological characteristics explored within the current work in the sense of a biomarker. This needs to be taken into account when interpreting current results and drawing conclusions for further clinical applications. Furthermore, identified associations are correlational in nature, not yet allowing for conclusions on causal relationships. Subsequent studies are warranted replicating current findings and explicitly proving biomarker criteria (as proposed by Thome et al., 2012). In addition, within our study, there was a focus on specific neural processes of interest. However, others might be relevant and reliably associated with impulsivity (e.g. Cai et al., 2020). Currently, this study should be seen as a starting point in exploring neurobiological correlates of the latent dimensions of trait and decisional impulsivity using fMRI and future studies are warranted extending current results. Furthermore, using CFA, data were reduced by estimating predicted values for each participant with the aim to calculate one factor for some of the latent constructs of interest. However, a higher validity of assessment might have been obtained by combining more than one measure per concept. Finally, associations and their developmental trajectories have been explored from adolescence to young adulthood. Earlier changes during the period from childhood to adolescence could not be analyzed. Future longitudinal projects should start assessing brain-behavior relationships in childhood age to explore developmental trajectories across the lifespan.

2.3.5.4 Conclusions

The current study contributes important knowledge to the understanding of the multidimensional nature of the transdiagnostic construct of impulsivity, various assessment methods available, and associated developmental processes. Within this work, inter-correlations among measures of latent facets included in the rather heterogeneous conceptualization of impulsivity, developmental trajectories, and neurobiological correlates were explored. We found significant associations between measures of trait impulsivity and behavioral facets of decisional impulsivity as well as with brain activity in pre-SMA and IFG during inhibitory-control and in the VS

during reward anticipation along the period from adolescence to young adulthood. Associations between measures of trait and decisional impulsivity and brain activity change substantially until young adulthood due to relevant changes on the level of neural processing, resulting in distinct developmental patterns. However, relationships identified within the current work are rather small. Future studies are needed to replicate and extend current findings, explicitly reviewing biomarker-criteria of sufficient sensitivity and specificity for the neural biomarker-candidates explored. Current results highlight the need for taking brain-developmental processes into account when exploring brain-activity correlates of impulsivity.

3 GENERAL DISCUSSION

3.1 SUMMARY OF FINDINGS AND RELEVANCE OF RESULTS

Within the current thesis, the three studies presented evaluated neurobiological correlates of ADHD and the latent cognitive and behavioral dimension of impulsivity as a core symptom of ADHD using EEG/ERPs and fMRI. A special focus was on the exploration of developmental effects and maturational processes. Furthermore, EEG data quality was explored as an essential prerequisite for drawing valid conclusions from neurophysiological studies.

The main findings of the studies can be summarized as follows: in study 1 using a meta-analytical approach, we identified significant medium to large effect sizes for ERP differences between patients diagnosed with ADHD and non-ADHD controls ($-0.32<d<-0.57$) which were larger for later cognitive ERPs. For these later components, individuals with ADHD showed smaller Cue-P300-amplitudes, longer Go-P300-latencies, smaller NoGo-P300-amplitudes, longer NoGo-P300-latencies, smaller CNV-amplitudes, and smaller Pe-amplitudes. Additionally, for earlier ERPs individuals with ADHD showed shorter Go-P100-latencies than non-ADHD controls. Further, we found substantial heterogeneity in effect sizes that could be explained by several demographic and methodological moderators. With regard to developmental effects, our age moderator analyses identified stronger group differences in children compared to adolescents or adults for the NoGo-P300-amplitude, the Pe-amplitude, the Go-P100-latency, the Go-P300-latency, and the NoGo-N200-latency. However, for the Cue-P300-amplitude component, largest mean effect sizes were obtained in adults indicating distinct developmental effects on different ERPs across the lifespan. Only the CNV-component remained unaffected by maturational processes, therefore potentially representing a stable ADHD biomarker-candidate across the lifespan. Study 2 showed that EEG data quality was strongly influenced by demographic and clinical characteristics of the participants but not by methodological study-specific

aspects. Specifically, a positive associations between data quality and age was identified and a negative relationship with symptoms of hyperactivity/impulsivity, indicating higher data quality with increasing age and less pronounced hyperactivity/impulsivity. Furthermore, we found subsequent effects of data quality on standard EEG-analyses by showing that lower data quality significantly increases spectral power beyond effects of maturation and ADHD symptom severity. In study 3, we replicated relevant correlations between measures of the latent facets of trait impulsivity and decisional impulsivity assessed in adolescence and young adulthood. Further, we identified negative associations between trait impulsivity and probabilistic discounting with frontal brain activity in pre-SMA and IFG during inhibitory control in adolescents, respectively. Those brain-behavior relationships were found to change substantially until young adulthood: at follow-up, a positive association emerged between trait impulsivity and brain activity in VS during reward anticipation, but no longer further associations were found with inhibitory-control activity. As indicated by post-hoc analyses, changes in those relationships were mainly driven by changes on the level of neural processing. No predictive value of brain activity during adolescence for impulsivity in young adulthood was identified. All three studies presented thus revealed substantial developmental effects on neurobiological characteristics related to ADHD and impulsivity. Across all studies, we found a relevant influence of age (group) on neural processes as well as on EEG data quality. Effects on neural brain activity show up across different modalities used to assess human brain functioning (EEG/ERPs and fMRI).

The current results provide important new evidence for a deeper understanding and characterization of the diagnostic category of ADHD and for the multidimensional construct of impulsivity using a neuroscience-based approach. Besides providing a broad range of implications for clinical application, our findings address methodological shortcomings of earlier work and close some important gaps of knowledge.

Within our meta-analysis (study 1), we showed that later ERPs might represent relevant biomarker-candidates for the ADHD diagnostic category, in line with current neuropsychological theories on higher-order executive functioning deficits in those patients (Kofler et al., 2019). Especially, the P300-components show promising and reliable effects and might therefore in the future be applicable for an additional characterization of ADHD and for the identification of more homogeneous subgroups (Szuromi et al., 2011). Further and somewhat surprisingly, we also found shorter P100-latencies in ADHD compared to non-ADHD controls. This relatively early effect might be interpreted as a failure to sufficiently engage in early attentional processing necessary for successful cognitive modulation of sensory processing in ADHD (Leroy et al., 2018). This finding points out to the need to take also earlier processing deficits into account, as well as their subsequent effects on later neuropsychological and neurophysiological deficits. Impairments in bottom-up cognitive processing related to deficits in early visual processing are further supported by more recent data replicating P100-differences in adult ADHD patients compared to non-ADHD controls (alterations in P100-amplitude, Papp et al., 2020). Unexpectedly, no between-group effects emerged for the N200-component. However, N200-between-group effects might be diluted by the substantial heterogeneity within the ADHD diagnostic category on a phenotypic level, by demographic characteristics, or by further methodological differences related to the study design. For example, within our age moderator analysis relevant NoGo-N200 latency differences emerged for children but not for adolescents or adults indicating age-specific patterns. Although potentially relevant neurophysiological biomarker-candidates have been identified within the current meta-analyses, results are characterized by substantial heterogeneity due to study-specific factors. Therefore, the later ERPs identified as potentially promising neurophysiological markers not yet meet criteria for clinical application (see Gamma & Kara, 2016; Thome et al., 2012). The heterogeneity in effect sizes limits the practical implications of the results and reflects the *inescapable heterogeneity* of the ADHD phenotype that has already been

discussed in previous work (e.g. Arns & Gordon, 2014; Lenartowicz & Loo, 2014; Luo et al., 2019). The substantial variation in the distribution of effect sizes suggests further moderator variables being relevant such as varying clinical profiles, additional psychiatric comorbidities, different patterns of neurocognitive impairment, and developmental effects (e.g. Aasen et al., 2018). Within our work, several demographic and methodological characteristics were identified that impact on between-group effects when differentiating between ADHD and non-ADHD groups. Also in line with newer data (Häger et al., 2020), we found substantial age effects within our analyses indicating stronger differences between ADHD and non-ADHD groups for childhood age. These findings possibly reflect a reduction of ADHD symptoms during adolescence and early adulthood, which is reported to occur in approximately 40%-60% of individuals with ADHD (Faraone et al., 2006; Johnstone et al., 2007). However, consistent with results from Doehnert and colleagues (Doehnert et al., 2010), the CNV-amplitude showed no significant developmental effects in the differentiation between ADHD and non-ADHD groups, possibly representing a stable ERP-marker of the ADHD diagnostic category across the lifespan independent of age. This finding is further in line with earlier work that identified the CNV component to be a marker of ADHD persistence (Cheung et al., 2016). In addition, for the Cue-P300-amplitude even larger group differences emerged in adults, indicating that this component might become more important as a neurobiological correlate with increasing age and might represent a neuromarker-candidate specific for adult ADHD (see also meta-analysis on ERPs in adult ADHD: Szuromi et al., 2011). This finding is especially relevant with regard to the current debate on adult ADHD and age-of-onset (Kooij et al., 2019). Although further validation is needed addressing sensitivity and specificity of those neurophysiological markers (Mehta et al., 2020), later ERPs represent promising biomarker-candidates that might be most useful in (multimodal) classification approaches (Ging-Jehli et al., 2021; Mueller et al., 2011; Sur & Sinha, 2009; Thome et al., 2012; Vahid et al., 2019). In addition, the current results inform studies focusing

on individualized treatment planning and treatment effectiveness that could make use of ERP-markers as potential predictors of treatment outcome. Prior studies have already linked neurophysiological processes to treatment response after pharmacological (e.g. Banaschewski & Brandeis, 2007; Ogrim et al., 2016; Yamamuro, Ota, Iida, Nakanishi, Matsuura, et al., 2016) and non-pharmacological therapy options (Heinrich et al., 2004; Janssen, Bink, et al., 2016; Janssen, Geladé, et al., 2016). The potential predictive value of ERPs needs further replication (as, for example, currently done within the ESCAlife studies: Becker et al., 2020; Döpfner et al., 2017; Geissler et al., 2018; Zinnow et al., 2018) and might subsequently be used for implementing tailored, individualized treatment strategies.

Our study on EEG data quality in a large ADHD-cohort (study 2) underlines the relevance of study-specific variables influencing EEG data quality and highlights subsequent effects of data quality on results obtained in regular EEG analyses. Therefore, explicitly focusing on indices of data quality in EEG/ERP studies is highly recommended, especially when younger populations and clinical samples are explored that are prone to EEG artifacts (DiStefano et al., 2019; Kappenman & Luck, 2016). Our results have a high relevance for designing future EEG/ERP studies and for implementing adequate analytical data pre-processing strategies. Especially, demographic and clinical characteristics of study samples must be taken into account and appropriate pre-processing strategies should be implemented to adequately address issues on data quality. Further, explicit reports of sample characteristics and data quality are warranted and potential effects of data quality on EEG/ERP results in subsequent analyses should be taken into account. The additional effect of data quality on FFT spectral power in resting-EEG data beyond effects of maturation and ADHD-symptoms points out to the need for discussing and challenging EEG results. This study has relevant implications with regard to clinical application such as the classification of ADHD patients based on neurophysiological indices. In general, data quality effects might be explained by myogenic activity (that could be assessed via the electromyogram; EMG) as a potential confounder (diluting or mimicking spectral

power effects between clinical groups) subsequently contaminating EEG signals (Goncharova et al., 2003). However, especially in younger and clinical populations with psychiatric diagnoses such as ADHD, those indices might also have an additional diagnostic value as motor activity represents a central behavioral characteristic of the clinical populations explored (DiStefano et al., 2019). The information on EMG activity and data quality might be of high value for classification purposes to differentiate between clinical and non-clinical groups as well as between different clinical groups. Future studies could make use of those indices with regard to clinical characterization. Nevertheless, current results highlight the need to control for EEG data quality effects when EEG/ERP analyses are conducted for a clearer interpretation of study results. Ensuring reliability and validity of assessed data has substantial implications for the status quo of neuroscientific research. Our results further highlight that large-scale multicenter studies on ADHD patients prone to EEG artifacts are actually feasible. This demonstration of feasibility is urgently needed for further in-depth explorations of the diagnostic and predictive value of EEG/ERP markers in the highly prevalent neurodevelopmental disorder category of ADHD. Taken together, these findings provide relevant guidance for conducting EEG/ERP research in ADHD across the lifespan. In a first step, depending on the specific age group explored within an EEG study, monitoring of participants during measurements should be adapted accordingly, with a closer monitoring for younger age groups. In a subsequent step, age-specific pre-processing pipelines might be necessary to adequately address differences in data quality for distinct age groups.

As expected, within our longitudinal study on impulsivity (study 3) measures of trait impulsivity, temporal discounting, and probabilistic discounting were related to each other in adolescence and young adulthood. However and in line with results from previous work, correlations proved rather small (Cyders & Coskunpinar, 2011; Hasegawa et al., 2019; Sharma et al., 2014). These findings again indicate that facets of impulsivity assessed via different measurement instruments share common

variance but also represent distinct features of a complex theoretical construct. Further, the identified associations between facets of impulsivity and neural activity in pre-SMA and IFG during inhibitory control in adolescence might help in characterizing impulsivity during this developmental stage and in identifying early treatment needs. Especially, because adolescence represents a highly critical period for the development and manifestation of (future) psychiatric disorders, the early and objectively validated identification of neural risk factors of high impulsivity might be very helpful with regard to disease prevention (Dir et al., 2019). Until young adulthood, associations change substantially and emerging brain activity in the VS during reward anticipation might then be a useful characteristic when exploring trait impulsivity (in line with previous findings: Plichta & Scheres, 2014). However, future studies are needed to replicate the current findings and explore their specificity. Nevertheless, the neural correlates identified within this work might already be relevant for inclusion in machine-learning approaches (Bzdok & Meyer-Lindenberg, 2018). The developmental patterns found in the current data with the emergence of a relationship between reward-anticipation activity in the VS and impulsivity in young adulthood is consistent with previous findings that report on ongoing dramatic changes in neural functioning until early adulthood (Dhingra et al., 2020). Therefore, these results again highlight the need for taking into account changes on a neural level during the developmental phase of adolescence into adulthood (Thapar & Riglin, 2020). Another possible reason for changes in brain activity on a neural level (related to maturational processes) might be decreasing motion (artifacts) with increasing age being subsequently associated with higher data quality. However, future studies are needed exploring such confounding effects. Current findings might help in characterizing impulsivity, understanding its multifaceted nature, and selecting adequate assessment methods in future research. Further, these findings open up the possibility for identifying potential early treatment needs and targeting adequate neural processes for preventive purposes taking into account developmental changes during the critical time period from

adolescence to young adulthood. Finally, the results highlight that substantial maturational changes on the level of neural processing are ongoing (at least) until young adulthood.

All of the studies presented within the current thesis indicate relevant implications with regard to developmental effects: although earlier studies have already been concerned with maturational effects in normal and deviant human behavior, their impact on brain-behavior associations is still unknown in important aspects (Franke et al., 2018; Thapar & Riglin, 2020). The current studies contribute further important insights by including participants of a broad age-range within cross-sectional designs (studies 1 and 2) and by adopting a longitudinal approach (study 3). These design aspects allow for an explicit analysis of developmental trajectories, age effects, and individual maturational patterns. Findings show that there are substantial changes in brain-behavior associations that still occur until young adulthood, mainly driven by substantial developmental changes on a neurobiological level, and that different biomarker-candidates show up within distinct age groups. However, also some rather persistent neurobiological characteristics have been identified, e.g. CNV-component in ADHD. These results provide relevant implications for studies on biomarker-based diagnostics and therapy (as already introduced in section 1.3.3).

3.2 LIMITATIONS

In this section, the major shortcomings of the three studies forming this thesis are listed. First, within our meta-analysis (study 1) for some of the ERP components only a small number of studies could be included indicating a lower power of respective analyses. However, this is due to the focus of the available studies and points to the need of further broader replication work. Second, we did not include unpublished data. Thereby, results might be slightly biased towards published findings (Higgins et al., 2019). Nevertheless, publication-bias analyses were conducted to explicitly address those effects. Further, due to the low number of

studies included for some of the ERPs, separate analyses had to be conducted for each moderator of interest. For higher validity and for explicitly exploring interaction effects between moderators, all variables would have to be included in one model. In addition, for some of the moderators the number of studies included per category varied substantially affecting reliability of respective comparisons: first, there were only a few studies conducted on adolescents. Second, most of the studies focused on male participants. Third, most of the studies were conducted on the ADHD combined subtype. No analyses could be performed on the influence of comorbidities or medication status due to the fact that this information is often not explicitly reported within primary studies. All this needs to be taken into account when drawing conclusions for clinical application. Furthermore, within our meta-analyses we were not able to analyse dimensional effects of symptom severity. Due to the small number of studies for some of the ERPs, a lack of reporting in primary studies, and the many differences in the methodological implementation, we are still in need of future studies that would enable a more detailed exploration of the heterogeneity in effect sizes.

In addition, a few limitations of study 2 are subsequently displayed: first, no adults above the age of 45 years were recruited for the current study due to the study design. Further, only a few datasets were available for adolescents. Therefore, effects are primarily driven by data from children and young adults. Furthermore, only a small non-ADHD sample in school-age could be included for comparison purpose. This is again due to the study design with a focus on longitudinal therapeutic effects within a stepped-care treatment-design in patients, rather than on patient-control comparisons. Within the current study, the focus was on a few potentially relevant participant-related and methodological variables influencing data quality. Besides those, other factors might also be relevant. Future studies are warranted at this stage. In addition, the percentage of artifact-free segments was defined as the relevant index of data quality. However, other indices could have been calculated and further replication is needed comparing different data quality indices.

Finally, a few limitations of study 3 have to be mentioned: first, a healthy population-based sample was recruited excluding clinical patients diagnosed with impulsivity-related disorders and further severe mental-health disease. So it needs to be taken into account that the variance of impulsivity-scores in the clinical range was somewhat restricted. Further, the current study started to assess participants from adolescent age onwards; future longitudinal studies are needed that already start measuring participants in childhood age. Also, a focus was set on a priori selected neural activity patterns based on findings from previous literature. However, other task-related brain-activity markers might reliably be associated with impulsivity. At this stage, the current study should be seen as a starting point and future studies are warranted. Furthermore, CFAs were used for aggregating data and combining different measures to estimate predicted values, thereby reducing dimensionality. However, the combination of more than one measure per construct of interest might lead to a higher assessment-validity by taking into account more information. Finally, effect sizes were rather small and significant results obtained within the mixed-effects models did not explain a substantial amount of variance in the data. This needs to be taken into account when interpreting the current results and particularly when drawing conclusions for further clinical application.

Taken together, current neuroscience studies are restricted by a few limitations that need to be addressed in future work. Among others, the most relevant ones that apply to all studies are listed in the following: first, a restricted age range of included participants not taking into account very young children under the age of 6 years, and adults above the age of 45 years; second, the focus on specific neural structures and processes of interest; and finally, except for study 2, studies did (study 3) or could (study 1) not (yet) combine categorical and dimensional approaches for a more comprehensive understanding of the neurobiological link between ADHD and impulsivity. Further work is planned at this stage.

3.3 OUTLOOK

In general, future work is needed to explore the diagnostic and predictive value of neurobiological markers in ADHD and of related latent symptom dimensions, such as impulsivity, combining categorical and dimensional perspectives. So far, only a few earlier studies focused on the neurobiological mechanisms in the association between ADHD and different impulsivity-facets as well as on their relation to comorbidity and treatment effects (DeVito et al., 2009; Ortal et al., 2015; Paloyelis et al., 2009; Patros et al., 2016; Wilbertz et al., 2012). Using multidimensional assessment methods, large samples should be explored within longitudinal designs. Thereby, different brain structures and processes should be measured and combined using sophisticated analytical methods for a deeper characterization of phenotypical behavior (e.g. Sudre et al., 2020). Within these longitudinal studies, treatment options should be implemented to allow for exploring therapeutic effects on neurobiological marker-candidates and their predictive value. Further, the effectiveness of neuromodulation treatment based on previously identified marker-candidates should be evaluated. Additionally, future work should aim at further disentangling developmental and disease-related effects in neurobiological data within longitudinal studies, especially when focusing on neurodevelopmental disorders within a personalized-medicine framework. Normative modeling might be a valuable framework for statistically addressing the needs of those large-scale longitudinal datasets (Marquand et al., 2019; Marquand et al., 2016).

In more detail, implications for future research from each of the studies presented within this thesis are subsequently summarized: (1) our meta-analysis showed that, in general, more studies are needed to validate relevant ERP markers for multimodal classification approaches (Ging-Jehli et al., 2021; Mueller et al., 2011) and to understand the heterogeneity of neurophysiological findings in ADHD (Häger et al., 2020). In addition, to further explore the validity of ERPs as ADHD biomarkers, the question of how specific these neuromarkers are needs to be

addressed (Thome et al., 2012): further studies are required comparing different ADHD (sub-) groups as well as addressing effects of comorbid symptoms (Rostami et al., 2020; Sur & Sinha, 2009). Beyond that, future studies should try to link ERPs to continuous symptom dimensions in healthy as well as clinical populations adopting the RDoC approach (Hilger et al., 2020; Insel et al., 2010). The current meta-analysis suggests to (further) explicitly test the predictive value of ERPs as neuromarkers in a personalized-medicine framework. We are aware of a few already published as well as ongoing studies using EEG/ERPs to predict response to different therapeutic interventions (e.g. Becker et al., 2020; Döpfner et al., 2017; Geissler et al., 2018; Ogrim et al., 2014; Zinnow et al., 2018). In addition, our meta-analysis suggests to explore later ERPs as relevant targets for neuromodulation treatment (e.g. for neurofeedback or transcranial alternating current stimulation (tACS); see Dallmer-Zerbe et al., 2020). (2) Our multicenter ADHD-study on EEG data quality in children, adolescents, and young adults highlights that future neuroscientific studies should explicitly take into account variables influencing data quality and potential subsequent effects on regular EEG/ERP analyses. In addition, later work should assess further methodological variables related to the study-design and data (pre-)processing potentially impacting on data quality and include samples with a larger age range of participating ADHD patients. Also, (larger) non-ADHD samples should be recruited to better address the influence of data quality when differentiating between clinical and non-clinical groups. Further, studies on the impact of data quality on subsequent EEG/ERP analyses are needed taking into account different types of subsequent biomarker-validation analyses. Within our large multicenter ADHD-cohort, future work is planned exploring the diagnostic and predictive value of neurophysiological markers in ADHD combining a categorical and dimensional perspective (Becker et al., 2020; Döpfner et al., 2017; Geissler et al., 2018; Zinnow et al., 2018). Those markers will be related to ADHD status as well as to latent symptom dimensions of the disorder category across different age groups from childhood into adulthood. The heterogeneity of ADHD will be explicitly modelled by taking into account effects of

age, symptom severity, and comorbid disorders. Further, those neurophysiological markers will be linked to other indices derived from MRI measurements and from neuropsychological testing and their common diagnostic and predictive value will be analysed. While exploring the predictive value of neurobiological markers within this trial, a focus will be on non-pharmacological treatment options, especially BT and NF therapy, and the sensitivity of neurophysiological characteristics with regard to treatment effectiveness will be evaluated. (3) Our longitudinal population-based cohort study on impulsivity indicates that future studies are warranted exploring facets of impulsivity in healthy, subclinical as well as clinical samples with the latter suffering from impulsivity-related disorders to further address confounding effects of psychiatric diagnoses on brain-behavior relationships. Thereby, different facets of impulsivity should explicitly be assessed and directly compared to each other to replicate and extend current findings. In addition, later work should address a broad variety of different neurobiological correlates of impulsivity, combine different sensitive markers that have been identified previously using machine-learning approaches, and analyse their common diagnostic and predictive value (Bzdok & Meyer-Lindenberg, 2018). Biomarker-criteria (see Thome et al., 2012) should be established to further prove clinical relevance of (current) findings. Specifically, future longitudinal projects should start assessing the relationship between facets of impulsivity and neural activity patterns in childhood age to explore developmental trajectories in a broader age-range (Franke et al., 2018; Morgan et al., 2018; Thapar & Riglin, 2020). Thereby, normative modeling might be used to improve the study of individual differences and to parse the heterogeneity in healthy, subclinical, and clinical cohorts (Marquand et al., 2019; Marquand et al., 2016). Furthermore, future fMRI studies should take into account potential effects of neurobiological data quality in developmental trajectories of brain-behavior relationships.

3.4 CONCLUSIONS

Within study 1, we conducted the first meta-analysis quantitatively summarizing relevant literature on ERPs in ADHD across the lifespan, explicitly addressing the heterogeneity in previous research. In line with current executive functioning-deficit theories of ADHD, the findings confirm that on a group level ADHD is associated with specific neurophysiological alterations, particularly during later cognitive processing-stages. Compared to non-ADHD controls, individuals with ADHD show medium to large differences, mainly regarding later ERP components such as the P300, the CNV, and the error-related Pe. Further studies are needed to fully understand the heterogeneity in effect sizes and to clarify the potential of cognitive ERPs for clinical application. Especially, developmental effects seem to play an important role and should therefore be taken better into account in future work, e.g. by implementing longitudinal study-designs. The identification and independent validation of variables contributing to larger effect sizes and the understanding of associated mechanisms is needed before ERPs can be used as tools within a personalized-medicine framework.

Study 2 highlights the relevance of EEG data quality, participant-related variables influencing it, and additional effects of data quality on results obtained from subsequent FFT analyses beyond demographic and clinical characteristics. Thereby, a large ADHD-cohort in childhood, adolescent, and adult age was explored and compared to a small non-ADHD control group in school-age. The results of this investigation show that demographic variables, especially age and symptoms of hyperactivity/impulsivity, have a substantial impact on data quality. Additionally, we found that data quality affects spectral power beyond participant-related, clinical characteristics. These findings provide relevant implications for designing future studies, analyzing and publishing EEG data, and for drawing valid conclusions on scientific results obtained from EEG studies.

The third study addresses the multifaceted construct of impulsivity within a large population-based cohort of adolescents assessed longitudinally into young

adulthood. We conducted the first study systematically analyzing several measures of the multidimensional construct of impulsivity, their inter-correlations, and a priori selected brain-activity correlates during the critical developmental period from adolescence to young adulthood. The identified changes in associations between impulsivity-facets and brain-activity patterns are mainly driven by ongoing substantial changes on the level of neural processing. This study thereby contributes to our understanding of the multifaceted nature of impulsivity and relevant changes in brain-behavior associations that still occur until young adulthood. In adolescence, brain activity in pre-SMA and IFG during inhibitory control is implicated in impulsivity and might therefore represent a promising biomarker-candidate. However, during young adulthood VS activity during reward anticipating becomes more relevant, indicating a potential diagnostic value for a VS-hyper-activation in healthy young adult in participants. These results again highlight the need for taking developmental processes into account.

All of the studies reviewed within the current work show substantial effects of age and maturation on phenotypic behavior, neurobiological markers as well as on data quality. Distinct effects for different age groups as well as substantial effects across development from adolescence into young adulthood in associations between ADHD or impulsivity and neural activity have been identified. Although some neurobiological characteristics might be related to behavioral symptom dimensions and diagnostic status independent of age, others show distinct developmental patterns, indicating that their potential biomarker-value might be restricted to and specific for a distinct developmental period. Therefore, results highlight the importance of taking maturational effects into account when planning and evaluating neuroscientific studies as well as when drawing conclusions for clinical application.

Altogether, the current studies help in delineating neurobiological correlates of ADHD and impulsivity, with the latter representing one core diagnostic criterion of the neurodevelopmental disorder. Further, substantial developmental effects have

been shown, especially on the level of neural processing. In addition, the current thesis highlights the relevance of data quality in neurobiological assessments for drawing reliable and valid conclusions from neuroscientific data with a special focus on the EEG. Finally, all studies point out to the need for combining categorical and dimensional approaches in psychiatric research for a deeper understanding of the complexity of typically-developing as well as clinically relevant, deviant human behavior in future research and common underlying neurobiological mechanisms.

4 SUMMARY

The current thesis addresses neurobiological characteristics associated with Attention-Deficit/Hyperactivity Disorder and the transdiagnostic symptom dimension of impulsivity. A special focus was set on developmental effects in brain-behavior relationships for a more detailed understanding of the relevance of identified neuromarker-candidates within distinct maturational stages. Further, the current work took into account the highly relevant topic of electroencephalographic data quality as an essential prerequisite for validly translating neurophysiological study results into clinical practice. Due to its ease of administration, its high tolerability, and the rather low costs, electroencephalography was the focus of most of the current work.

Therefore, three meta-analytical or empirical studies were conducted and reviewed within this thesis: first, our meta-analysis on event-related potential-differences between patients with Attention-Deficit/Hyperactivity Disorder (n=1576) and healthy controls (n=1794) in childhood, adolescence, and young adulthood was presented. We identified relevant medium to large effect sizes between patients diagnosed with Attention-Deficit/Hyperactivity Disorder and healthy controls ($-0.32<d<-0.57$), mainly regarding later cognitive event-related potentials (P300, Contingent Negative Variation, and error-related positivity), indicating deficits in higher-order cognitive functioning (study 1). Second, results on electroencephalographic data quality were reported from our ESCAlife trial exploring Attention-Deficit/Hyperactivity Disorder patients in childhood (n=184), adolescent (n=39), and young adult (n=57) age compared to a small sample of healthy controls in school-age (n=25). We were able to show that participant-related characteristics, especially age and symptoms of hyperactivity/impulsivity, affect electroencephalographic data quality subsequently impacting on results obtained from spectral power analyses (study 2). And finally, we introduced our analyses on the large population-based IMAGEN-cohort of healthy adolescents (n=2034) assessed

longitudinally into young adulthood (*n*=1383). We found that measures of different facets of impulsivity are related to brain activity in the pre-supplementary motor area and inferior frontal gyrus during inhibitory control during adolescence and in the ventral striatum during reward anticipation in young adulthood with distinct effects for different age groups. Associations between brain activity and impulsivity change substantially from adolescence to young adulthood, especially due to maturational changes on a neural level (study 3). Across all studies relevant developmental effects were identified.

The studies presented here indicate that a variety of neurobiological characteristics and processes can be related to Attention-Deficit/Hyperactivity Disorder and impulsivity from either a categorical or a dimensional perspective and possibly represent promising biomarker-candidates. However, the current findings are in line with previous literature highlighting that no single biomarker might be sufficient to characterize aspects of healthy as well as deviant, clinically relevant human behavior. Future large-scale longitudinal studies using multidimensional assessment methods are needed to disentangle effects and further prove sensitivity and specificity of already identified neuromarker-candidates, thereby combining categorical and dimensional approaches. Additionally, data quality should be in the focus of future work to ensure a valid translation of neuroscientific study results into clinical practice. Specifically, developmental effects need to be explicitly taken into account. Further, future studies should address the predictive value of the neuromarker-candidates identified and prove their effectiveness as targets of neuromodulation-treatment within a personalized-medicine framework.

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6 SUPPLEMENTAL MATERIAL

6.1 SUPPLEMENT STUDY 1: Earlier versus later cognitive event-related potentials (ERPs) in attention-deficit/hyperactivity disorder (ADHD): A meta-analysis

Supplemental material related to this article can be found in the online version at doi: https://doi.org/10.1016/j.neubiorev.2020.01.019

Appendix A

Literature Search

PubMed 08.01.2018

"Attention Deficit Disorder with Hyperactivity"[Mesh] AND "Electroencephalography"[Mesh]
1355 results
Filters: Clinical Trial
(#3 AND #5) AND Clinical Trial[ptyp]
158 results
Filters activated: Clinical Trial, Publication date from 1987/01/01 to 2018/12/31.
(#3 AND #5) AND (Clinical Trial[ptyp] AND ("1987/01/01"[PDAT]: "2018/12/31"[PDAT]))
148 results

Cochrane Central 05.01.2018

Search Manager:
ADHD and EEG
#1 and #2
78 results

Clinical Trials 05.01.2018

47 results

Terms and Synonyms searched:

Terms		Search Results*	Entire Database**
	Synonyms		
eeg		47 studies	1,680 studies
	Electroencephalogram	13 studies	362 studies
	Electroencephalography	11 studies	442 studies
Adhd		47 studies	1,043 studies
	Attention deficit	41 studies	927 studies
	hyperactivity disorder	40 studies	785 studies
	Hyperkinetic Syndrome	--	2 studies

-- No studies found

* Number of studies in the search results containing the term or synonym

** Number of studies in the entire database containing the term or synonym

A **ADHD**
Attention
Attention Deficit
Attention Deficit Disorder
Attention Deficit Hyperactivity
B Behavior
Behavior Disorders
Disruptive Behavior Disorders
Disruptive Behavior
Disruptive Behavior Disorders
biofeedback
Brain
brain activity
C Child
computer
D **Deficit**
Attention Deficit
Attention Deficit Disorder
Attention Deficit Hyperactivity
Disorders
Attention Deficit Disorder
Behavior Disorders
Disruptive Behavior Disorders
Hyperactivity Disorder
Neurodevelopmental Disorders
Disruptive Behavior
Disruptive Behavior Disorders
E **EEG**
electroencephalogram (EEG)
electroencephalography (EEG)
electroencephalogram
electroencephalogram (EEG)
electroencephalography
electroencephalography (EEG)
H **Hyperactivity**
Attention Deficit Hyperactivity
Hyperactivity Disorder
M Methylphenidate
N Neurodevelopmental Disorders
Neurofeedback
T task
training

PsychInfo + PsychARTICLES 08.01.2018

adhd AND eeg
Search modes - Boolean/Phrase
539 results

SEARCH ADHD AND ERP

PubMed 10.04.2018

"Attention Deficit Disorder with Hyperactivity"[Mesh]) AND "Evoked Potentials"[Mesh]
611 results
Filters: Clinical Trial
(#3 AND #5) AND Clinical Trial[ptyp]
83 results

Cochrane Central 10.04.2018

Search Manager:
ADHD and ERP
#1 and #2
29 results

Clinical Trials 10.04.2018

15 results

Terms and Synonyms searched:

Terms	Search Results*	Entire Database**
Synonyms		
erp	14 studies	686 studies
Evoked Potential	2 studies	444 studies
Early Repolarization	--	5 studies
Endoscopic retrograde pancreatography	--	1 studies
potential evoked	--	1 studies
Adhd	14 studies	1,062 studies
Attention deficit	10 studies	943 studies
hyperactivity disorder	9 studies	798 studies
disorder hyperactivity	--	1 studies
Hyperkinetic Syndrome	--	2 studies

PsychInfo + PsychARTICLES 11.04.2018

adhd AND erp
Search modes - Boolean/Phrase
262 results

Appendix B

Coding sheet

A Study type/reference

- First author
- Year of publication
- Peer-reviewed journal
- Age group
  1 children (6.0 – 11.11 mean years of age)
  2 adolescents (12.0 – 17.11 mean years of age)
  3 adults (> 18.0 mean years of age)
- Study quality rating[11]

E ADHD group

- Sample size, n
- Mean age, years
- Male, %
- IQ
- ADHDcom subtype
  1 yes
  2 no

[11] A study quality rating was implemented (based on Newcastle-Ottawa quality assessment scale for case-control studies plus rating scale for EEG signal quality) and moderator analyses were conducted to check if study quality significantly affected results. No significant effects were obtained.

- ADHDin subtype
  1 yes
  2 no
- ADHDhyp/imp subtype
  1 yes
  2 no
- Comorbidity
  1 yes
  2 no
- Medication status ADHD
  1 yes
  2 no
  3 washout 24h
  4 washout 48h

O Non-ADHD group

- Sample size, n
- Mean age, years
- Male, %
- IQ

U Moderators

- Cognitive function/research area
  1 inhibitory control
  2 attention
  3 working memory (WM)
  4 error/process monitoring
- Task type category
  1 Continuous performance task (CPT)
  2 CPT Flanker version
  3 Go/NoGo task
  4 Stroop/Simon task
  5 Oddball task
  6 Selective attention/reaction time task
  7 Fast task
  8 Covert orienting task
  9 Easy/Hard task
  10 Posner cueing paradigm
  11 Match-to-sample task
  12 2-back task
  13 Flanker task
- Modality
  1 visual
  2 auditory
  3 visual-auditory (multimodal)
- ISIcalc, ms
- Target, % (Stimulus proportion)
- Location(s)
- Latency range(s), lower bound
- Latency range(s), upper bound
- Electrode(s)
- Reference channel
- Impedance

- Baseline correction
  1 yes
  2 no
- Type baseline correction
  1 200 ms pre-stimulus baseline
  2 100 ms pre-stimulus baseline
  3 zero baseline
  4 other
- Filter low cut-off, Hz
- Filter high cut-off, Hz

AI ERP components

Coding of means (M) and standard deviations (SD) for all ERP components: P100, N100, P200, N200, P300, CNV, ERN/Ne, Pe – amplitudes and latencies.

BQ Performance data

Coding of means (M) and standard deviations (SD) for (behavioral) performance data.

Appendix C

Datasets

Per ERP component:

Dataset.meta.analysis.ADHD.ERPs.08082018.P1
Dataset.meta.analysis.ADHD.ERPs.26022019.N1
Dataset.meta.analysis.ADHD.ERPs.26022019.P2
Dataset.meta.analysis.ADHD.ERPs.26022019.N2
Dataset.meta.analysis.ADHD.ERPs.26022019.P3
Dataset.meta.analysis.ADHD.ERPs.18102018.CNV
Dataset.meta.analysis.ADHD.ERPs.18102018.ERN
Dataset.meta.analysis.ADHD.ERPs.18102018.Pe

Per condition (Cue – Go – NoGo) across all ERPs:

Dataset.meta.analysis.ADHD.ERPs.19032019.all.ERPs.analyses.cue
Dataset.meta.analysis.ADHD.ERPs.19032019.all.ERPs.analyses.go
Dataset.meta.analysis.ADHD.ERPs.19032019.all.ERPs.analyses.nogo

Appendix D

Characteristics of included studies

Table S1

Characteristics of included studies

Study	Age group	N_{ADHD}	Age, mean (years)	Male, mean (%)	IQ, mean	Comorbidity	Medication status	$N_{non-ADHD}$	Age, mean (years)	Male, mean (%)	IQ, mean	Task	Cognitive Function	Modality	ISI	Electrodes
Albrecht et al., 2008	Children	68	11.33	100	104.4	yes	Washout 48h	22	11.18	100	110.3	Flanker	Error processing	visual	1400	23
Albrecht et al., 2013	Children	97	11.5	100	109	no	no	43	11.33	100	115	CPT	Inhibition	visual	1650	24
Baijot et al., 2013	Children	8	10	87.5	n.a.	no	Washout 48h	9	10.3	66.66	n.a.	CPT	Attention	visual	1500	9
Barry et al., 2009	Adults	18	21.9	n.a.	104.5	n.a.	no	18	20.6	n.a.	110	Oddball	Attention	intermodal	n.a.	19
Bluschke et al., 2016	Children	20	11.1	90	102	n.a.	yes	20	13.4	70	107	Go-NoGo	Inhibition	visual	n.a.	60
Cao et al., 2013	Children	19	7.3	78.26	n.a.	n.a.	no	19	7.3	54.55	n.a.	Stroop/Simon	Inhibition	visual	1750	128
		19	8.5	72.73			no	24	8.5	65.38						
		18	9.5	81.82			no	22	9.4	72.00						
		15	10.8	83.33			no	15	10.6	55.56						
Chang et al., 2009	Adults	32	23.69	50	113.22	yes	yes	29	23.68	50	117.31	Flanker	Error processing	visual	950	33
Cheung et al., 2017	Adolescents	93	18.83	77	96.27	n.a.	Washout 48h	174	17.75	84	109.42	Fast task	Attention	visual	n.a.	62
Czobor et al., 2017	Adults	22	30.6	77.3	n.a.	no	yes	29	30.1	65.5	n.a.	(affective) Go-NoGo	Error processing	visual	600	256
Dhar et al., 2010	Adults	16	33.1	100	110.3	n.a.	n.a.	16	33.7	100	116.4	CPT	Attention	visual	1500	72
Du Rietz et al., 2016	Adolescents	48	18.54	81	98.25	n.a.	yes	167	17.77	76	110.23	(cued) Flanker	Attention	visual	1500	62
Fallgatter et al., 2004	Children	16	9.55	100	106.5	no	no	19	9.9	100	111	CPT	Inhibition	visual	1650	21
Fisher et al., 2011	Adults	14	24.6	n.a.	n.a.	no	Washout 24h	14	24.7	n.a.	n.a.	Go-NoGo	Inhibition	auditory	1500	21
Grane et al., 2016	Adults	33	31.3	42.42	93.7	yes	no	31	31.9	45.16	98.9	(cued) Go-NoGo	Inhibition	visual	1000	19
Groom et al., 2008	Adolescents	27	15.69	92.59	n.a.	n.a.	Washout 24h	35	17.19	41.67	n.a.	Go-NoGo	Inhibition	visual	1750	128

Study	Age group	N_{ADHD}	Age, mean (years)	Male, mean (%)	IQ, mean	Comorbidity	Medication status	$N_{non-ADHD}$	Age, mean (years)	Male, mean (%)	IQ, mean	Task	Cognitive Function	Modality	ISI	Electrodes
Groom et al., 2010	Adolescents	23	16.2	91.3	93.41	yes	Washout 24h	19	16.14	52.63	105.16	Go-NoGo	Error processing	visual	1750	128
Herrmann et al., 2010	Adults	34	33.1	52.94	n.a.	n.a.	Washout 72h	34	32	52.94	n.a.	Flanker	Error processing	visual	625	26
Janssen et al., 2016	Children	36	10.03	72.22	95.97	n.a.	no	49	10.04	61.22	108.96	Oddball	Attention	auditory	1200	128
Jonkman et al., 2000	Children	14	9.6	92.86	97	n.a.	no	14	10.1	85.71	109.5	Easy/hard task	Attention	visual	4300	4
Jonkman et al., 1999	Children	14	9.5	92.86	98	n.a.	Washout 48h	14	10.5	85.71	109	Flanker	Inhibition	visual	2050	7
Jonkman et al., 2004	Children	18	10.6	88.89	93.9	n.a.	no	18	10	100	102.8	Two-channel color-selection task	Attention	visual	1950	31
Jonkman et al., 2007	Children	10	9.5	n.a.	97.9	n.a.	no	10	10.76	n.a.	107.5	Flanker	Error processing	visual	300	n.a.
Karayanidis et al., 2000	Children	17	7.17	100	111.12	yes	no	17	7.66	100	116.65	Choice-RT task	Attention	visual	2400	30
Kim et al., 2014	Adults	32	n.a.	47	n.a.	yes	no	25	n.a.	44	n.a.	Delayed match-to-sample task	Working memory	visual	400	128
Linden et al., 1996	Children	21	n.a.	n.a.	n.a.	n.a.	no	14	n.a.	n.a.	n.a.	Oddball	Attention	auditory	n.a.	1
López et al., 2006	Children	10	11.6	100	112.3	no	Washout 48h	10	11.3	100	110.5	Oddball	Attention	visual	775	64
Marzinzik et al., 2012	Adults	15	32.4	40	n.a.	no	no	15	29.9	33.34	n.a.	(modified) Oddball	Attention	visual	2000	20
Mayer et al., 2012	Adults	10	28.4	60	112.5	n.a.	yes	8	26.71	62.5	115	Go-NoGo	Attention	auditory	2200	22
McLoughlin et al., 2010	Adults	19	32.51	100	118	no	Washout 48h	20	30	100	122	CPT	Attention	visual	1500	19
McLoughlin et al., 2009	Adults	19	32.51	100	118	no	Washout 48h	16	30	100	122	Flanker	Error processing	visual	1400	19
Michelini et al., 2016	Adults	87	18.27	82.76	96.2	yes	Washout 48h	169	18.77	76.33	109.98	Flanker (adaption)	Error processing	visual	1500	62
Perchet et al., 2001	Children	24	8.5	87.5	n.a.	n.a.	n.a.	13	7.4	76.92	n.a.	Posner	Attention	visual	1500	19
Rodriguez et al., 2007	Adults	16	n.a.	n.a.	n.a.	no	Washout 24h	16	n.a.	n.a.	n.a.	Go-NoGo	Inhibition	visual	750	128

Study	Age group	N_{ADHD}	Age, mean (years)	Male, mean (%)	IQ, mean	Comorbidity	Medication status	$N_{non-ADHD}$	Age, mean (years)	Male, mean (%)	IQ, mean	Task	Cognitive Function	Modality	ISI	Electrodes
Rommel et al., 2017	Adolescents	69	18.5	88.4	97.7	n.a.	Washout 48h	135	17.8	75.6	110.4	(cued) Flanker CPT	Attention	visual	1500	62
Senderecka et al., 2012a	Children	20	9	80	108.3	no	Washout 24h	20	9.5	80	111	Oddball	Attention	auditory	1550	32
Senderecka et al., 2012b	Children	20	9	80	108.3	no	Washout 24h	20	9.5	80	111	Stop-Signal	Inhibition	multimodal	275	33
Smith et al., 2004	Children	12	10.2	100	98.8	n.a.	Washout 24h	12	10.3	100	104.5	(cued) Go-NoGo	Inhibition	auditory	2000	19
Sokhadze et al., 2012	Children[12]	16	13.2	87.5	98.45	yes	yes	16	14.6	81.25	n.a.	Oddball	Working memory	visual	1200	128
Stroux et al., 2016	Adults	40	30.08	52.5	102.58	yes	Washout 24h	41	31.22	56.1	104.07	2-back	Working memory	visual	1750	27
Sunohara et al., 1999	Children	20	10.5	80	n.a.	yes	Washout 24h	20	10.8	80	n.a.	CPT (double)	Attention	visual	1000	27
Tamayo-Orrego et al., 2015	Children	56	9.25	n.a.	n.a.	n.a.	Washout 24h	90	9.25	n.a.	n.a.	Oddball	Attention	auditory	n.a.	3
Taylor et al., 1997	Children	11 10	8.04 10.01	72.73 80	n.a.	n.a.	no no	11 10	8.03 9.1	72.73 60	n.a.	Serial task	Attention	visual	n.a.	27
Tsai et al., 2012	Children	50	8.9	84	n.a.	n.a.	no	51	9	78.43	n.a.	Oddball	Attention	auditory	n.a.	3
Tye et al., 201	Children	16	10.48	100	104.11	n.a.	Washout 48h	25	10.56	100	120.04	(cued) Flanker CPT	Attention	visual	1500	62
van der Stelt et al., 2001	Children	24	9.1	100	n.a.	no	no	24	9.3	100	n.a.	Color selective attention task	Attention	visual	1600	29
Wild-Wall et al., 2009	Adolescents	15	13.9	93.33	104	n.a.	n.a.	12	13.2	25	105	(modified) Flanker	Inhibition	visual	640	29
Winsberg et al., 1997	Children	14	9.28	n.a.	99.79	no	Washout 24h	14	10.56	n.a.	118.21	Oddball/CPT	Attention	auditory	1300	6
Woltering et al., 2013	Adults	54	25.1	51.85	n.a.	yes	yes	29	25.2	44.83	n.a.	Go-NoGo	Inhibition	visual	800	129
Yamamuro et al., 2016a	Children	14	11.43	78.57	101.29	n.a.	no	14	10.21	78.57	95.64	Oddball	Attention	auditory	1450	5
Yamamuro et al., 2016b	Children	44	10.28	79.55	95.33	yes	no	15	11.4	80	100.07	Oddball	Attention	auditory	1450	3

[12] Mean age suggests coding of adolescent age group, but as children with 9 years of age were included, the age group "Children" was selected for coding.

Study	Age group	N_{ADHD}	Age, mean (years)	Male, mean (%)	IQ, mean	Comorbidity	Medication status	$N_{non-ADHD}$	Age, mean (years)	Male, mean (%)	IQ, mean	Task	Cognitive Function	Modality	ISI	Electrodes
Yorbik et al., 2016	Children	41	9.3	100	n.a.	no	no	24	10.3	100	n.a.	Discrimination task	Attention	auditory	n.a.	4
Yorbik et al., 2008	Children	28	9.5	100	n.a.	n.a.	no	24	8.5	100	n.a.	Discrimination task	Attention	auditory	n.a.	4

Appendix E

Tables S2 and S3 – S9: Demographic information (per ERP component) and results from sensitivity analyses

Table S2

Description of included trials: Further demographic and methodological information (across all ERP components)

Group characteristic/technical information	*k* [absolute number of studies]	%
Age group (*k*=56)		
Children (mean age 6.00 – 11.11 years)	34[1]	60.71%
Adolescents (mean age 12.00 – 17.11 years)	6	10.71%
Adults (mean age > 18.00 years)	16	28.57%
ADHD subtype (*k*=29)[2]		
ADHDcom	20	68.97%
ADHDin	1	3.45%
ADHDhyp/imp	0	0%
ADHDcom + ADHDin	6	20.69%
ADHDcom + ADHDhyp/imp	1	3.45%
All subtypes	1	3.45%
Comorbidity (*k*=27)[2]		
yes	12	44.44%
no	15	55.56%
Medication status (*k*=53)[1, 2]		
yes	7	13.21%
no	24	45.28%
yes, but washout 24h	11	20.75%
yes, but washout 48h	11	20.75%
Task (*k*=52)		
Oddball	13	25.00%
Go/NoGo	10	19.23%
Flanker task	8	15.38%
RT tasks	6	11.54%
CPT	6	11.54%
Flanker-CPT	3	5.77%
Easy/Hard task	1	1.92%
Fast task	1	1.92%
Match-to-sample taks	1	1.92%
Posner cueing paradigm	1	1.92%
Stroop/Simon	1	1.92%
2-back task	1	1.92%
Cognitive function (*k*=52)		
Attention	28	53.85%
Inhibitory control	13	25.00%
Error/process monitoring	9	17.31%
Working memory (WM)	2	3.85%
Modality (*k*=52)		
visual	37	71.15%
auditory	12	23.08%
multimodal	3	5.77%

Note. [1]Two studies provide data for more than one participant group (age group/medication group). [2]Information regarding moderator variable provided only for subset of studies (*k*<52).

Table S3

Demographic information (for each ERP component)

			ADHD				Non-ADHD			
ERP amplitude	***k***	**Number of studies**	**N**	**Age, mean (years)**	**Male, mean (%)**	**IQ, mean**	**N**	**Age, mean (years)**	**Male, mean (%)**	**IQ, mean**
P100										
Cue	0	0	0	*n.a.*	*n.a.*	*n.a.*	0	*n.a.*	*n.a.*	*n.a.*
Go	10	7	180	12.60 (6.77)	84.9 (21.94)	104.5 (*n.a.*)	134	12.86 (7.00)	78.18 (23.39)	107 (*n.a.*)
NoGo	2	2	68	**24.85 (0.35)****	51.85	*n.a.*	43	**24.95 (0.35)****	44.83 (*n.a.*)	*n.a.*
N100										
Cue	0	0	0	*n.a.*	*n.a.*	*n.a.*	0	*n.a.*	*n.a.*	*n.a.*
Go	14	8	181	12.72 (6.63)	93.5 (7.90)	**104.78 (4.35)***	243	13.13 (6.20)	87.11 (15.28)	**112.57 (4.71)***
NoGo	5	3	84	19.75 (8.84)	75.93 (34.05)	106.5 (*n.a.*)	62	19.93 (8.69)	72.42 (39.01)	111.00 (*n.a.*)
P200										
Cue	0	0	0	*n.a.*	*n.a.*	*n.a.*	0	*n.a.*	*n.a.*	*n.a.*
Go	16	9	190	12.69 (6.65)	90.8 (9.12)	**105.37 (4.15)***	187	13.17 (6.18)	85.69 (13.61)	**112.31 (4.26)***
NoGo	4	2	30	17.08 (10.64)	100 (*n.a.*)	106.5 (*n.a.*)	33	17.3 (10.47)	100 (*n.a.*)	111 (*n.a.*)
N200										
Cue	0	0	0	*n.a.*	*n.a.*	*n.a.*	0	*n.a.*	*n.a.*	*n.a.*
Go	48	20	554	13.57 (7.73)	90.24 (13.65)	**105.14 (5.97)****	638	13.71 (7.46)	84.37 (20.04)	**112.65 (5.37)****
NoGo	16	10	282	21.14 (9.42)	84.91 (22.07)	103.46 (9.02)	342	21.10 (9.25)	78.58 (27.21)	111.65 (8.59)
P300										
Cue	18	6	257	16.92 (8.57)	92.82 (8.27)	105.41 (8.42)	399	16.29 (7.56)	86.38 (15.29)	115.53 (5.41)°
Go	76	32	924	15.81 (8.50)	83.64 (18.33)	**102.73 (6.40)****	971	15.77 (8.18)	75.86 (22.56)	**109.56 (6.79)****
NoGo	37	15	472	18.95 (8.82)	85.16 (18.31)	**104.53 (7.14)***	592	19.04 (8.51)	71.15 (25.56)	**111.60 (7.02)***
CNV	15	8	385	21.26 (8.54)	81.10 (20.99)	**103.69 (8.71)***	603	20.48 (8.14)	80.41 (19.89)	**112.62 (7.21)***
ERN/Ne	23	11	346	19.21 (9.24)	81.51 (17.59)	**103.76 (8.22)°**	376	19.08 (8.46)	68.37 (23.75)	**111.03 (5.91)°**
Pe	23	10	330	19.81 (9.51)	80.85 (18.53)	104.43 (8.52)	360	19.53 (8.78)	66.93 (24.73)	111.03 (5.91)

Note. Results for Welch-two-sample t-test (between-group comparison): *** $p < .001$, ** $p < .01$, * $p < .05$, ° $p < .1$. *n.a. not available.*

Table S3 (continued)
Demographic information (for each ERP component)

			ADHD				Non-ADHD			
ERP latency	***k***	**Number of studies**	**N**	**Age, mean (years)**	**Male, mean (%)**	**IQ, mean**	**N**	**Age, mean (years)**	**Male, mean (%)**	**IQ, mean**
P100										
Cue	0	0	0	*n.a.*	*n.a.*	*n.a.*	0	*n.a.*	*n.a.*	*n.a.*
Go	10	7	172	12.42 (6.84)	86.90 (22.95)	98.8 (*n.a.*)	126	12.24 (7.07)	84.18 (24.59)	104.5 (*n.a.*)
NoGo	3	3	80	19.97 (8.46)	75.93 (34.05)	98.80 (*n.a.*)	55	20.07 (8.46)	72.42 (39.01)	104.5 (*n.a.*)
N100										
Cue	0	0	0	*n.a.*	*n.a.*	*n.a.*	0	*n.a.*	*n.a.*	*n.a.*
Go	13	8	161	12.76 (6.59)	92.80 (9.96)	**104.14 (5.05)***	165	12.94 (5.77)	91.69 (11.40)	**112.07 (5.51)***
NoGo	6	4	96	17.36 (8.65)	83.95 (27.80)	102.65 (5.44)	74	17.53 (8.58)	81.61 (31.85)	107.75 (4.60)
P200										
Cue	0	0	0	*n.a.*	*n.a.*	*n.a.*	0	*n.a.*	*n.a.*	*n.a.*
Go	15	10	196	12.40 (6.26)	92.81 (8.91)	**103.12 (5.716)***	193	12.67 (5.83)	90.69 (10.48)	**111.56 (5.08)***
NoGo	5	3	42	14.78 (8.51)	100 (0)	102.65 (5.44)	45	14.97 (8.43)	100 (0)	107.75 (4.60)
N200										
Cue	0	0	0	*n.a.*	*n.a.*	*n.a.*	0	*n.a.*	*n.a.*	*n.a.*
Go	31	15	358	14.08 (8.60)	90.10 (15.03)	**103.90 (6.77)***	282	14.12 (8.24)	86.66 (17.81)	**111.36 (6.24)***
NoGo	5	4	99	23.10 (9.33)	83.95 (27.80)	108.4 (13.58)	75	22.55 (8.51)	81.61 (31.85)	113.25 (12.37)
P300										
Cue	2	1	19	32.51 (*n.a.*)	100 (*n.a.*)	118 (*n.a.*)	20	30 (*n.a.*)	100 (*n.a.*)	122 (*n.a.*)
Go	38	19	487	15.07 (9.16)	79.62 (20.26)	102.29 (6.95)	449	14.86 (8.63)	77.56 (20.87)	107.694 (8.85)
NoGo	9	3	49	28.56 (5.59)	100 (*n.a.*)	118 (*n.a.*)	50	27.35 (3.75)	100 (*n.a.*)	122 (*n.a.*)
CNV	0	0	0	*n.a.*	*n.a.*	*n.a.*	0	*n.a.*	*n.a.*	*n.a.*
ERN/Ne	12	6	168	17.74 (8.78)	85.76 (20.72)	104.23 (9.60)	112	17.73 (7.61)	76.78 (24.49)	112.45 (7.02)
Pe	8	3	74	24.13 (8.16)	80.43 (26.71)	108.21 (13.04)	64	23.27 (6.94)	67.54 (28.14)	114.82 (8.69)

Note. Results for Welch-two-sample t-test (between-group comparison): *** $p < .001$, ** $p < .01$, * $p < .05$, ° $p < .1$. *n.a. not available.*

Table S4

Overall mean estimated true effect sizes for random-effects models/multilevel linear models – Cue trials – Sensitivity analysis I (outlier excluded)

	ERP amplitude				ERP latency			
ERP component	*k*	*d*	[*95% CI*]	Q_W (*df*, *p*)	*k*	*d*	[*95% CI*]	Q_W (*df*, *p*)
P100	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*
N100	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*
P200	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*
N200	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*
P300	18	-0.56***	[-0.82 – (-0.30)]	22.04 (17, .18)	2	-0.35	[-0.80 – 0.10]	2.96 (1, .09)

Note. *** $p < .001$, ** $p < .01$, * $p < .05$, ° $p < .1$. *n.a. not available.*

Table S5

Overall mean estimated true effect sizes for random-effects models/multilevel linear models – Go trials – Sensitivity analysis I (outlier excluded)

	ERP amplitude				ERP latency			
ERP component	*k*	*d*	[*95% CI*]	Q_W (*df*, *p*)	*k*	*d*	[*95% CI*]	Q_W (*df*, *p*)
P1	9	-0.19	[-0.38 – 0.01]	5.09 (8, .75)	10	-0.33**	[-0.53 – (-0.13)]	8.28 (9, .51)
N1	13	-0.20	[-0.44 – 0.05]	29.89 (12, .003)	12	-0.05	[-0.48 – 0.38]	23.87 (11, .01)
P2	15	0.20	[-0.34 – 0.74]	58.14 (14, <.0001)	13	-0.04	[-0.60 – 0.512]	43.77 (12, <.0001)
N2	47	0.09	[-0.10 – 0.28]	113.33 (46, <.0001)	29	0.09	[-0.13 – 0.32]	45.06 (28, .02)
P3	74	-0.18*	[-0.34–(-0.02)]	157.66 (73, <.0001)	37	0.64***	[0.27 - 1.01]	164.70 (36, <.0001)

Note. *** $p < .001$, ** $p < .01$, * $p < .05$, ° $p < .1$. *n.a. not available.*

Table S6

Overall mean estimated true effect sizes for random-effects models/multilevel linear models (outlier excluded) – NoGo trials – Sensitivity analysis I

	ERP amplitude				ERP latency			
ERP component	*k*	*d*	[*95% CI*]	Q_W (*df*, *p*)	*k*	*d*	[*95% CI*]	Q_W (*df*, *p*)
P100	2	-0.19	[-0.58 – 0.19]	0.01 (1, .93)	2	-0.25	[-0.80 – 0.29]	0.04 (1, .85)
N100	4	-0.26°	[-0.56 – 0.04]	0.50 (4, .92)	4	0.06	[-0.29 – 0.42]	1.47 (3, .69)
P200	4	0.03	[-0.32 – 0.37]	7.63 (3, 0.05)	5	0.05	[-0.67 – 0.77]	10.65 (4, .03)
N2000	16	0.08	[-0.19 – 0.36]	34.76 (15, .00)	5	-0.59	[-2.49 – 1.32]	38.52 (4, <.0001)
P300	36	-0.42***	[-0.59 – (-0.26)]	57.98 (35, <.01)	9	0.35**	[0.11 – 0.58]	16.85 (8, .03)

Note. *** $p < .001$, ** $p < .01$, * $p < .05$, ° $p < .1$. *n.a. not available.*

Table S7

Overall mean estimated true effect sizes for random-effects models/multilevel linear models outlier excluded) – CNV, ERN/Ne, Pe – Sensitivity analysis I

	ERP amplitude				ERP latency			
ERP component	*k*	*d*	[*95% CI*]	Q_W (*df*, *p*)	*k*	*d*	[*95% CI*]	Q_W (*df*, *p*)
CNV	14	0.41**	[0.16 – 0.67]	25.48 (13, .02)	$k \leq 1$	*n.a.*	*n.a.*	*n.a.*
ERN/Ne	21	0.21	[-0.06 – 0.47]	113.59 (20, <.0001)	12	0.04	[-0.40 – 0.48]	26.02 (11, .01)
Pe	23	-0.39**	[-0.64 – (-0.13)]	58.33 (22, <.0001)	8	-0.01	[-0.40 – 0.39]	7.37 (7, .39)

Note. *** $p < .001$, ** $p < .01$, * $p < .05$, ° $p < .1$. *n.a. not available.*

Table S8

Overall mean estimated true effect sizes for random-effects models/multilevel linear models across all conditions (Cue vs. Go vs. NoGo) – Sensitivity analysis II

	ERP amplitude				ERP latency			
ERP component	*k*	*d*	[*95% CI*]	Q_W (*df*, *p*)	*k*	*d*	[*95% CI*]	Q_W (*df*, *p*)
P1	12	0.30	[-0.64 – 1.24]	62.21 (11, <.0001)	10	-0.26**	[-0.44 – (-0.08)]	11.69 (13, .55)
N1	19	-0.46	[-1.09 – 0.17]	76.49 (18, <.0001)	20	-0.07	[-0.40 – 0.27]	36.45 (19, .009)
P2	20	0.49	[-0.23 – 1.22]	103.45 (19, <.0001)	21	0.05	[-0.78 – 0.88]	117.04 (20, <.0001)
N2	64	0.10	[-0.08 – 0.28]	163.12 (63, <.0001)	37	-0.33	[-0.93 – 0.28]	179.85 (36, <.0001)
P3	132	-0.25**	[-0.43–(-0.08)]	375.72 (131, <.0001)	49	0.50*	[0.09 - 0.91]	237.95 (48, <.0001)

Note. *** $p < .001$, ** $p < .01$, * $p < .05$, ° $p < .1$. *n.a. not available.*

Table S9

Comparison of mean estimated true effect sizes for random-effects models/multilevel linear models for each condition (Cue vs. Go vs. NoGo) – Sensitivity analysis II

ERP component	ERP amplitude	ERP latency
P100	*n.s.*	*n.s.*
N100	*n.s.*	*n.s.*
P200	*n.s.*	*n.s.*
N2	Cue > Go** (d_{Cue} = 1.55 vs. d_{Go} = 0.10);	Cue > Go** (d_{Cue} = 1.16 vs. d_{Go} = -0.46);
	Cue > NoGo** (d_{Cue} = 1.55 vs. d_{NoGo} = -0.03)	Cue > NoGo** (d_{Cue} = 1.16 vs. d_{NoGo} = -0.63)
P3	Cue > Go*** (d_{Cue} = -0.39 vs. d_{Go} = -0.17);	Cue < Go* (d_{Cue} = -0.16 vs. d_{Go} = 0.54);
	Go < NoGo*** (d_{Go} = -0.17 vs. d_{NoGo} = -0.41)	Cue < NoGo* (d_{Cue} = -0.16 vs. d_{NoGo} = 0.55)

Note. *** $p < .001$, ** $p < .01$, * $p < .05$, ° $p < .1$. *n.s. not significant.*

Appendix F

Forest plots (non-significant results)

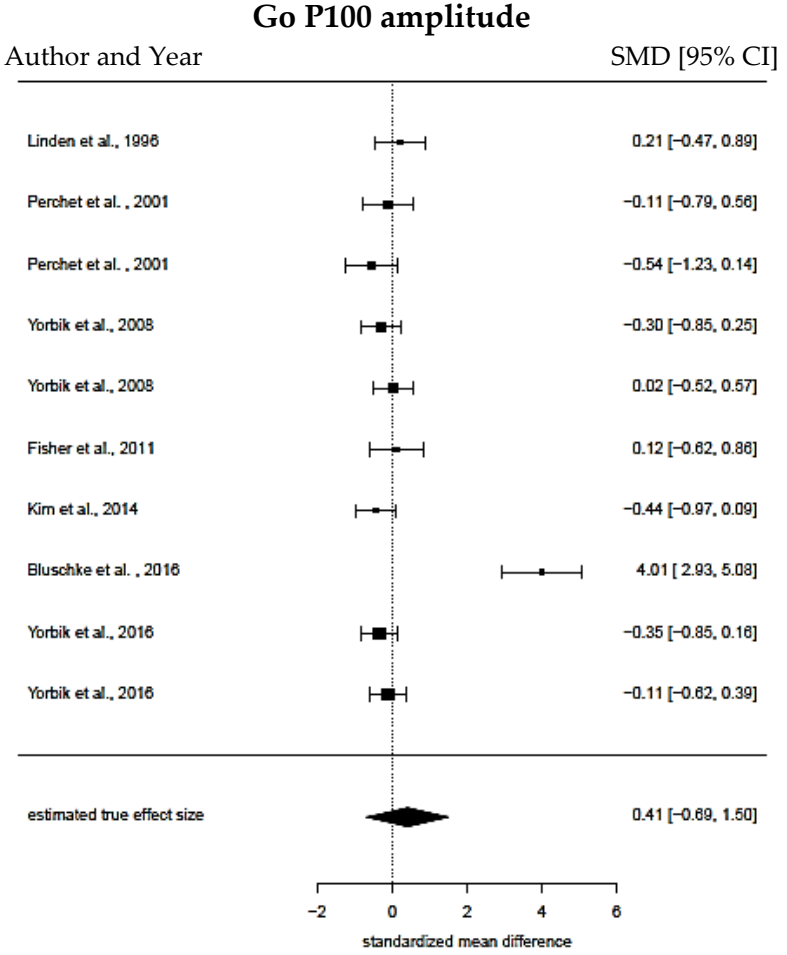

Figure S1. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to Go P100 amplitude data and addressing multilevel structure.

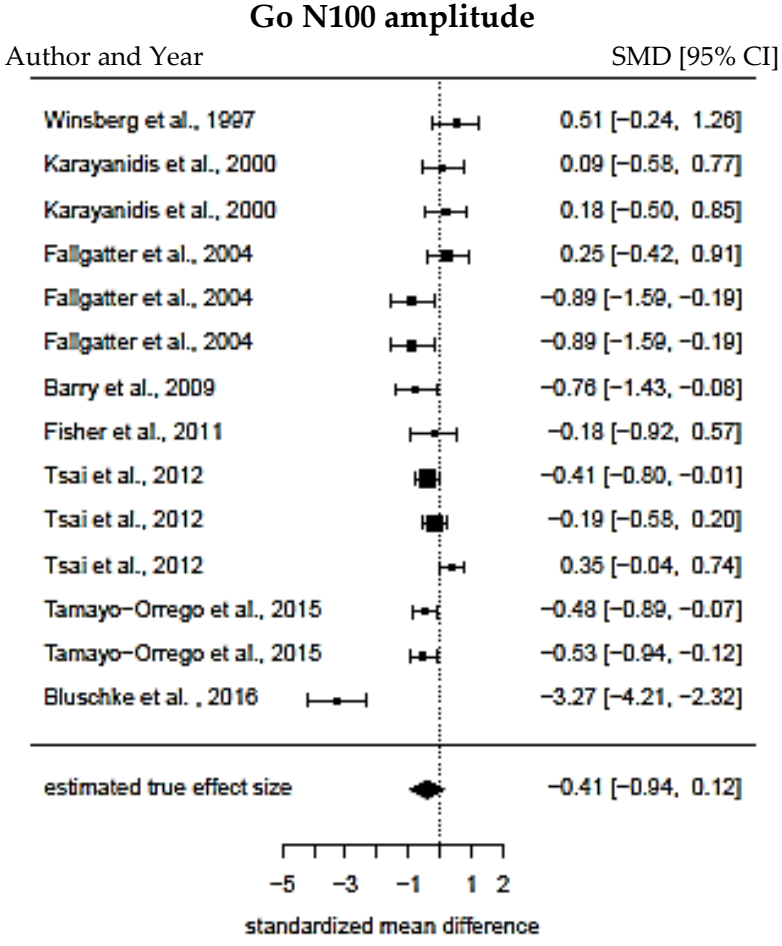

Figure S2. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to Go N100 amplitude data and addressing multilevel structure.

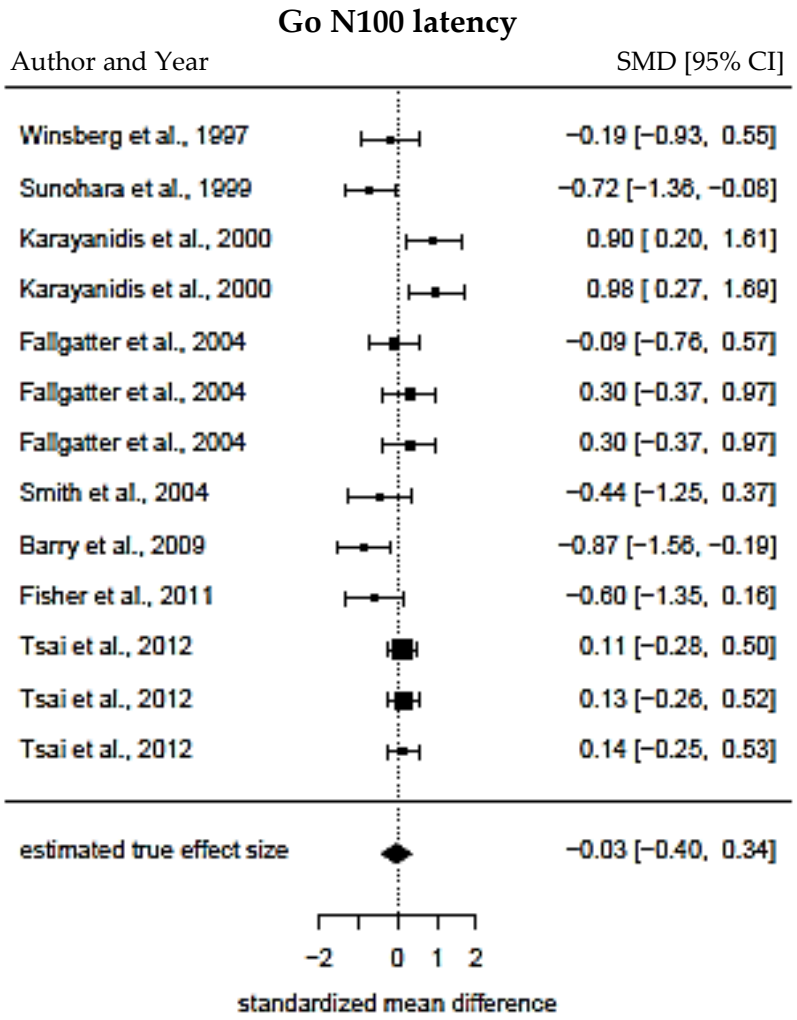

Figure S3. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to Go N100 latency data and addressing multilevel structure.

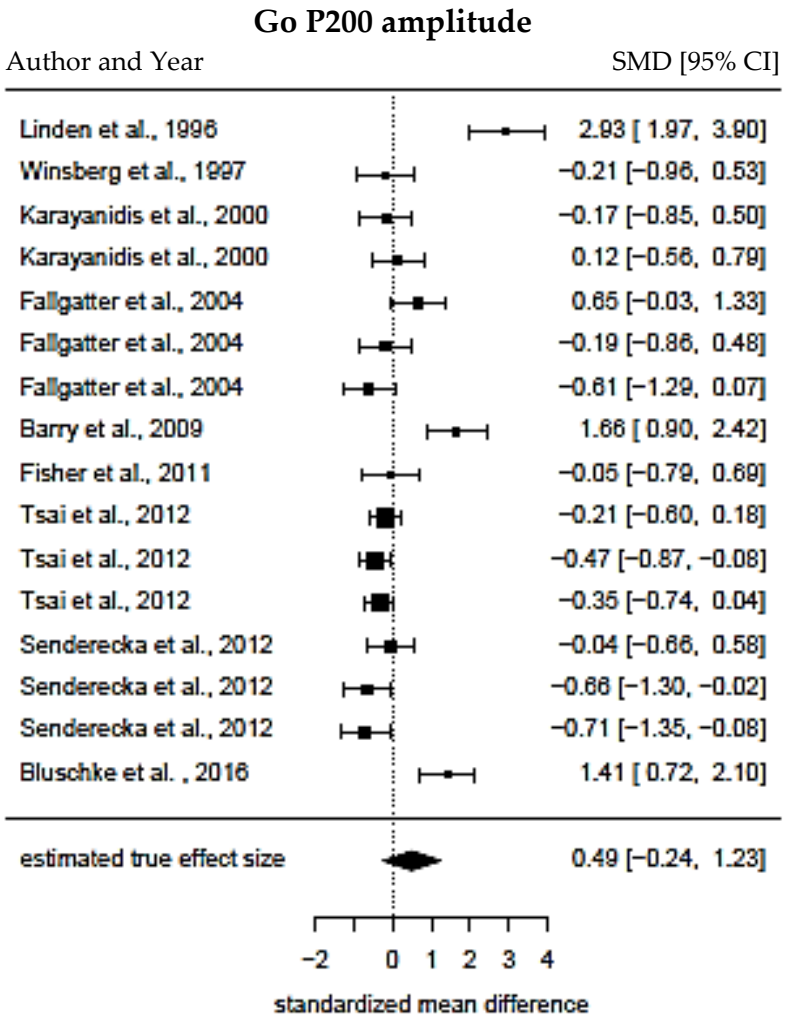

Figure S4. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to Go P200 amplitude data and addressing multilevel structure.

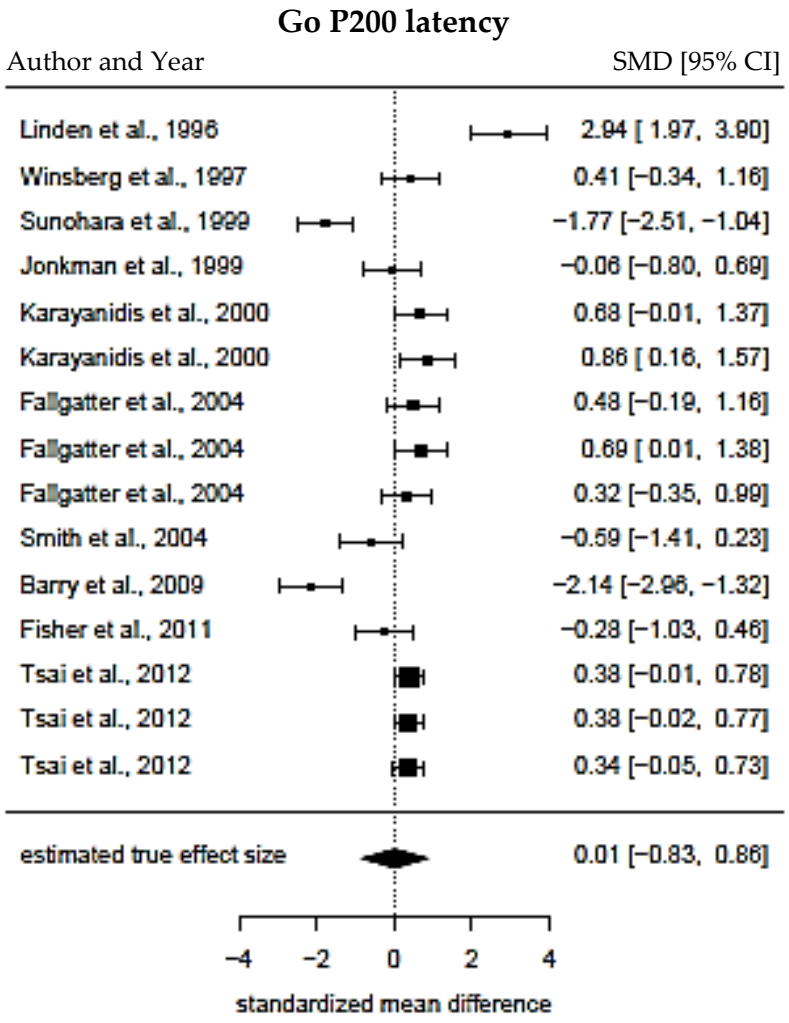

Figure S5. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to Go P200 latency data and addressing multilevel structure.

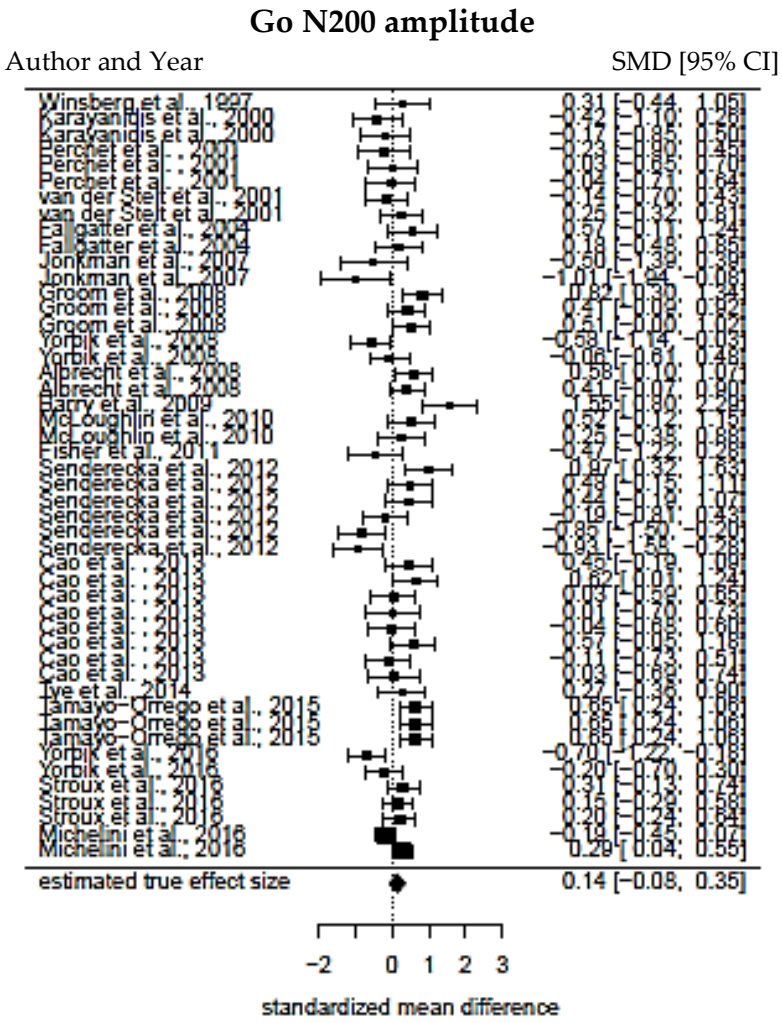

Figure S6. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to Go N200 amplitude data and addressing multilevel structure.

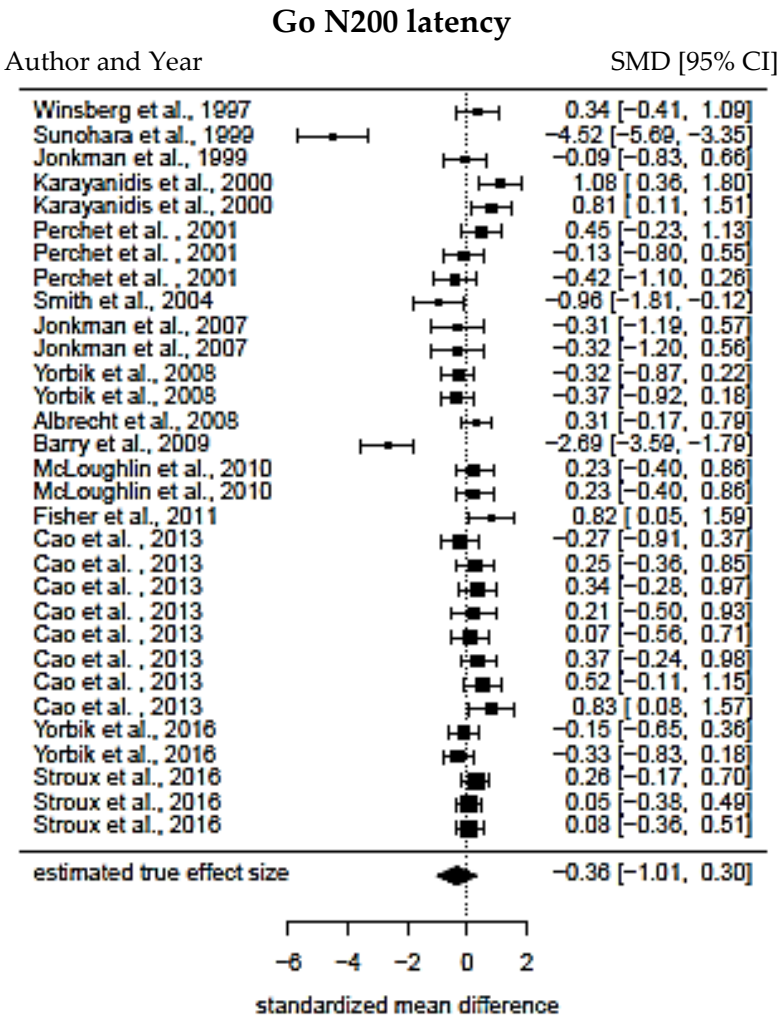

Figure S7. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to Go N200 latency data and addressing multilevel structure.

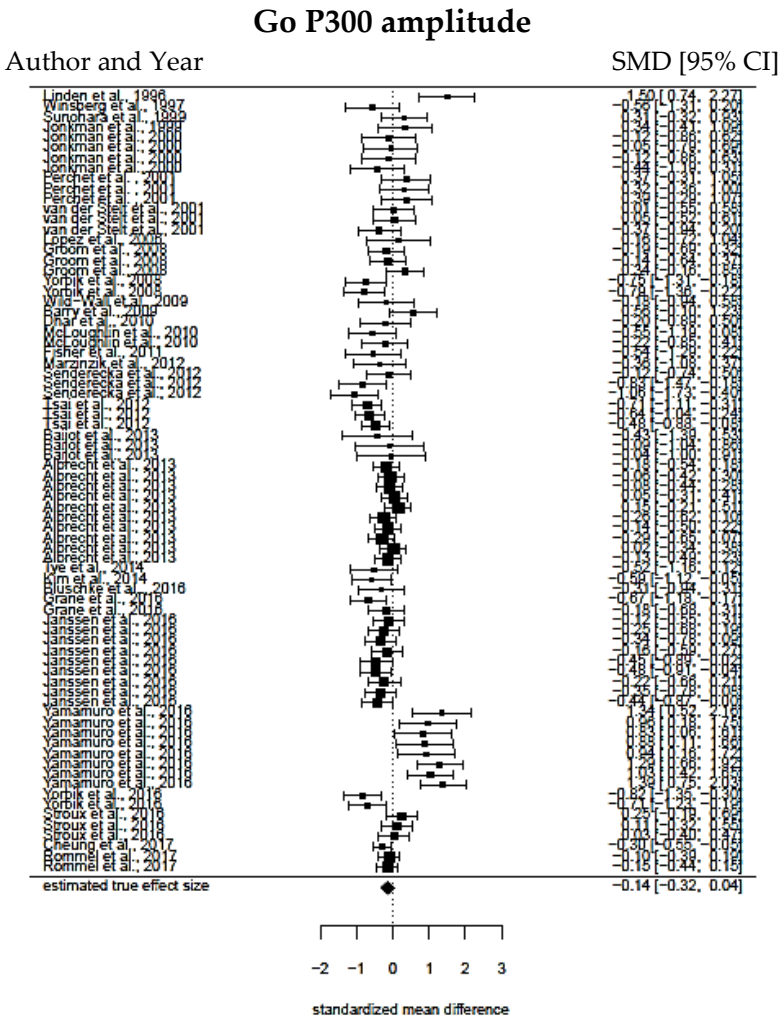

Figure S8. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to Go P300 amplitude data and addressing multilevel structure.

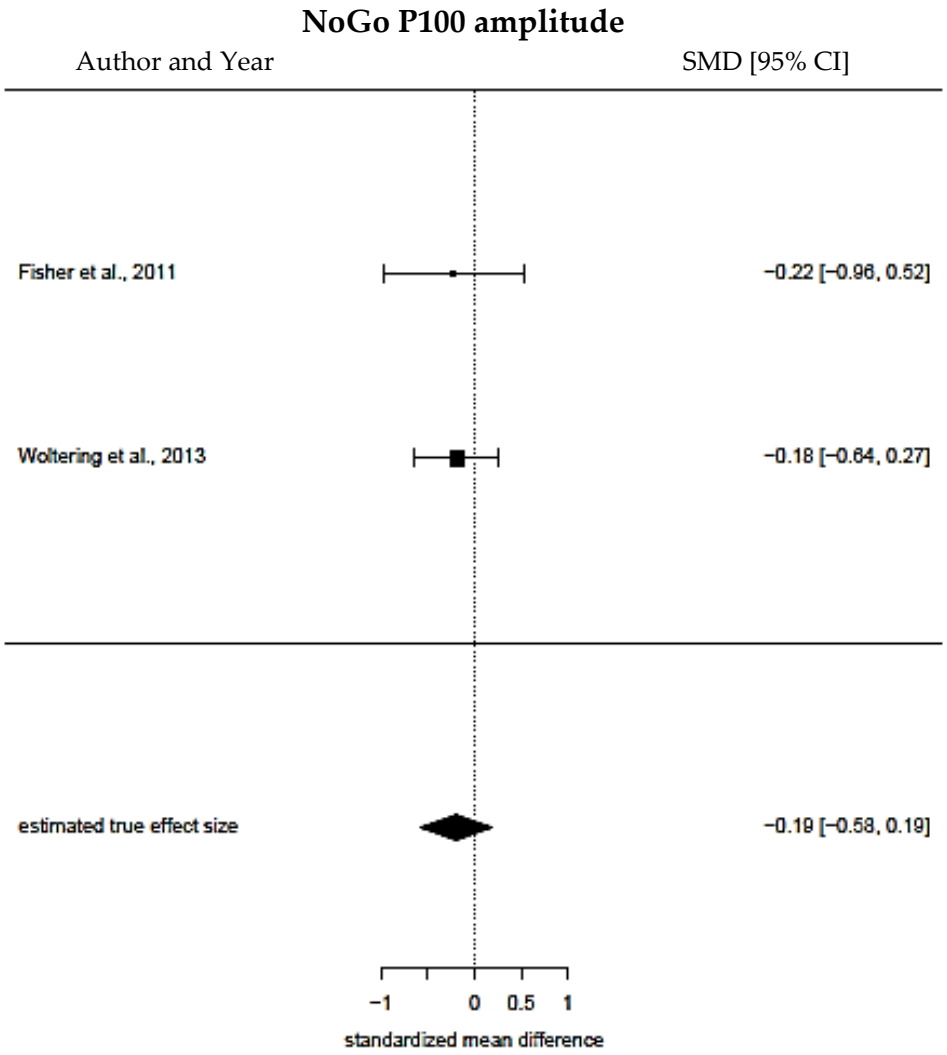

Figure S9. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to NoGo P100 amplitude data and addressing multilevel structure.

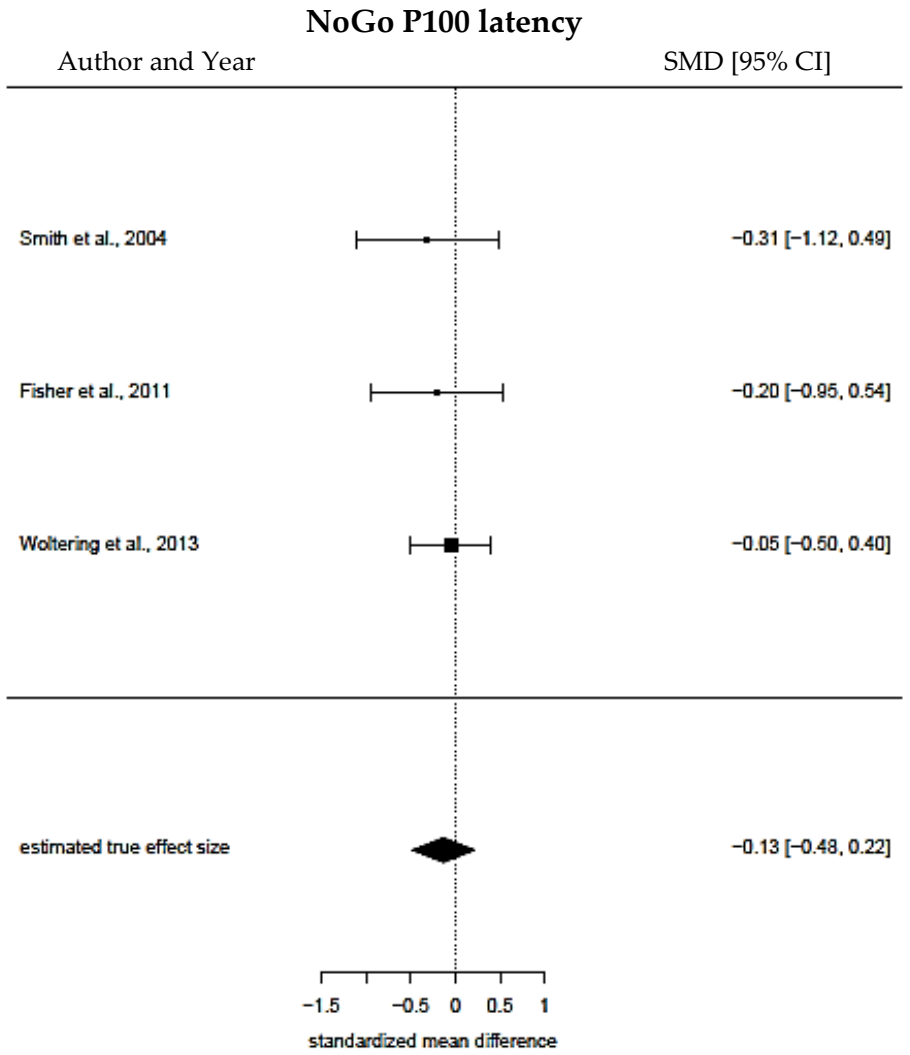

Figure S10. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to NoGo P100 latency data and addressing multilevel structure.

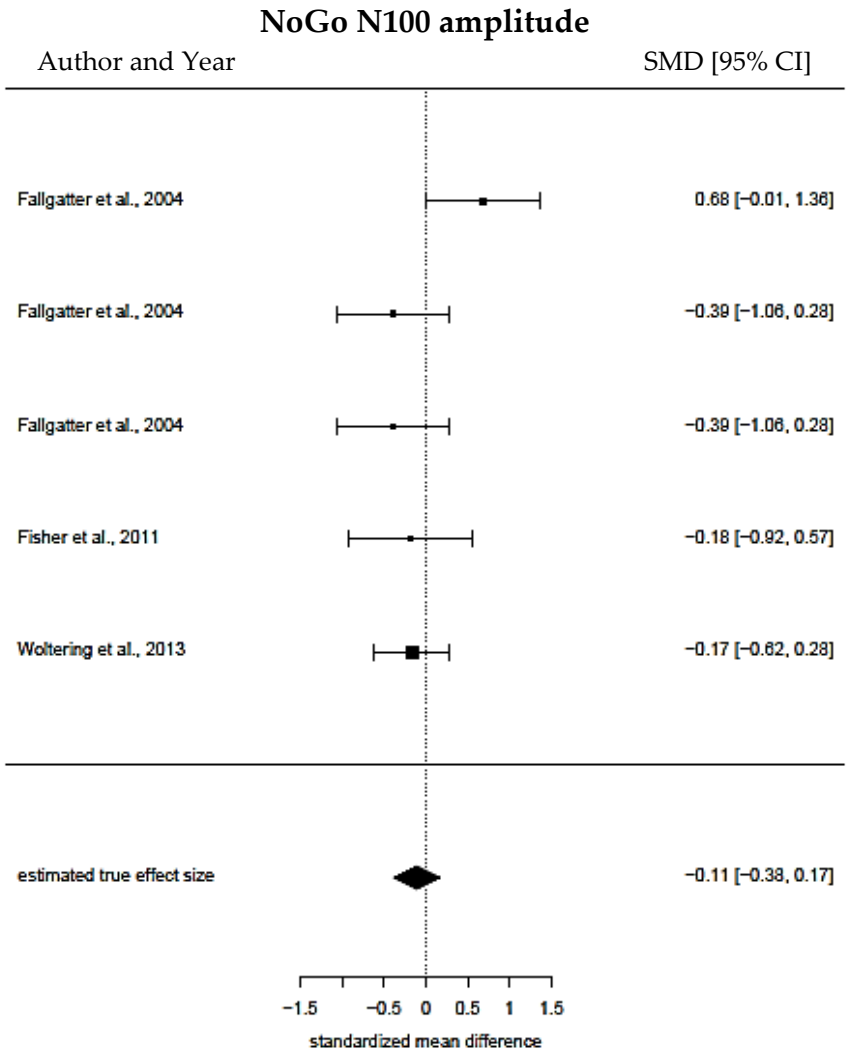

Figure S11. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to NoGo N100 amplitude data and addressing multilevel structure.

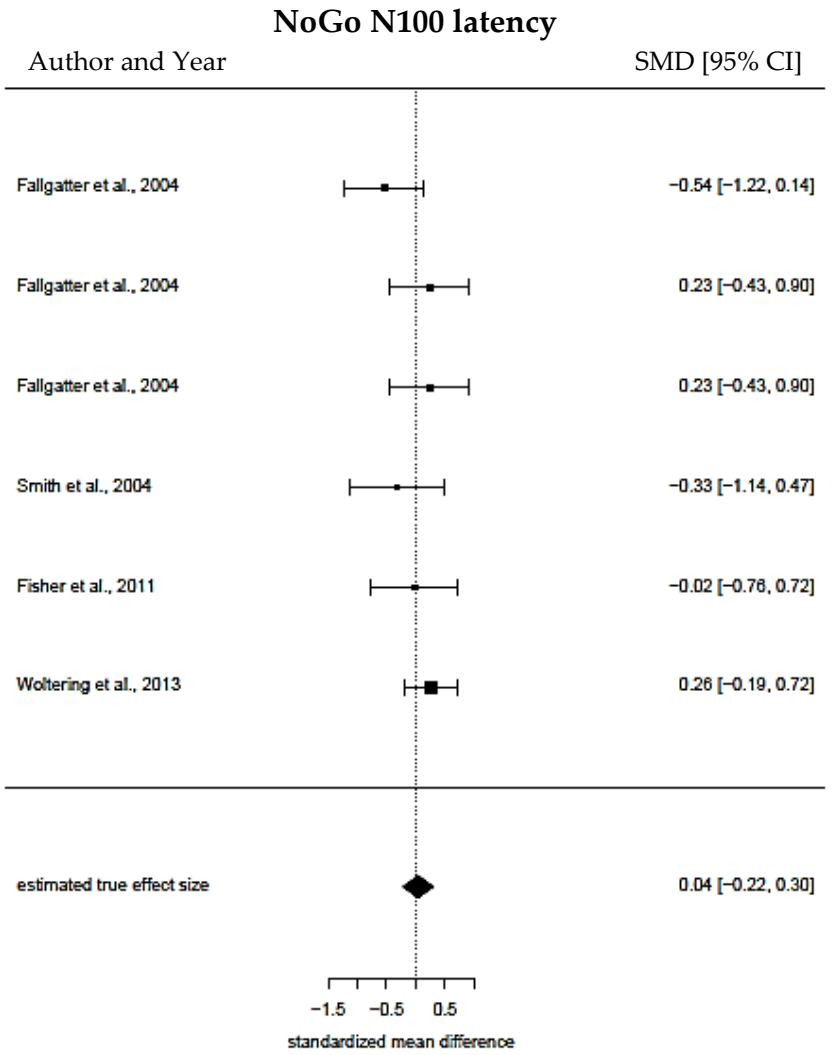

Figure S12. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to NoGo N100 latency data and addressing multilevel structure.

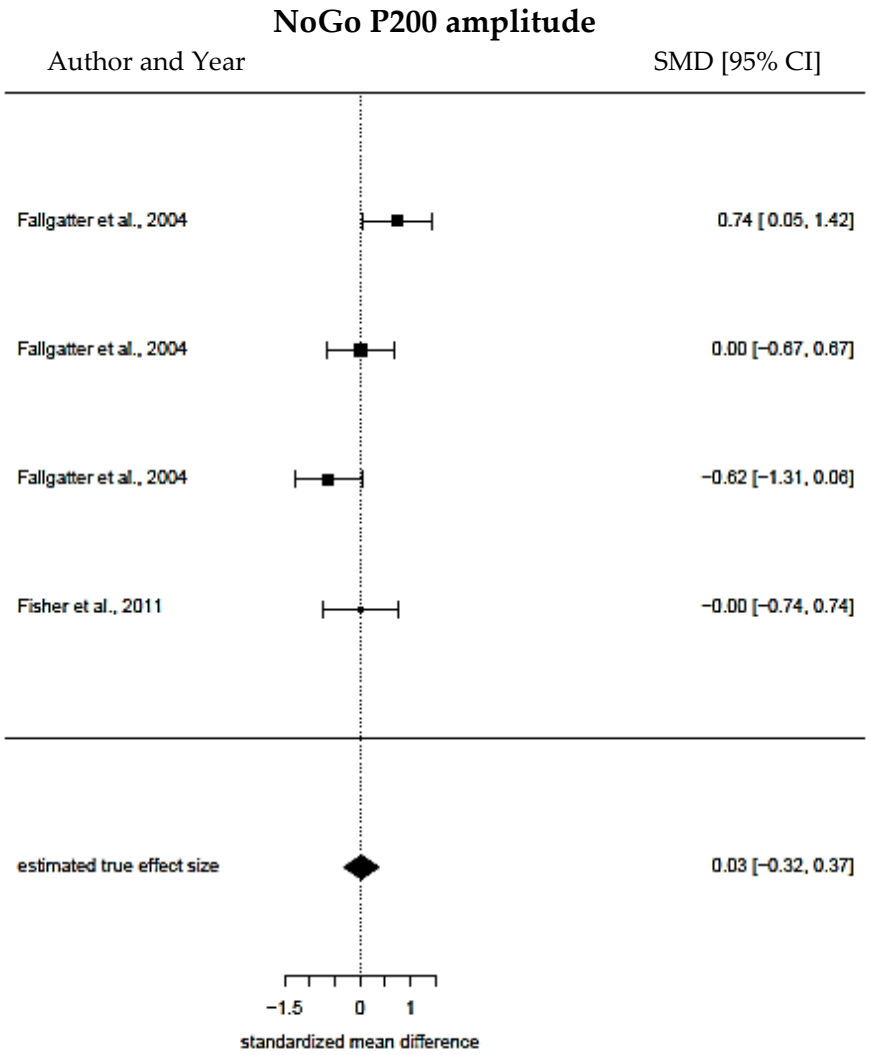

Figure S13. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to NoGo P200 amplitude data and addressing multilevel structure.

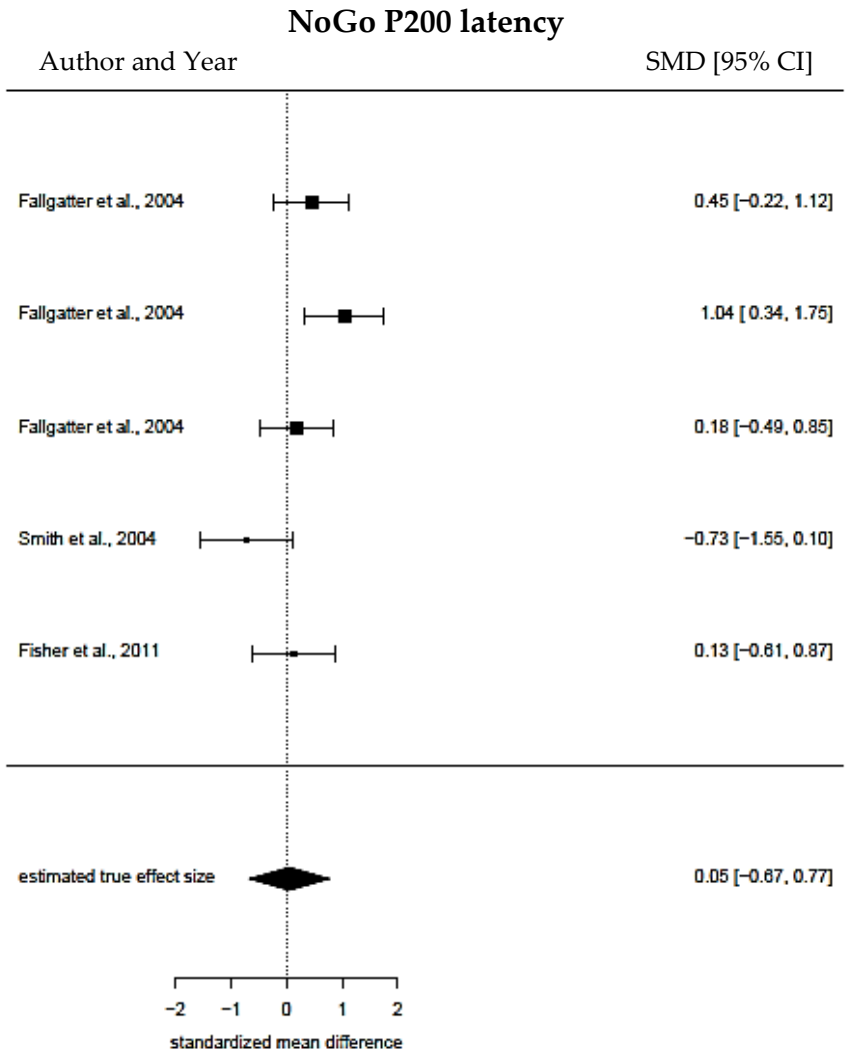

Figure S14. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to NoGo P200 latency data and addressing multilevel structure.

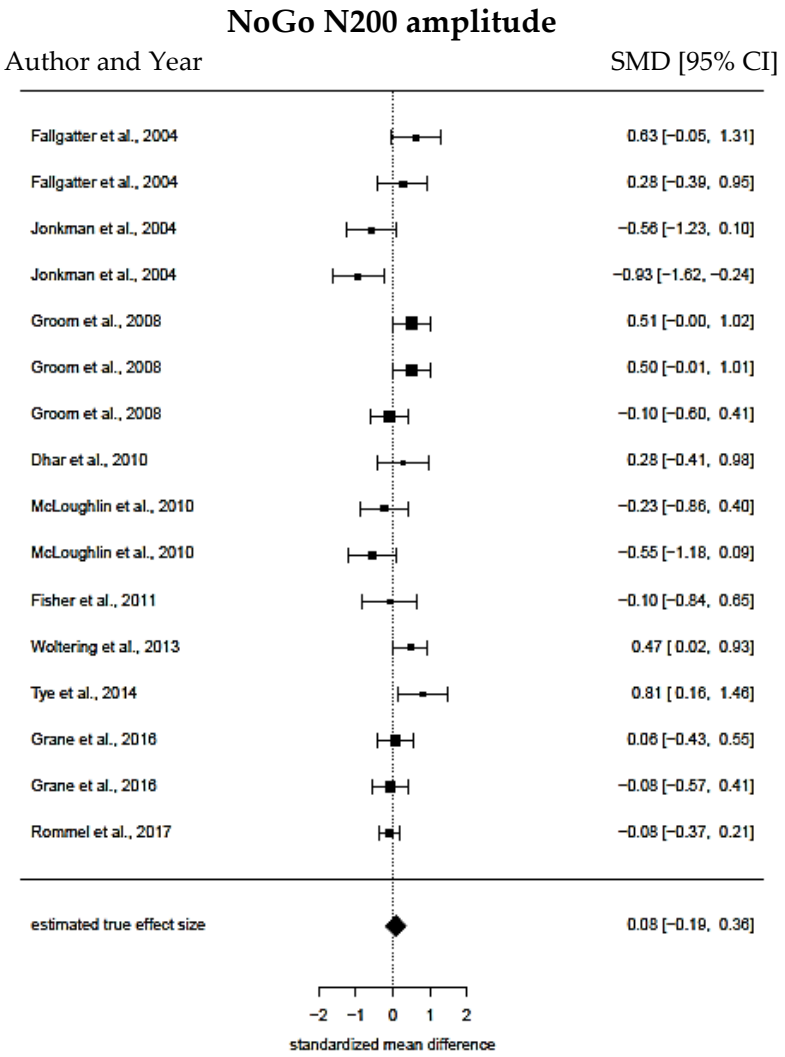

Figure S15. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to NoGo N200 amplitude data and addressing multilevel structure.

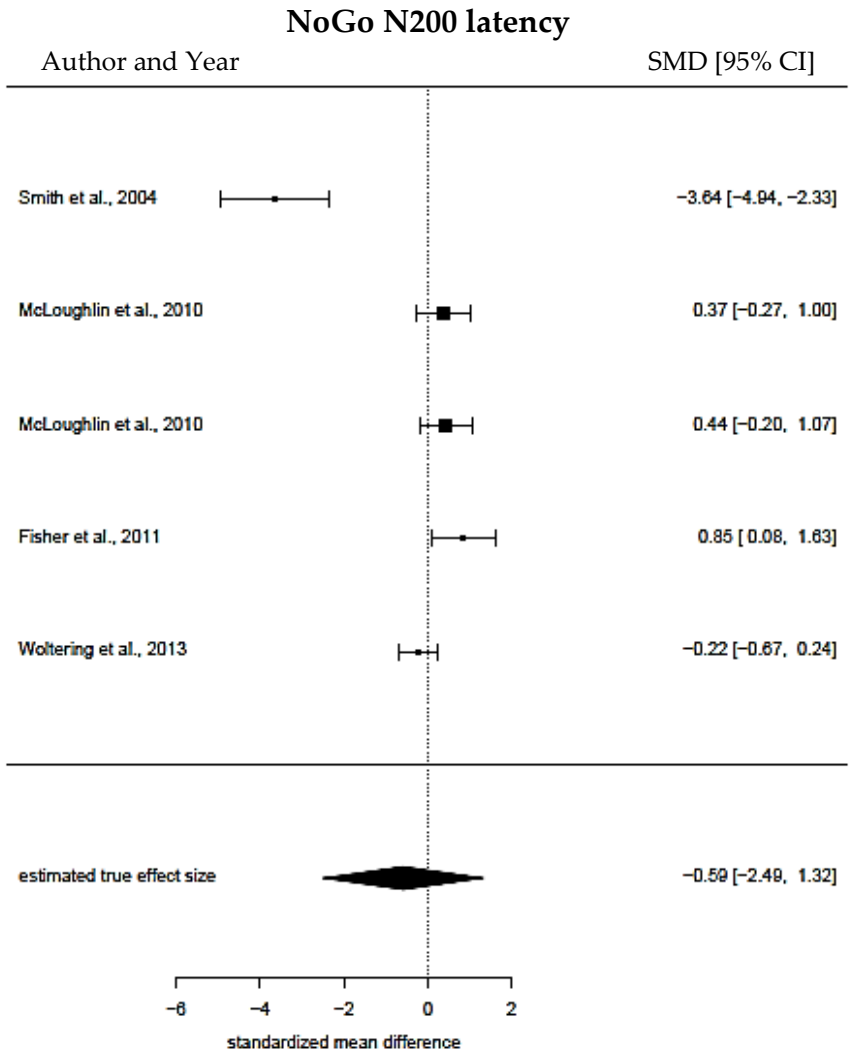

Figure S16. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to NoGo N200 latency data and addressing multilevel structure.

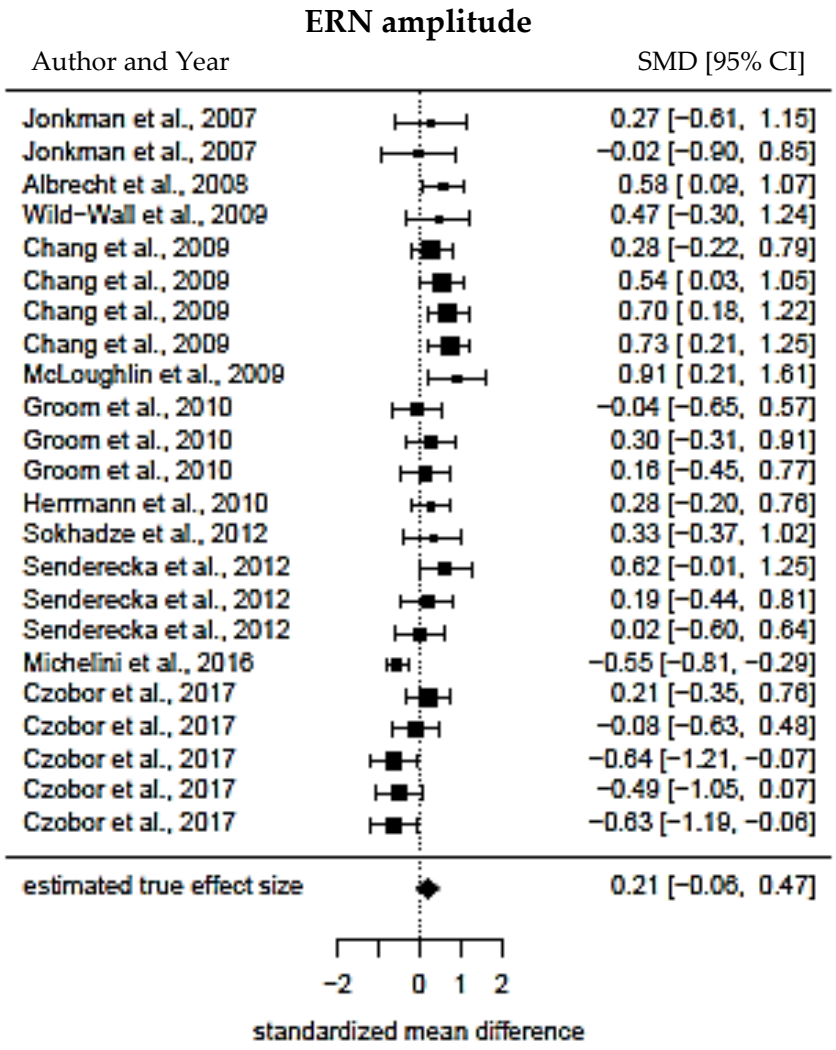

Figure S17. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to ERN amplitude data and addressing multilevel structure.

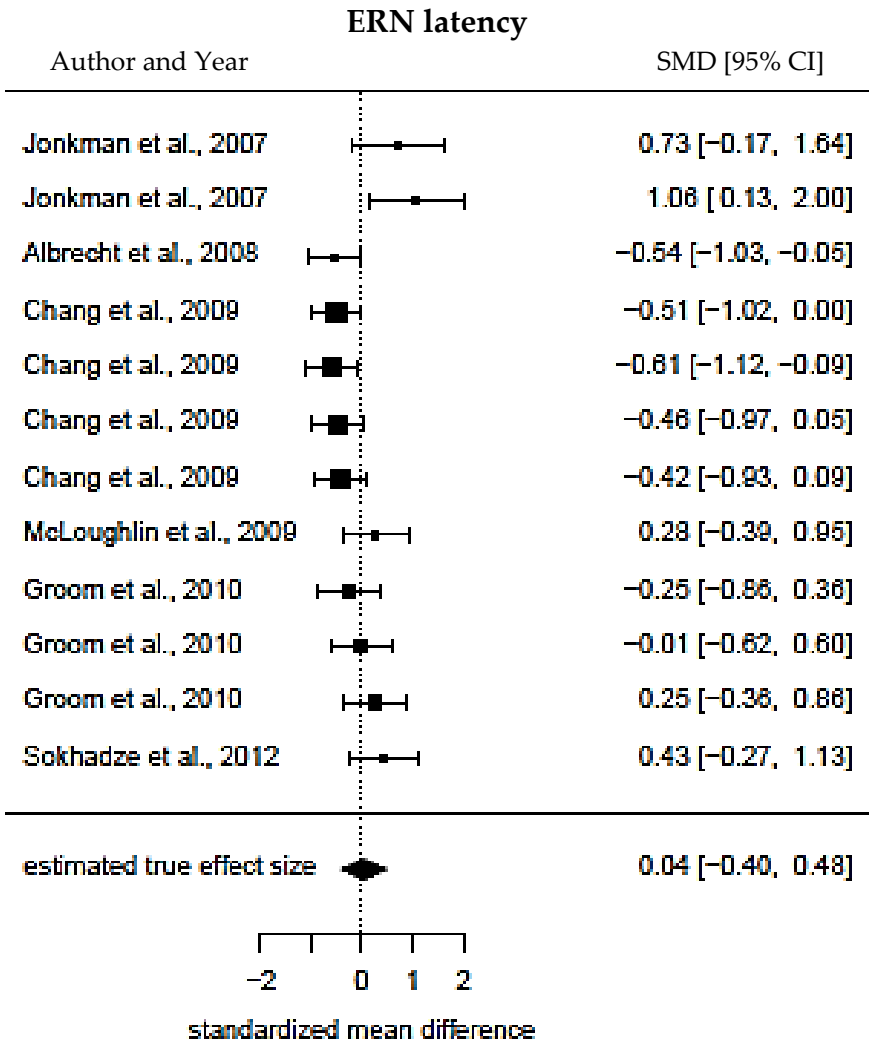

Figure S18. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to ERN latency data and addressing multilevel structure.

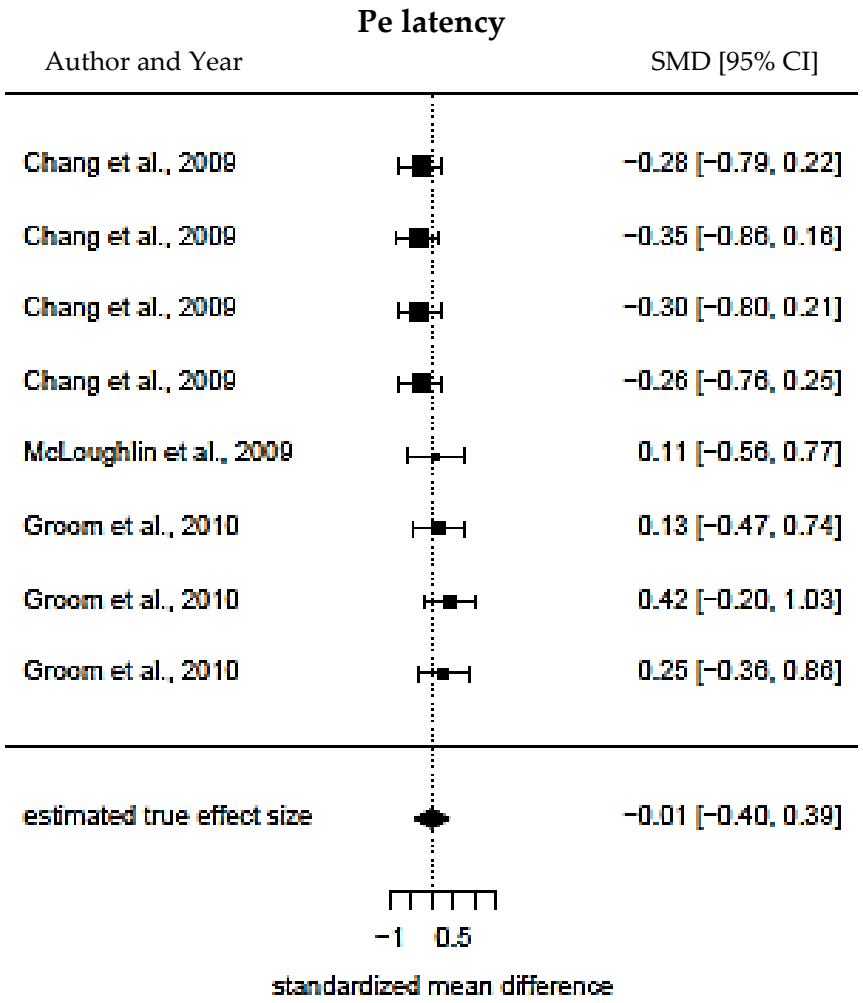

Figure S19. Cumulative forest plot displaying meta-analytical results obtained from fitting multilevel models to Pe latency data and addressing multilevel structure.

Appendix G

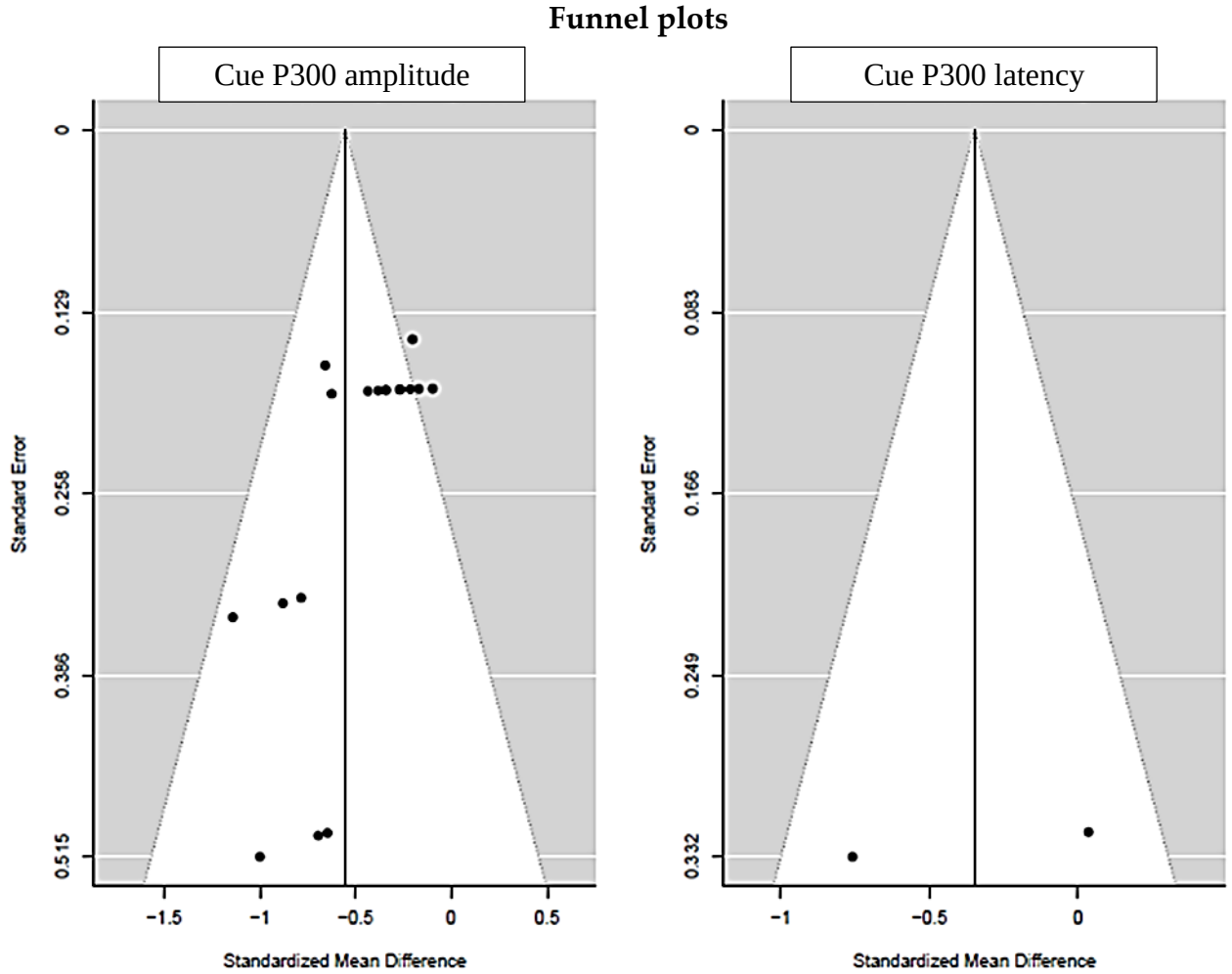

Figure S20. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to Cue P300 data.

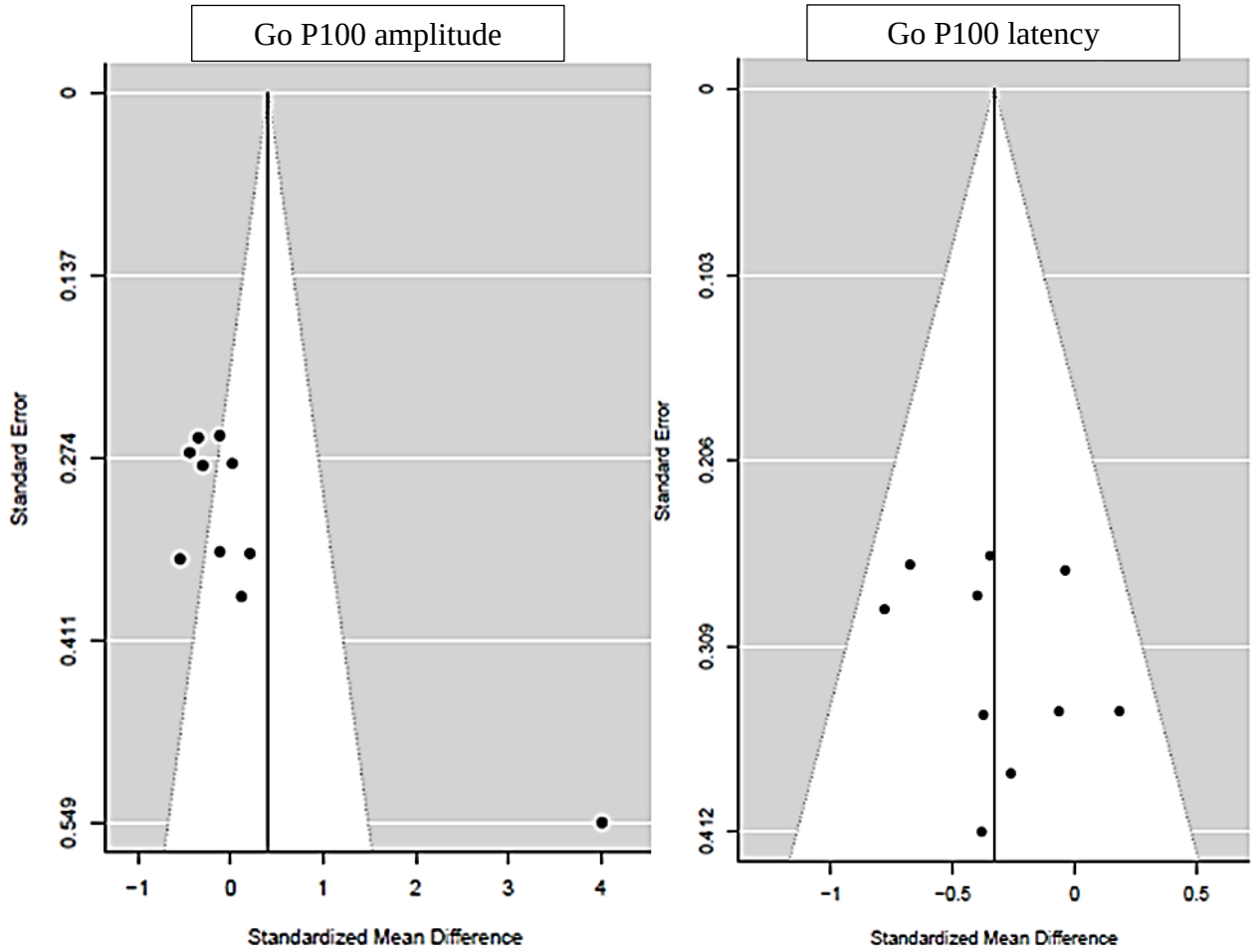

Figure S21. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to Go P100 data.

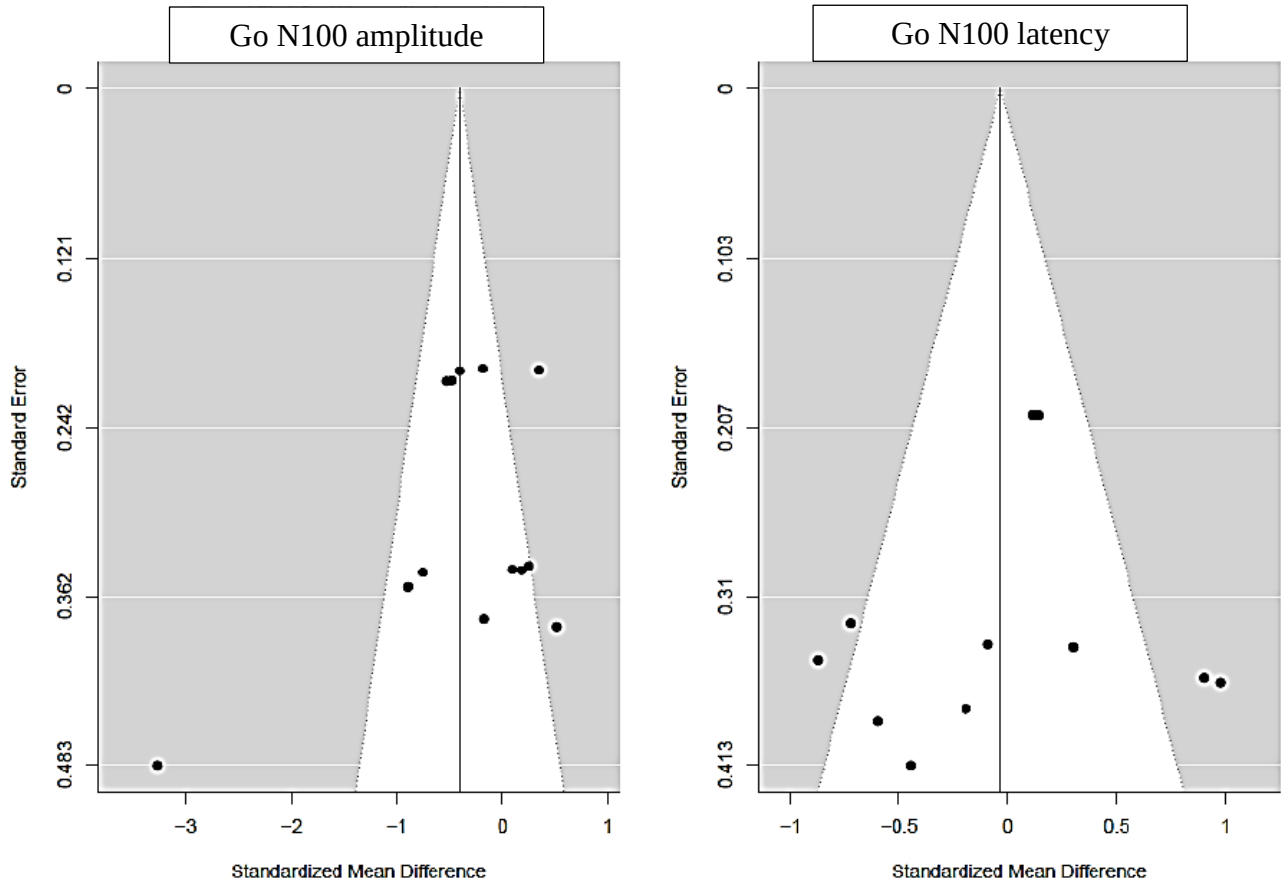

Figure S22. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to Go N100 data.

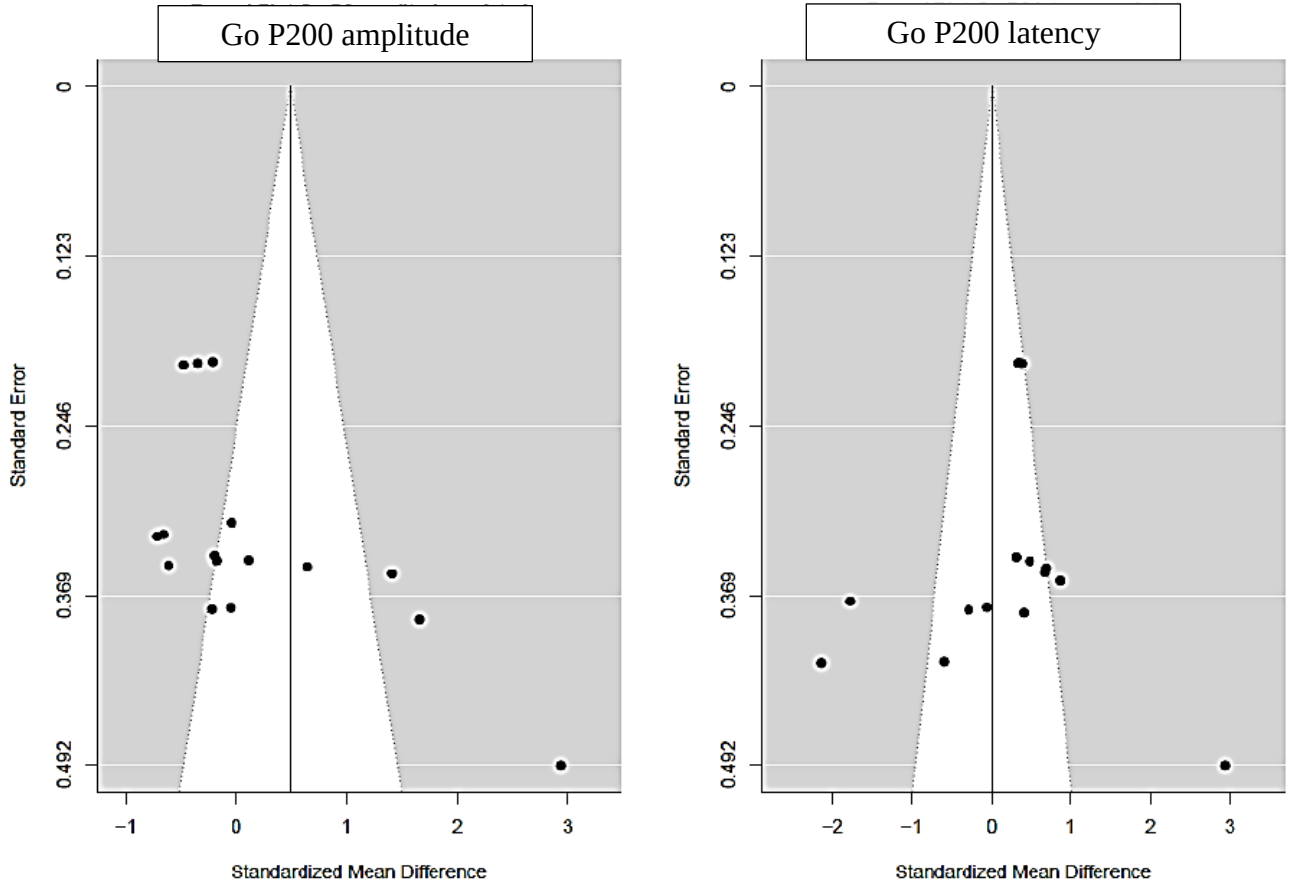

Figure S23. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to Go P200 data.

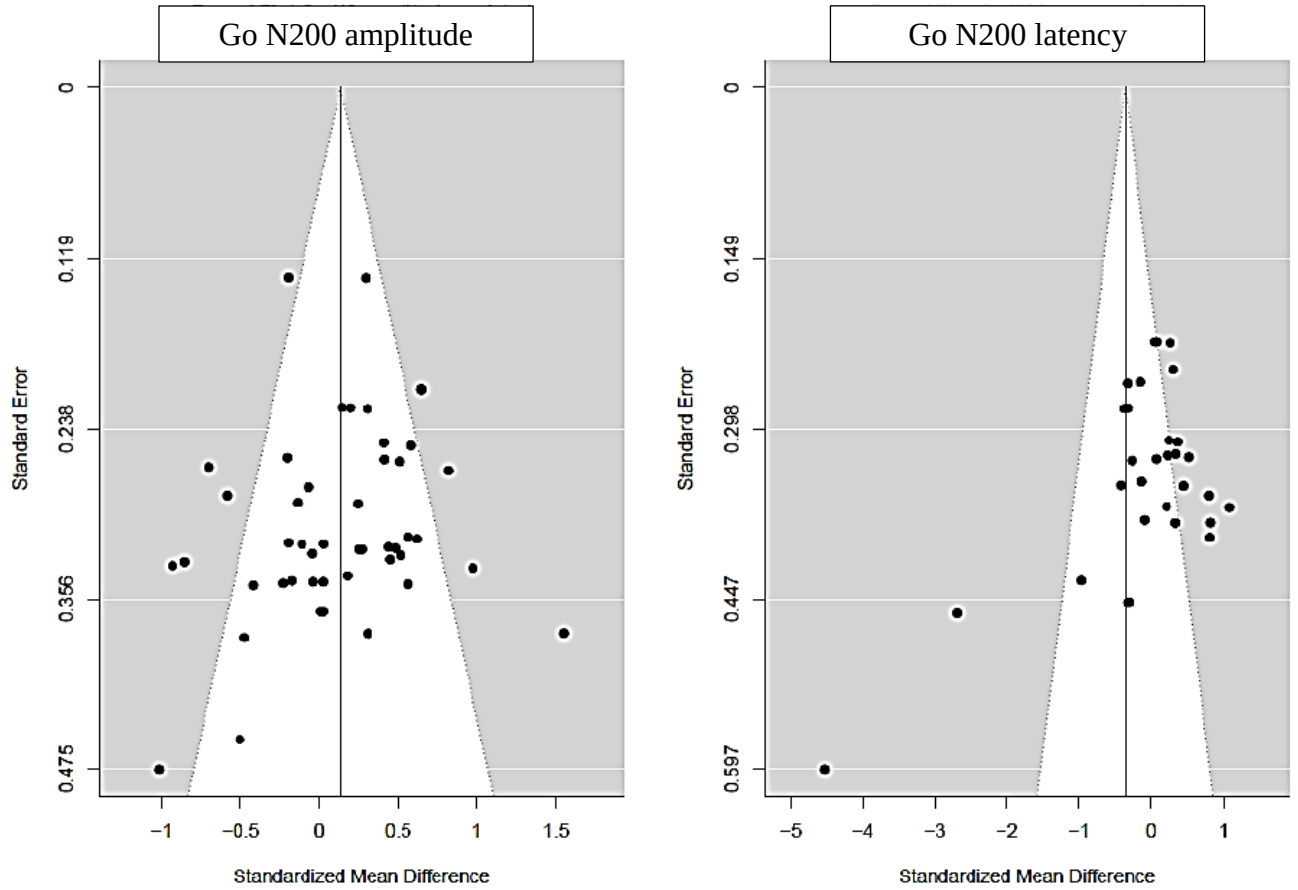

Figure S24. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to Go N200 data.

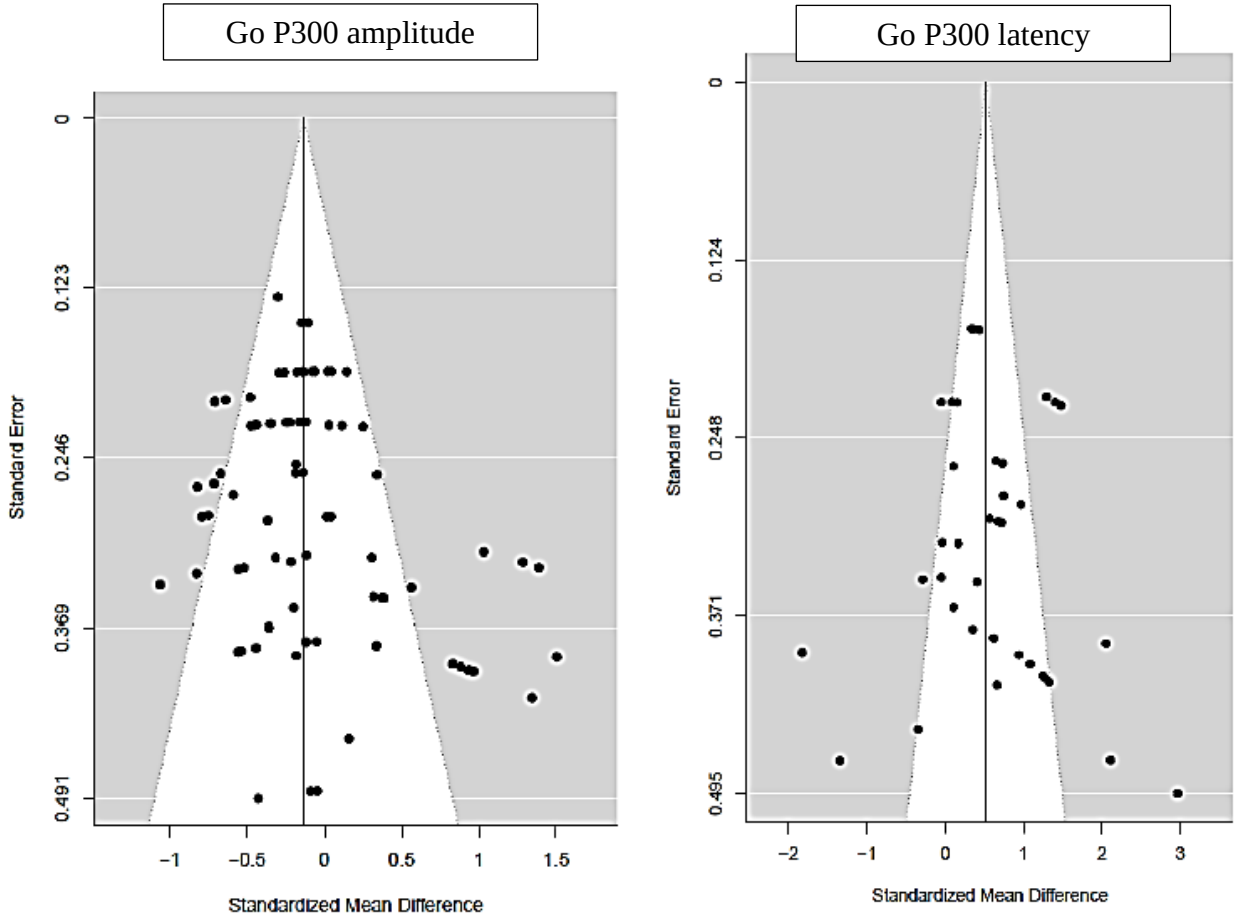

Figure S25. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to Go P300 data.

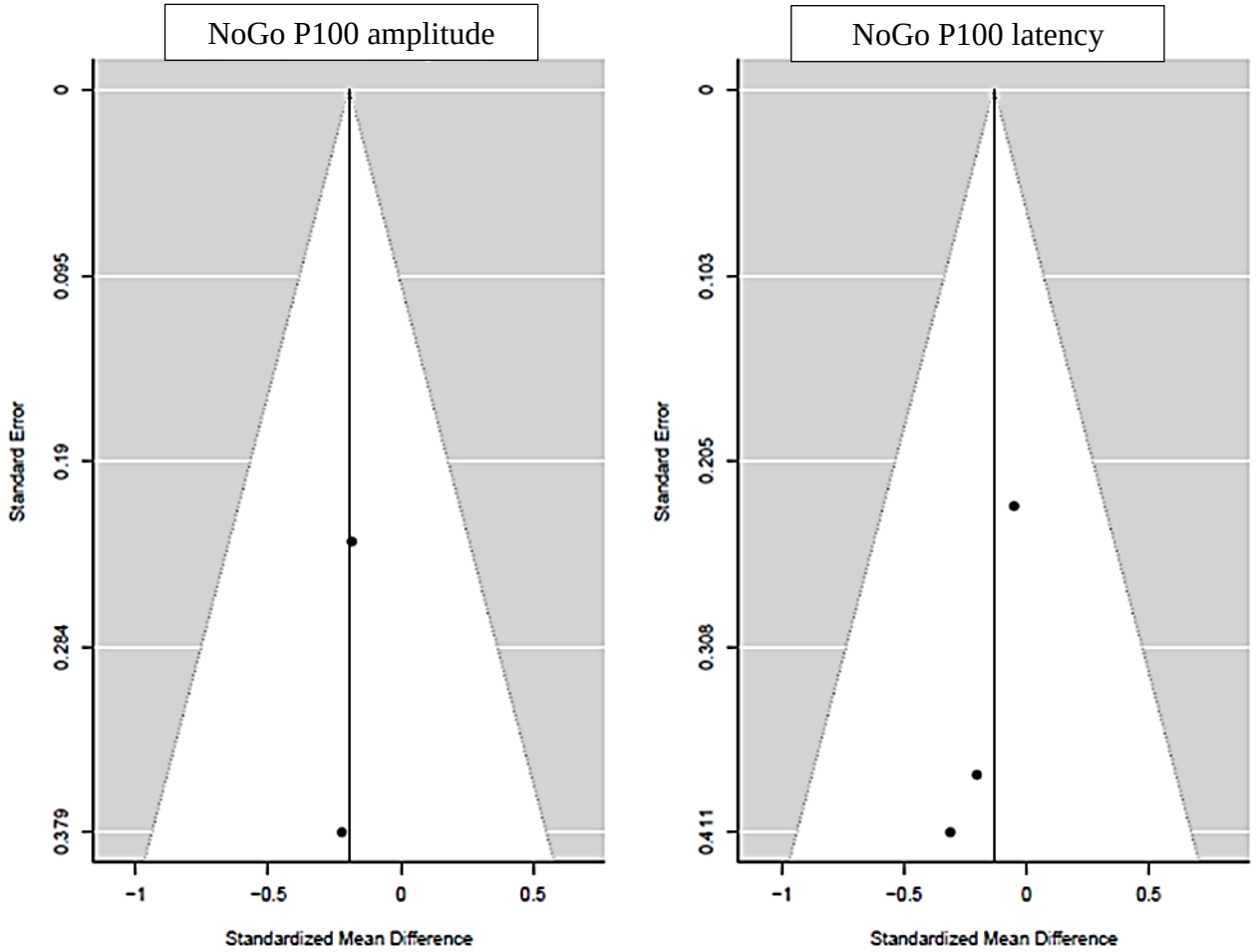

Figure S26. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to NoGo P100 data.

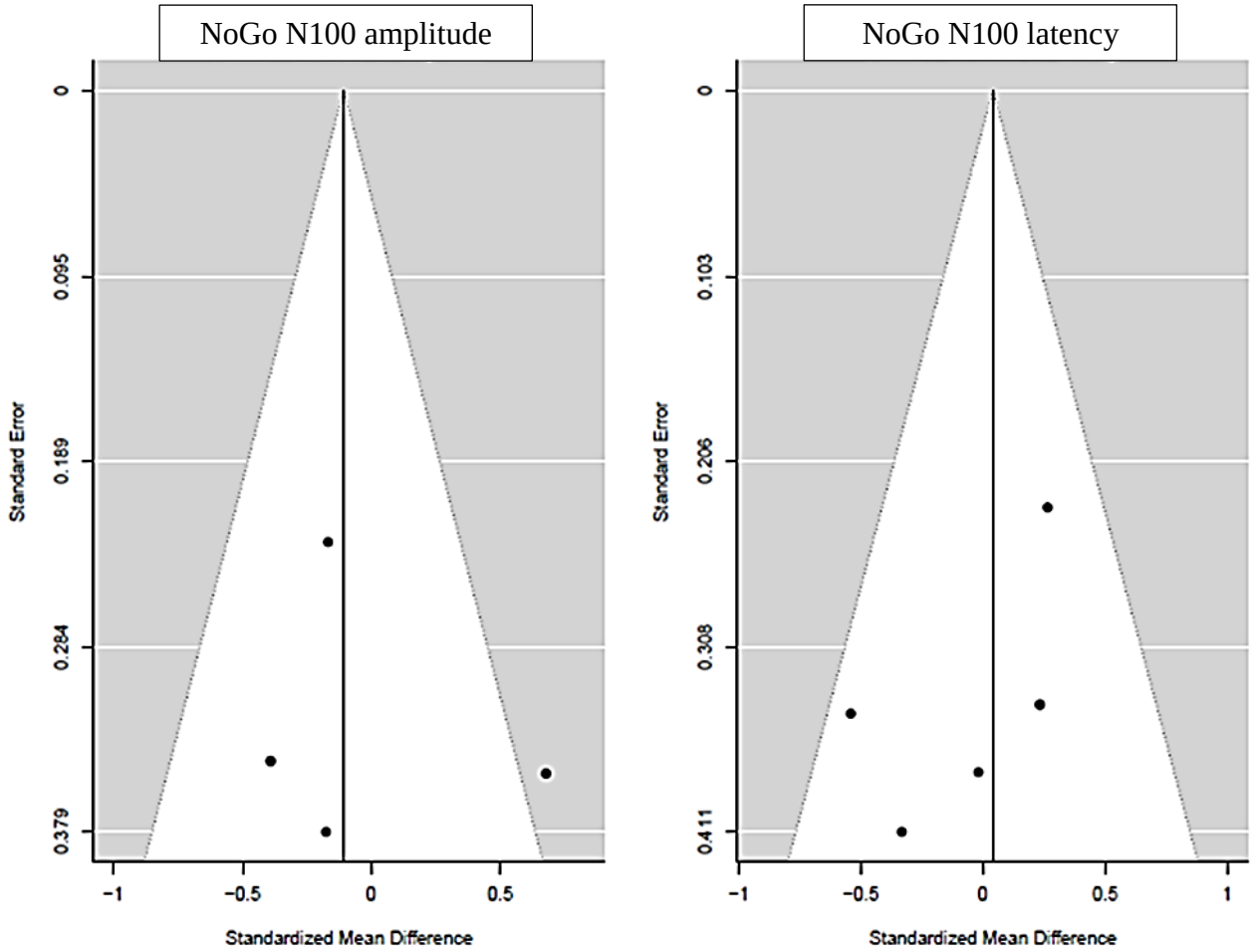

Figure S27. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to NoGo N100 data.

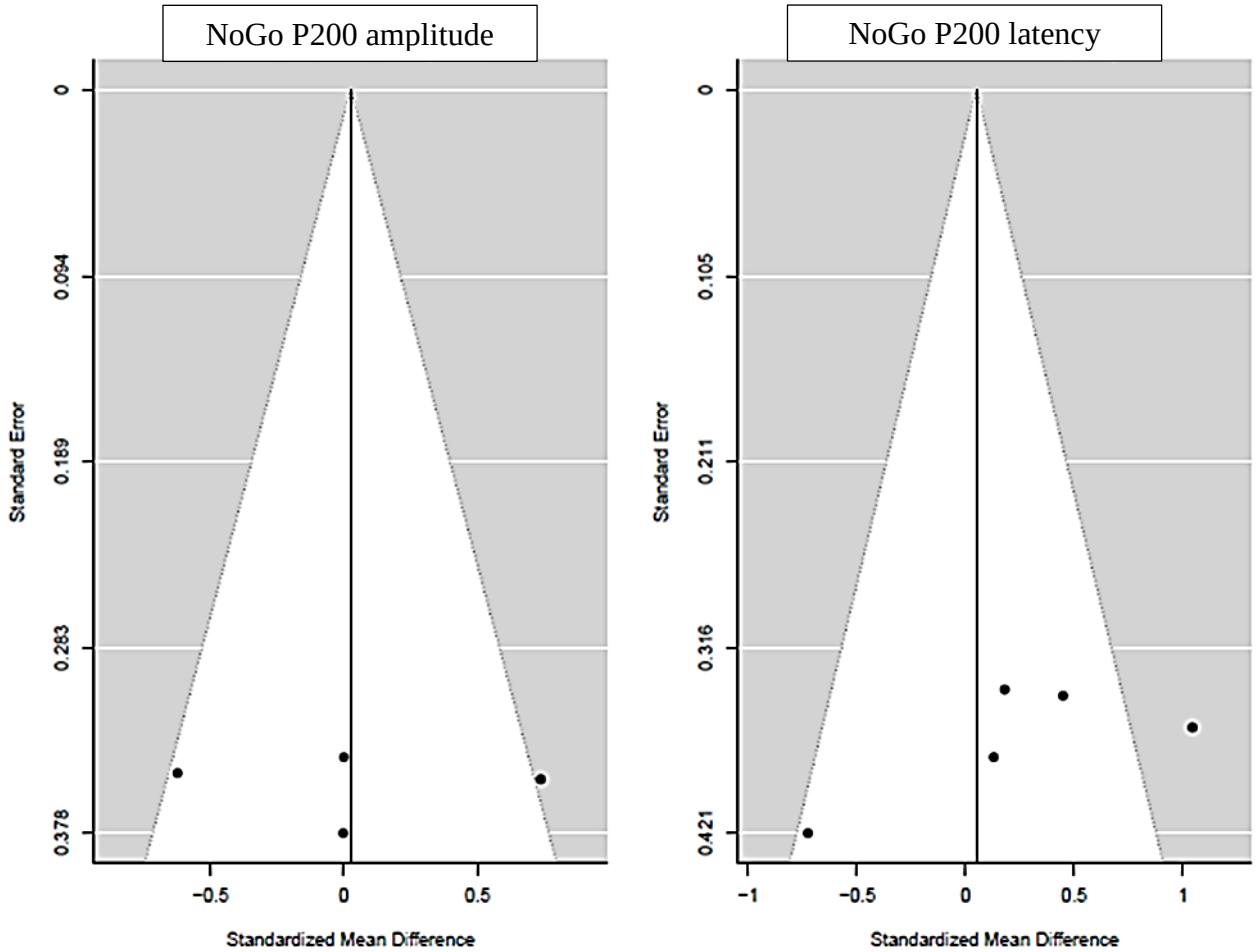

Figure S28. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to NoGo P200 data.

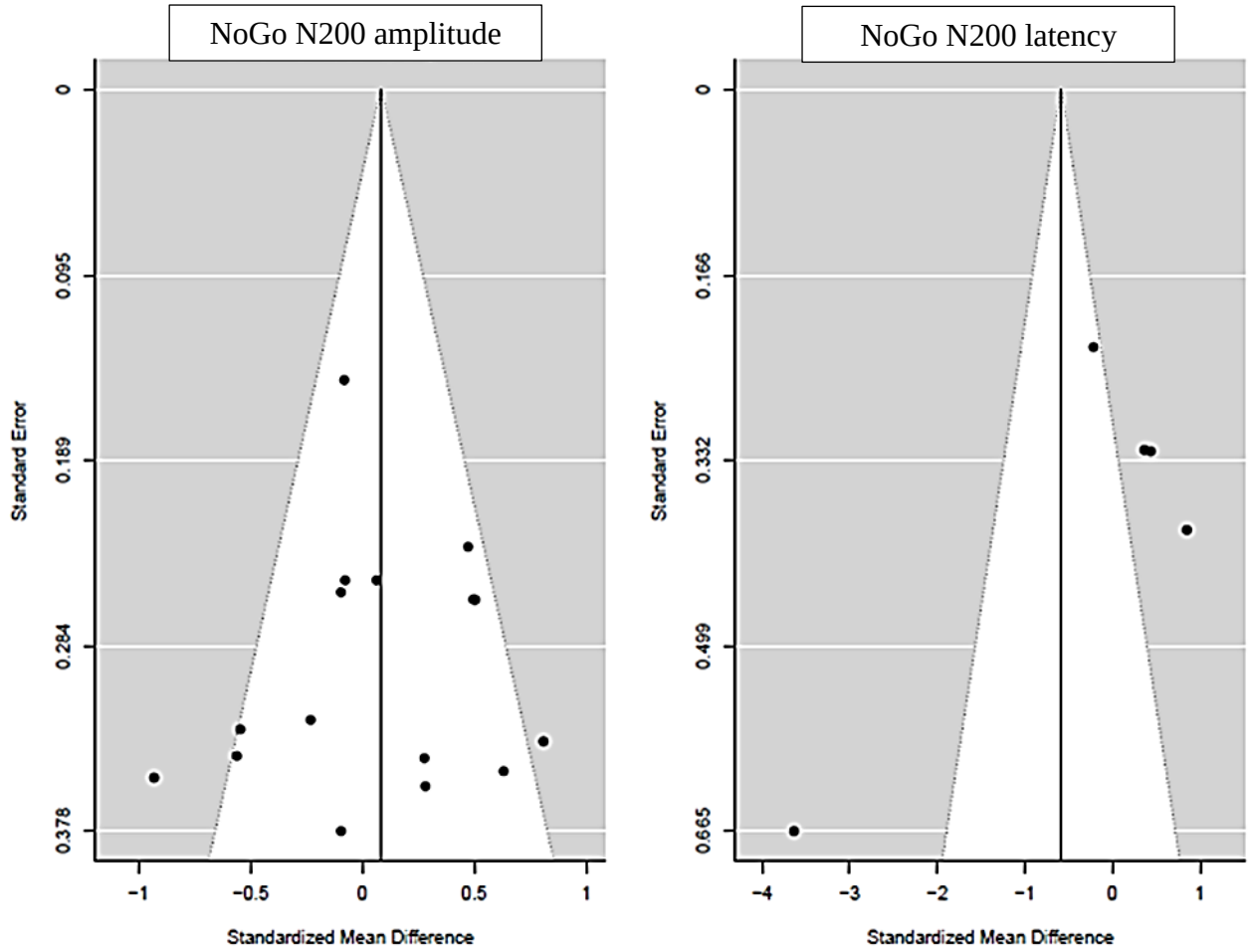

Figure S29. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to NoGo N200 data.

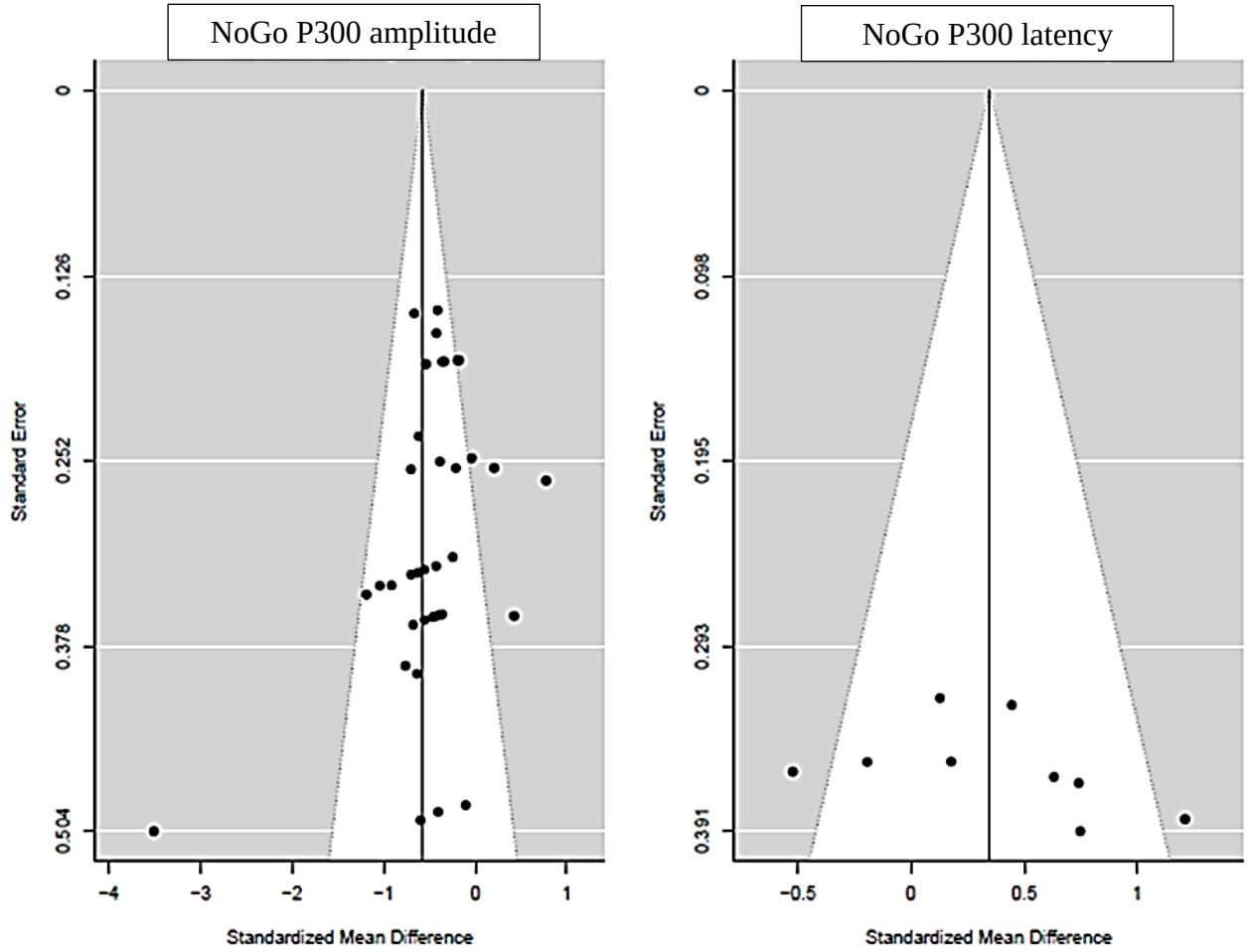

Figure S30. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to NoGo P300 data.

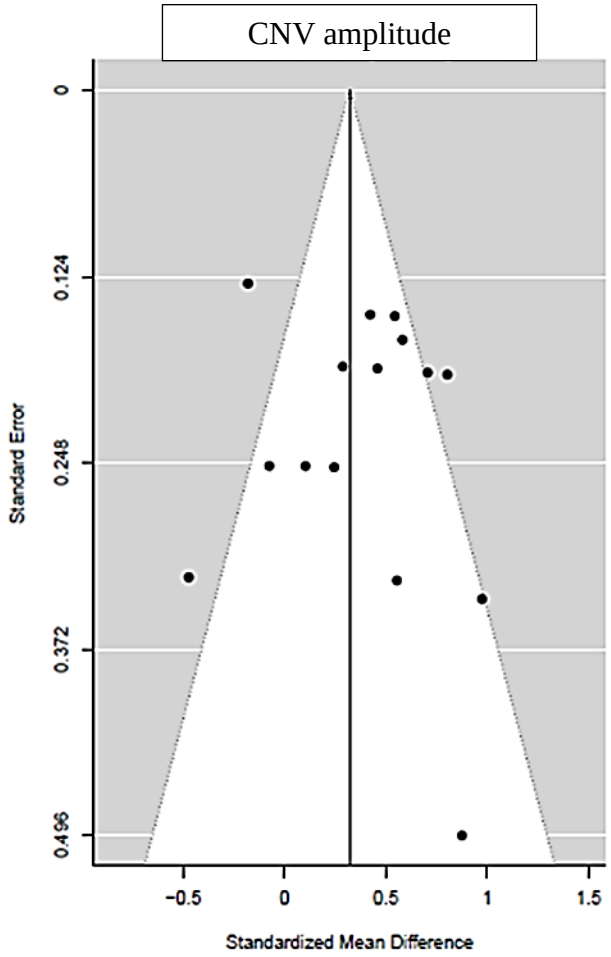

Figure S31. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to CNV data.

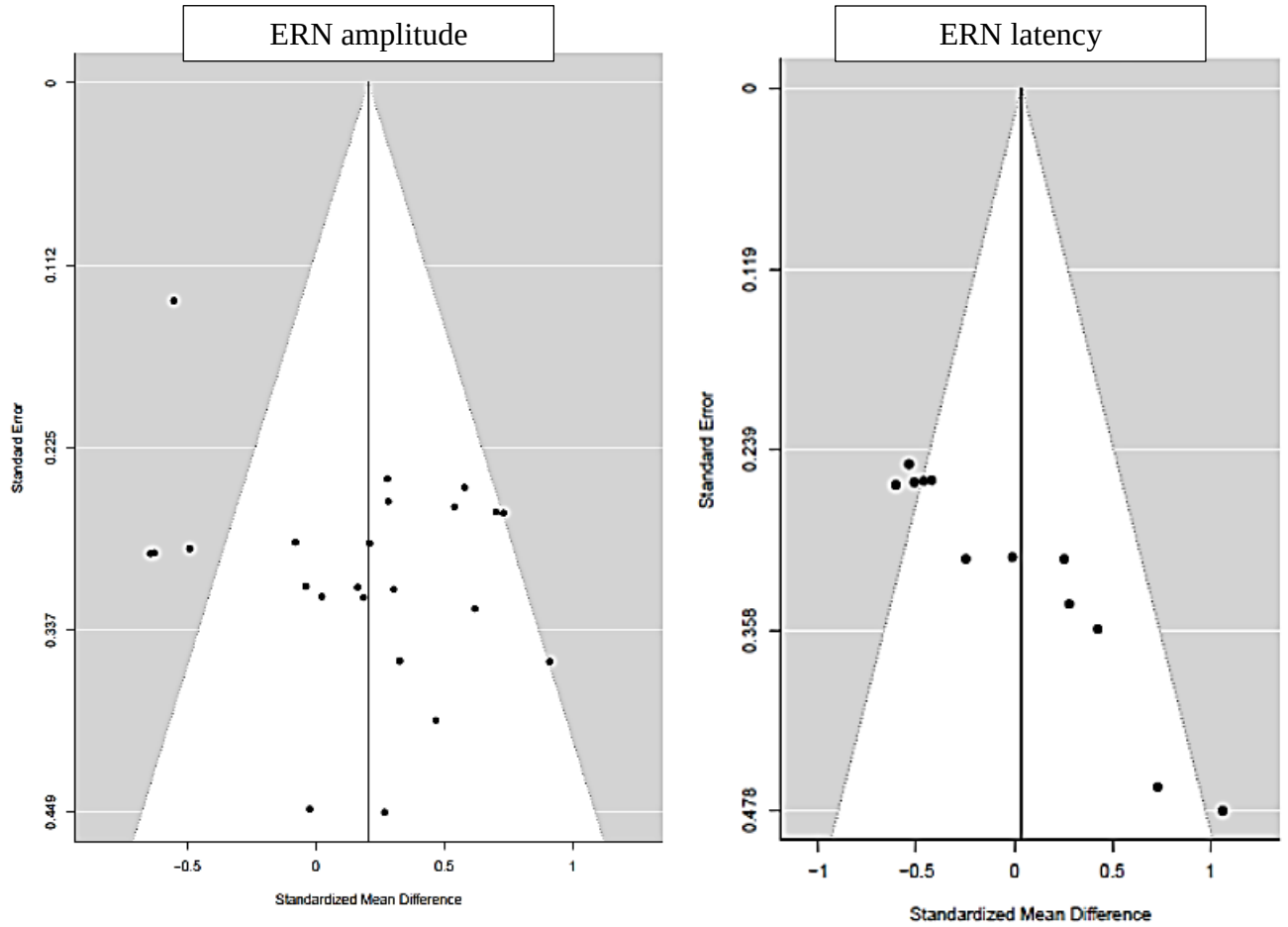

Figure S32. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to ERN data.

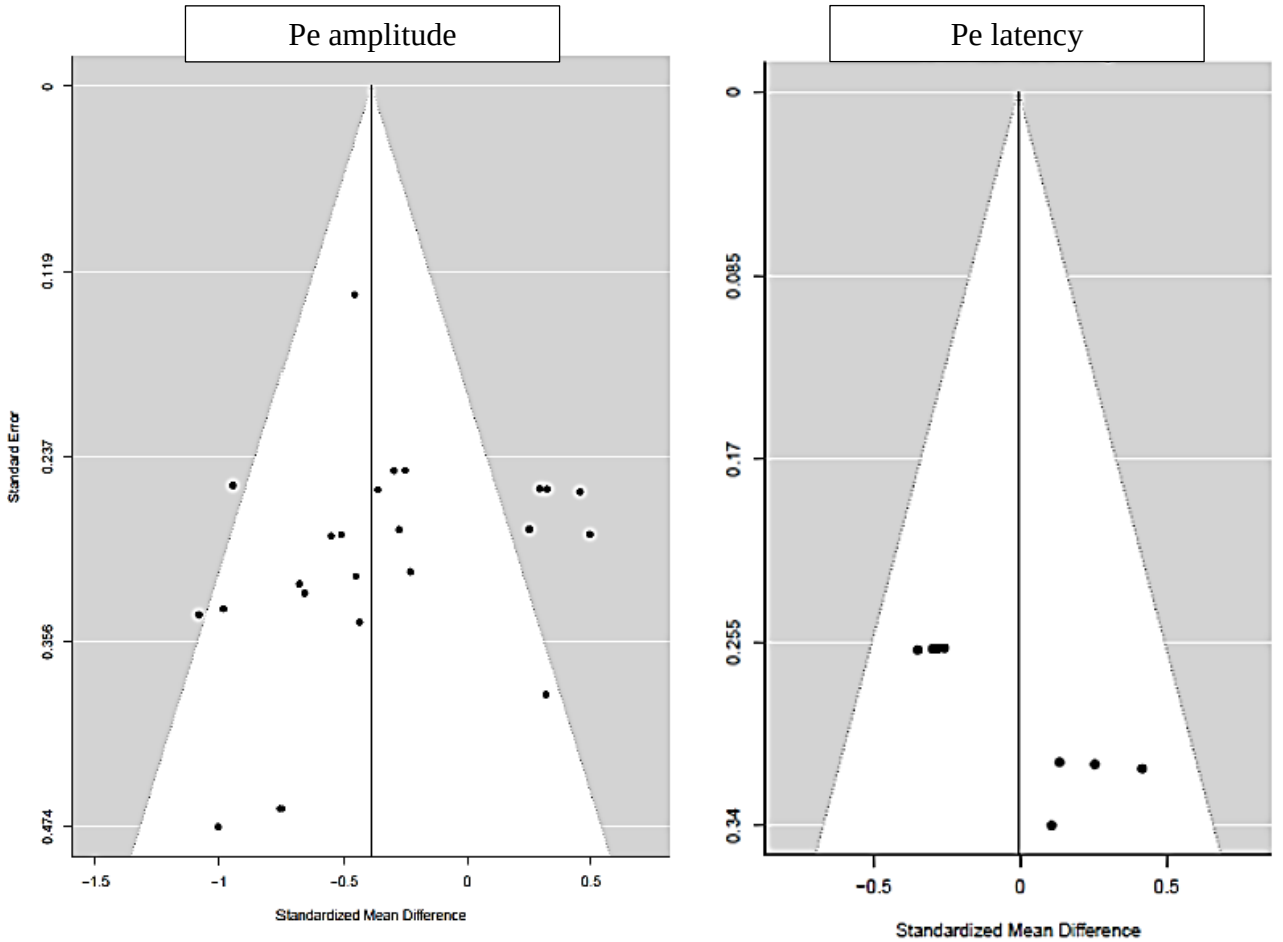

Figure S33. Funnel plot displaying meta-analytical results obtained from fitting multilevel models to Pe data.

6.2 SUPPLEMENT STUDY 2: EEG Data Quality: Determinants and Impact in a Multicenter Study of Children, Adolescents, and Adults with Attention-Deficit/Hyperactivity Disorder (ADHD)

Supplemental material related to this article can be found in the online version of the article itself at doi: https://doi.org/10.3390/brainsci11020214

Appendix A

Appendix A.1. Assessment of Demographic Information, and Clinical Characterization

Depending on age group and subtrial, the following assessment methods were implemented: for ESCAschool (6;0–11;11 years of age): the clinical interview "Diagnose-Checkliste für Aufmerksamkeitsdefizit−/Hyperaktivitätsstörungen" (DCL-ADHS; Döpfner & Görtz-Dorten, 2017), the "Clinical Global Impression Scale–Severity" (CGI-S; National Institute of Mental Health, 1976), FBB-ADHS-Parent/-Teacher, FBB-SSV-Parent/-Teacher, SDQ-Parent; for ESCAadol (12;0–17;11 years of age): DCL-ADHS-clinical interview, CGI-S, SBB-ADHS, FBB-ADHS-Parent/-Teacher, SBB-SSV, FBB-SSV-Parent/-Teacher, SDQ-Parent; and for ESCAlate (16;0–44;11 years of age): ADHD-DCQ, IDA interview.

Appendix A.2. EEG Data Acquisition – The Continous Performance (CPT) Task

The cued Continuous Performance Task (CPT-OX/Flanker CPT-OX) was used to probe attention, preparation, and inhibitory activity at pre- (T2) and post-assessment (T3). In ESCAschool, the simple version of the cued CPT was used. For participants in the ESCAadol, and ESCAlate trials, the Flanker-version of the cued CPT was implemented. The task consists of 400 black letters or letter arrays (for the Flanker-version), made up of a central black letter (and for the Flanker version: Plus additional incompatible flankers on each side to increase difficulty). The presented letters or arrays include the cue letter 'O', the target letter 'X' as well as further distractors ('H', 'B', 'C', 'D', 'E', 'F', 'G', 'J', and 'L'). For the Flanker version of the task in the ESCAadol, and ESCAlate trials, the cue and target letters ('O' and 'X', respectively) were flanked by distractor letters ('XOX' and 'OXO', respectively).

Letters were presented every 1.650 ms for 150 ms in a pseudo-randomized order. Participants were instructed to respond as quickly as possible to cue-target sequences ('O'–'X'). 80 cues were followed by the target in 40 trials (Go condition), and by neutral distractors in the other 40 trials (NoGo condition). One minute of practice trials was implemented before the main task and repeated, if required, to ensure participant understanding of the task. Participants were instructed to respond to Cue-Go trials by pressing a button as quickly as possible with the index finger of their preferred hand. Task duration was approximately 11 min.

Appendix B

Data Quality – Effects of Demographic Variables

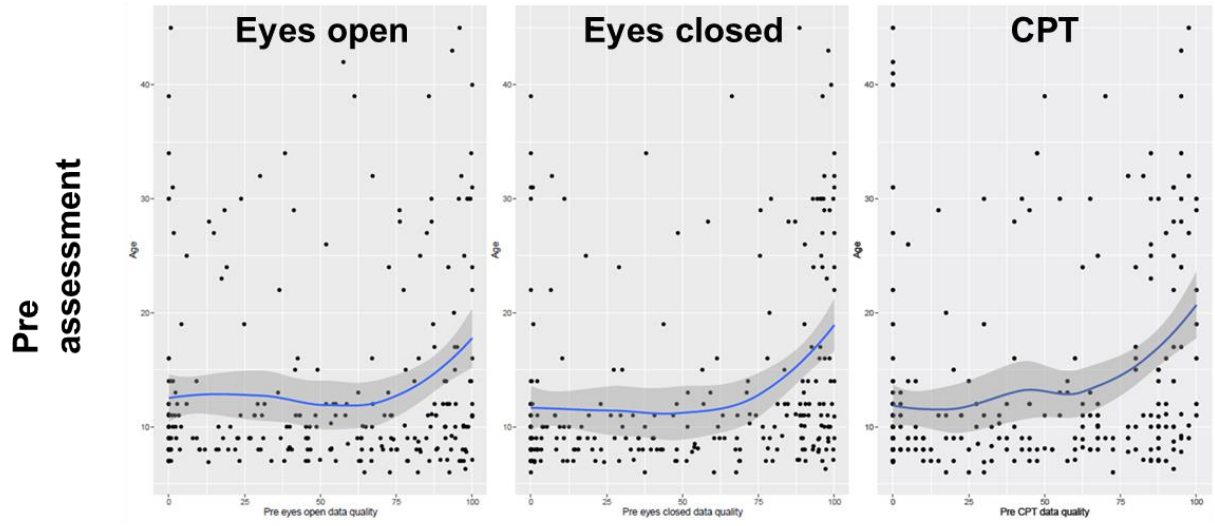

Figure A1. Association between age and data quality for all conditions at pre-assessment, respectively.

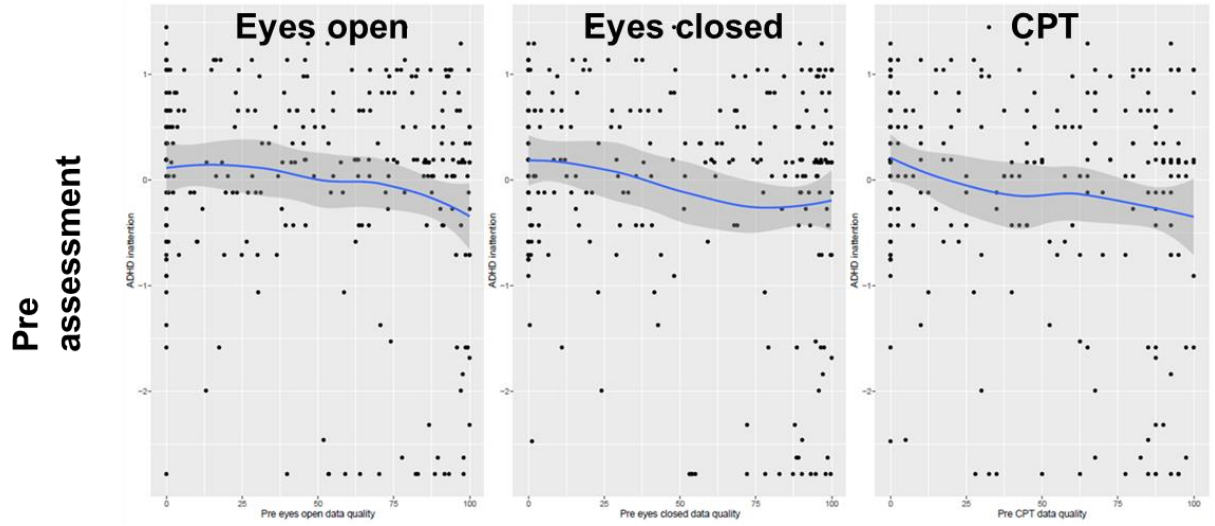

Figure A2. Association between ADHD symptoms of inattention and data quality for all conditions at pre-assessment, respectively.

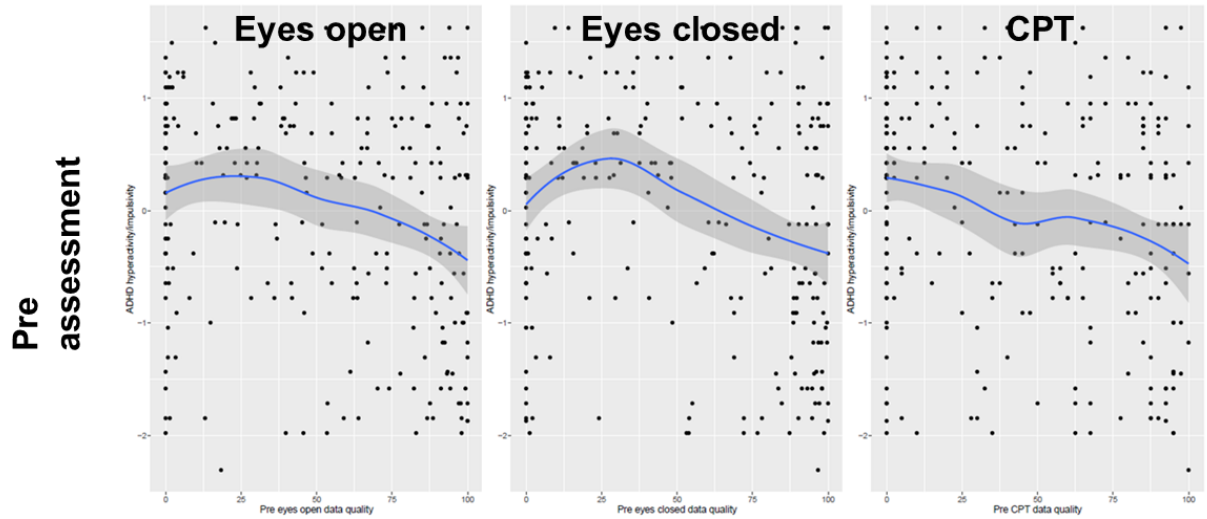

Figure A3. Association between ADHD symptoms of hyperactivity/impulsivity and data quality for all conditions at pre-assessment, respectively.

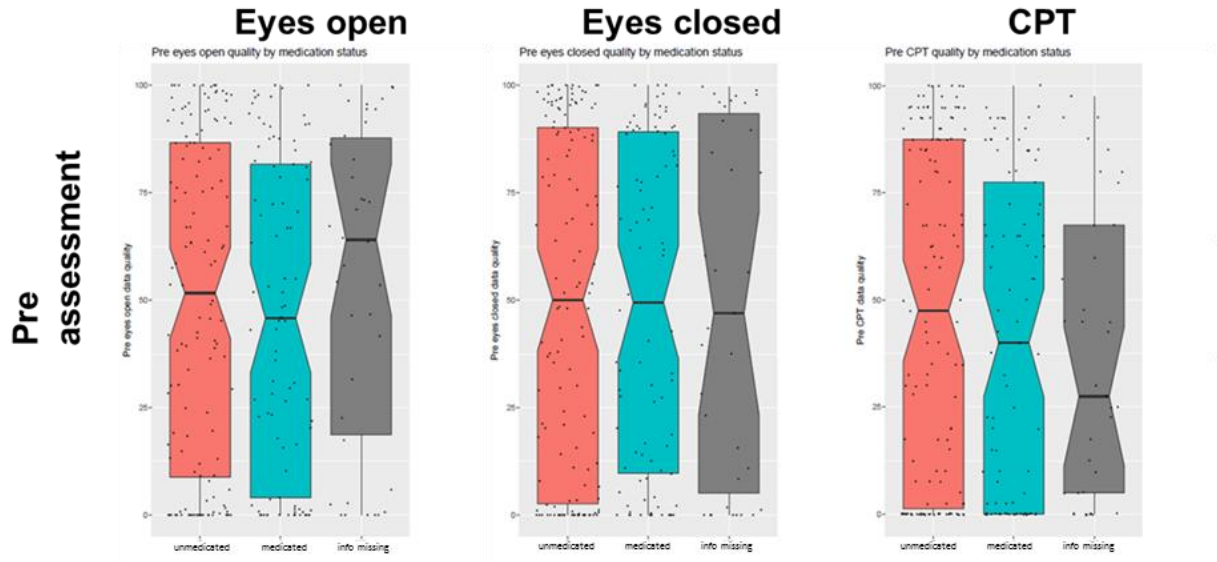

Figure A4. Differences in data quality for medication status at pre-assessment, respectively.

Appendix C

Appendix C.1. Data Quality – Effects of Methodological Variables

Appendix C.1.1. Effects of Pre-Processing/Ocular Correction Method

Table A1. Descriptive statistics: Effects of pre-processing/Ocular correction method (ICA versus Gratton and Coles)—non-ADHD controls only.

	Ocular Correction Method	N	Data Quality, M (%)	Data Quality, SD (%)
Eyes open	Gratton and Coles	24	75.85%	25.42%
	ICA	24	73.37%	27.32%
Eyes closed	Gratton and Coles	25	76.52%	25.54%
	ICA	25	75.80%	26.49%

Appendix C.1.2. Effects of Measurement Duration

Table A2. Descriptive statistics: Effects of measurement duration (segment 1 versus segment 2).

	Segment	N	Data Quality, M (Absolute Number)	Data Quality, SD (Absolute Number)
Eyes open	**Segment 1**	251	75.55	54.19
	Segment 2	222	80.43	55.75
Eyes closed	**Segment 1**	247	76.49	56.13
	Segment 2	216	79.85	58.26

Appendix C.1.3. Effects of Site

General linear models were used to explore effects of site on data quality for eyes open, eyes closed, and the CPT task-condition, respectively. Significant effects were identified for all conditions: Eyes open, $F(15, 251) = 3.2219$, $p < 0.0001$, eyes closed, $F(15, 247) = 4.2029$, $p < 0.0001$, and the CPT, $F(13, 251) = 4.9926$, $p < 0.0001$. However, as the study sites did not include participants for all age trials, site represents a confounded variable, and was therefore not included in subsequent analyses.

Appendix D

Associations between Age and EEG Spectral Power in Resting Conditions (Eyes Open, and Eyes Closed) at Pre-Assessment)

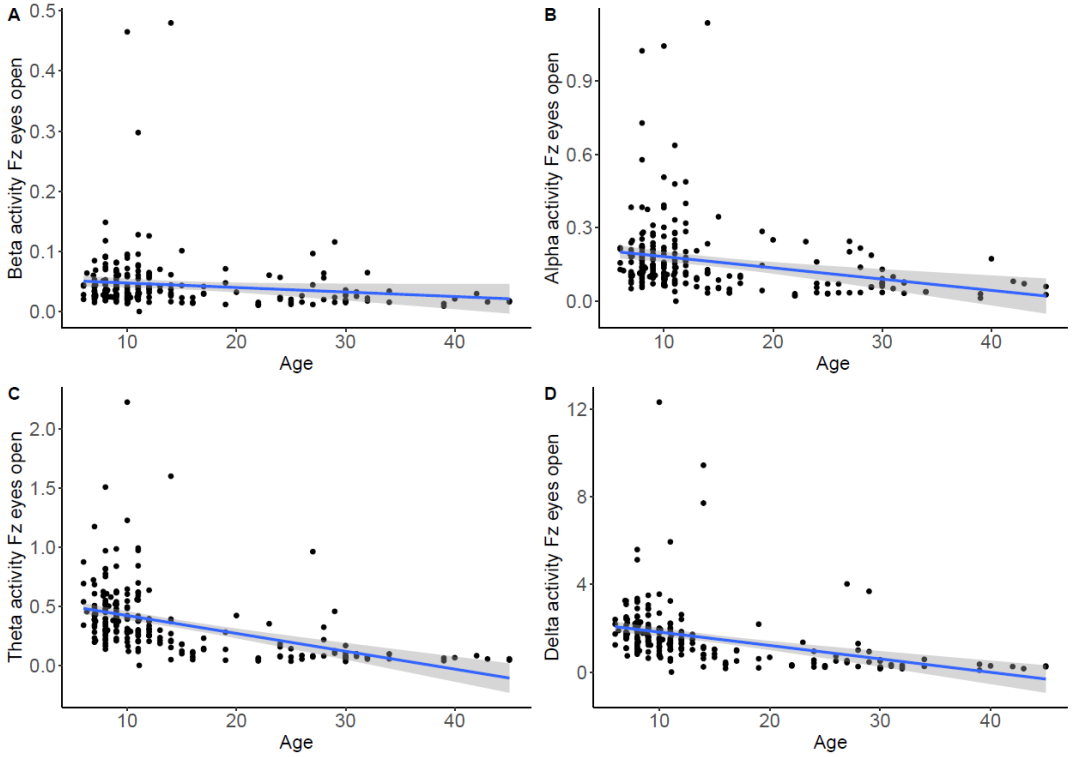

Figure A5. Association between age and spectral power in beta (**A**), alpha (**B**), theta (**C**), and delta (**D**) frequency bands for eyes open data at electrode position Fz.

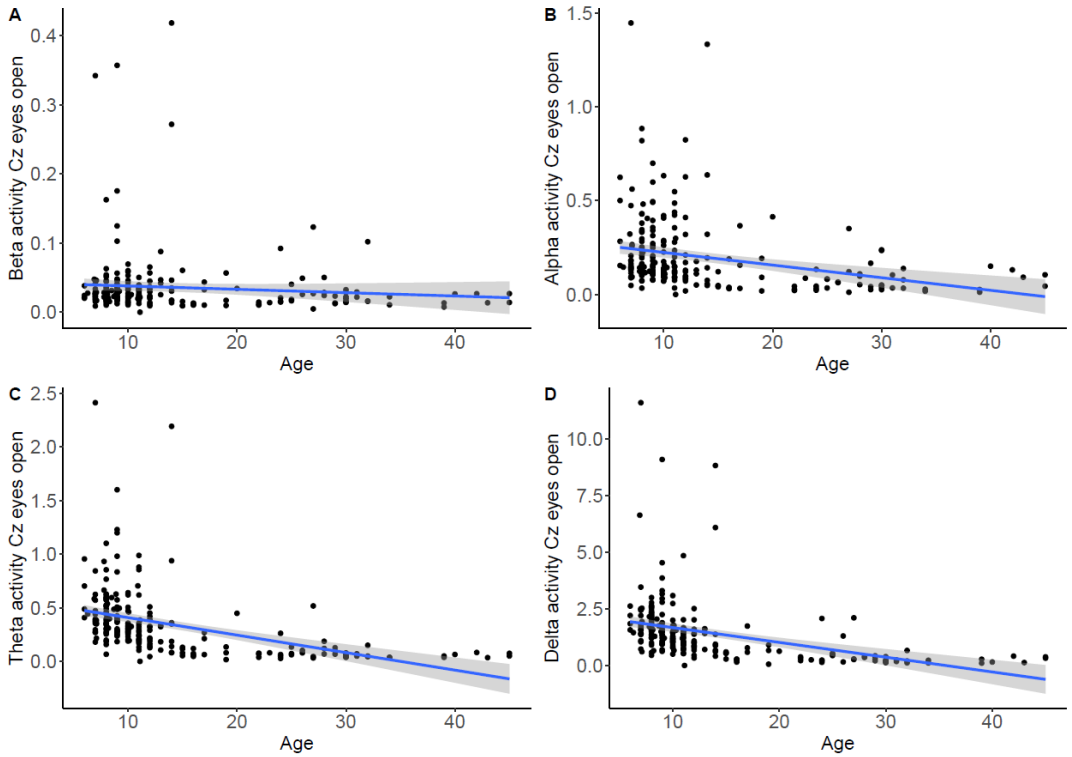

Figure A6. Association between age and spectral power in beta (**A**), alpha (**B**), theta (**C**), and delta (**D**) frequency bands for eyes open data at electrode position Cz.

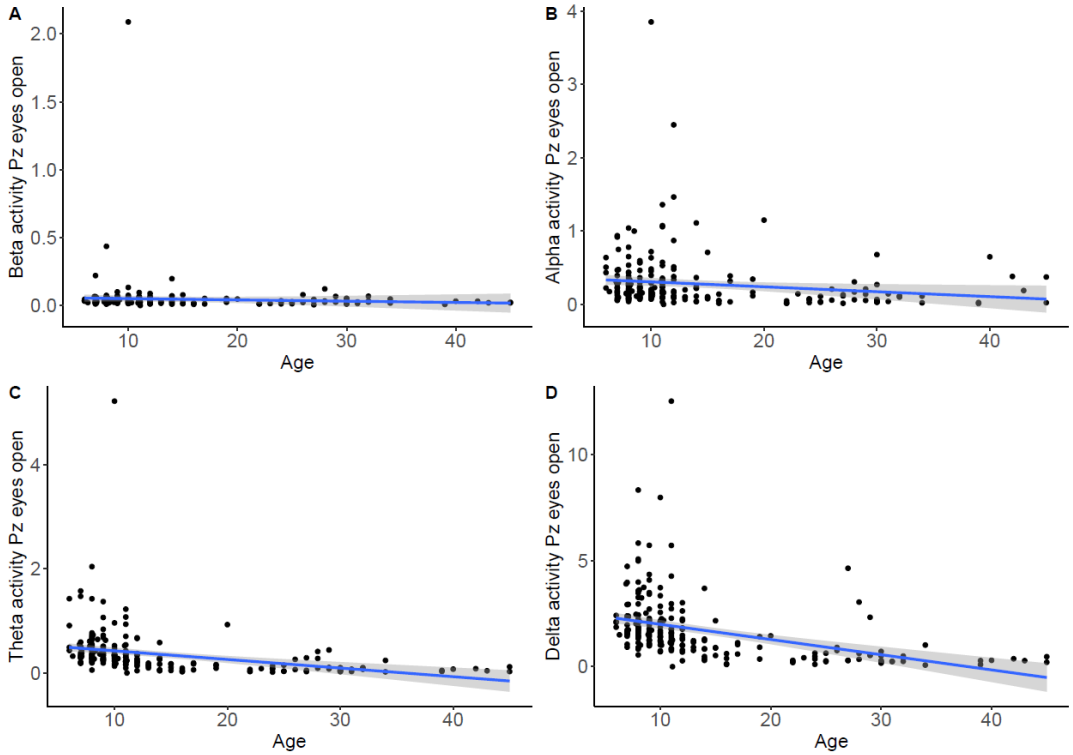

Figure A7. Association between age and spectral power in beta (**A**), alpha (**B**), theta (**C**), and delta (**D**) frequency bands for eyes open data at electrode position Pz.

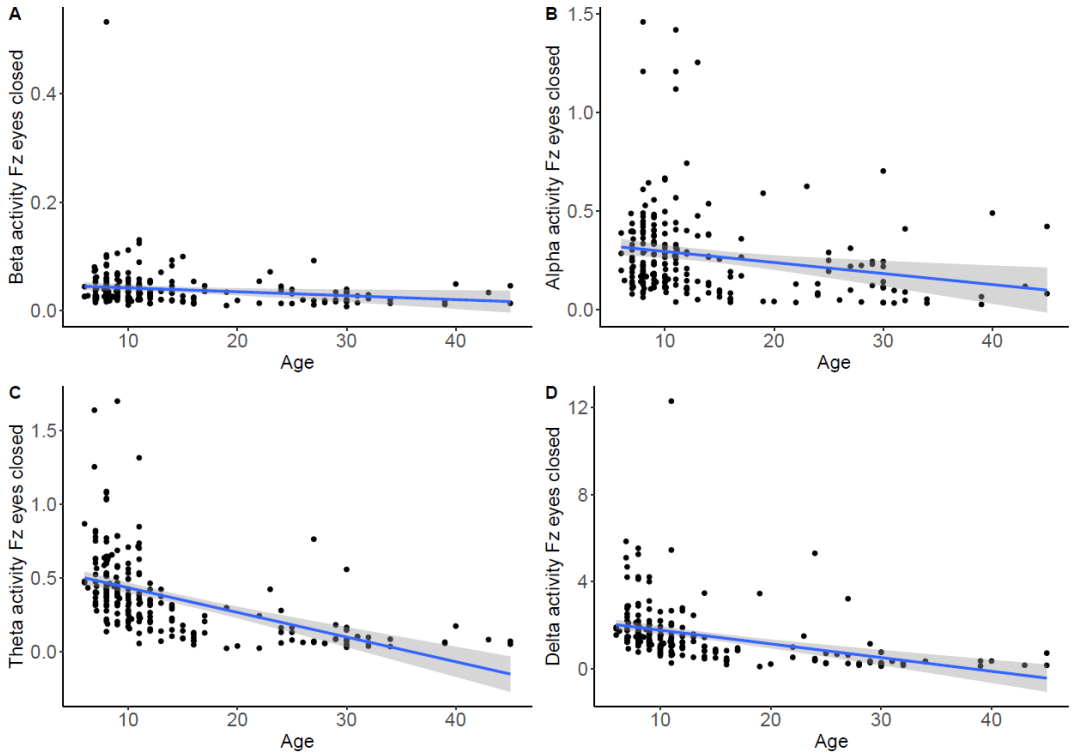

Figure A8. Association between age and spectral power in beta (**A**), alpha (**B**), theta (**C**), and delta (**D**) frequency bands for eyes closed data at electrode position Fz.

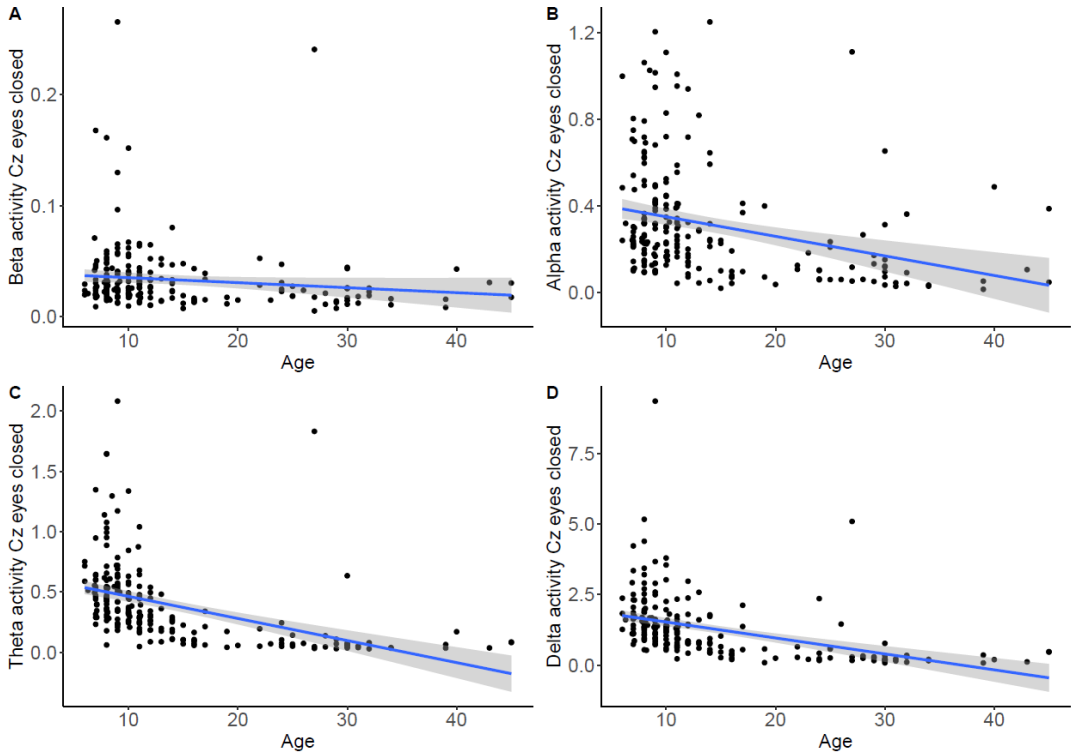

Figure A9. Association between age and spectral power in beta (**A**), alpha (**B**), theta (**C**), and delta (**D**) frequency bands for eyes closed data at electrode position Cz.

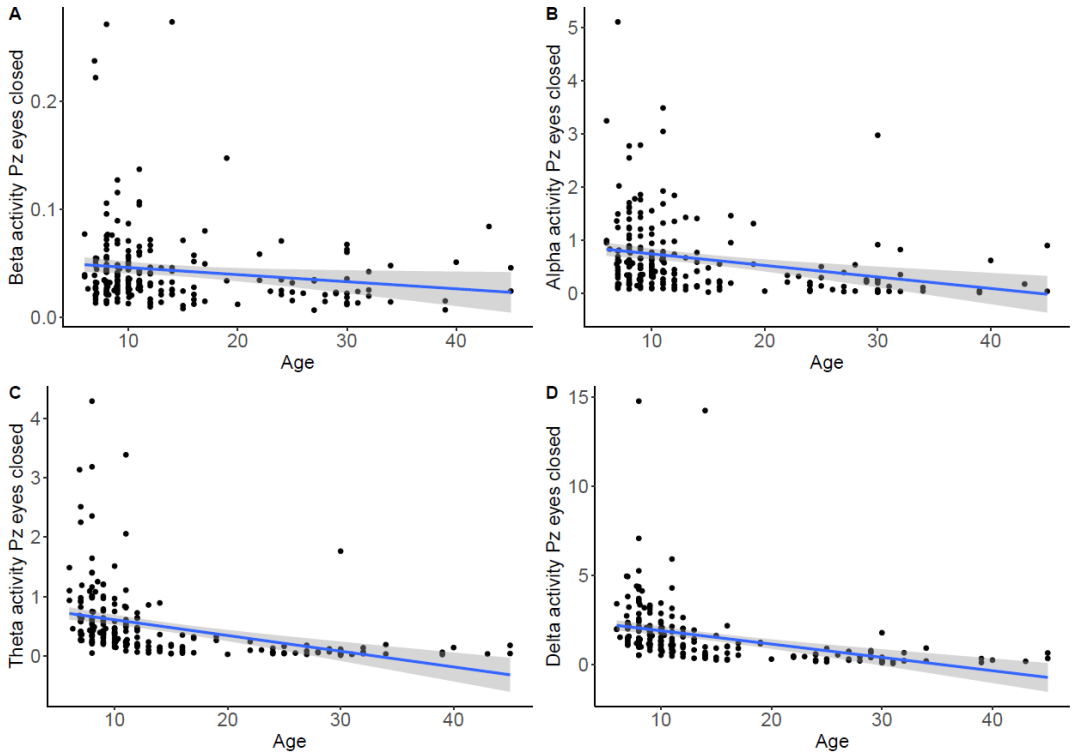

Figure A10. Association between age and spectral power in beta (**A**), alpha (**B**), theta (**C**), and delta (**D**) frequency bands for eyes closed data at electrode position Pz.

Table A3. Correlations between age and FFT frequency band activity at pre assessment—non-ADHD <16 years (n = 25).

	Eyes Open			Eyes Closed		
Electrode location	**Fz**	**Cz**	**Pz**	**Fz**	**Cz**	**Pz**
Beta (μV) × age (years)	−0.609 **	−0.456 *	−0.475 *	−0.492 *	−0.415 *	−0.330
alpha (μV) × age (years)	−0.410 *	−0.335	−0.276	−0.201	−0.189	−0.366
theta (μV) × age (years)	−0.478 *	−0.249	−0.449 *	−0.467 *	−0.111	−0.409 *
delta (μV) × age (years)	−0.566 **	−0.414 *	−0.548 **	−0.543 **	−0.373	−0.508 **

Frequency band widths: Beta (12.5 Hz–30 Hz), alpha (7.5 Hz–12.5 Hz), theta (3.5 Hz–7.5 Hz), and delta (0.5 Hz–3.5 Hz). Pearson product-moment correlations are displayed. ** $p \leq 0.001$, * $p \leq 0.01$.

Table A4. Correlations between age and FFT frequency band activity at pre assessment—ADHD <16 years (n = 150).

	Eyes Open			Eyes Closed		
Electrode location	**Fz**	**Cz**	**Pz**	**Fz**	**Cz**	**Pz**
beta (μV) × age (years)	0.093	0.044	−0.006	−0.075	−0.108	−0.108
alpha (μV) × age (years)	−0.038	−0.122	−0.000	−0.091	−0.163	−0.236 **
theta (μV) × age (years)	−0.260 **	−0.276 **	−0.240 **	−0.491 **	−0.476 **	−0.353 **
delta (μV) × age (years)	−0.126	−0.232 **	−0.243 **	−0.289 **	−0.381 **	−0.202 *

Frequency band widths: beta (12.5 Hz–30 Hz), alpha (7.5 Hz–12.5 Hz), theta (3.5 Hz–7.5 Hz), and delta (0.5 Hz–3.5 Hz). Pearson product-moment correlations are displayed. ** $p \leq 0.001$, * $p \leq 0.01$.

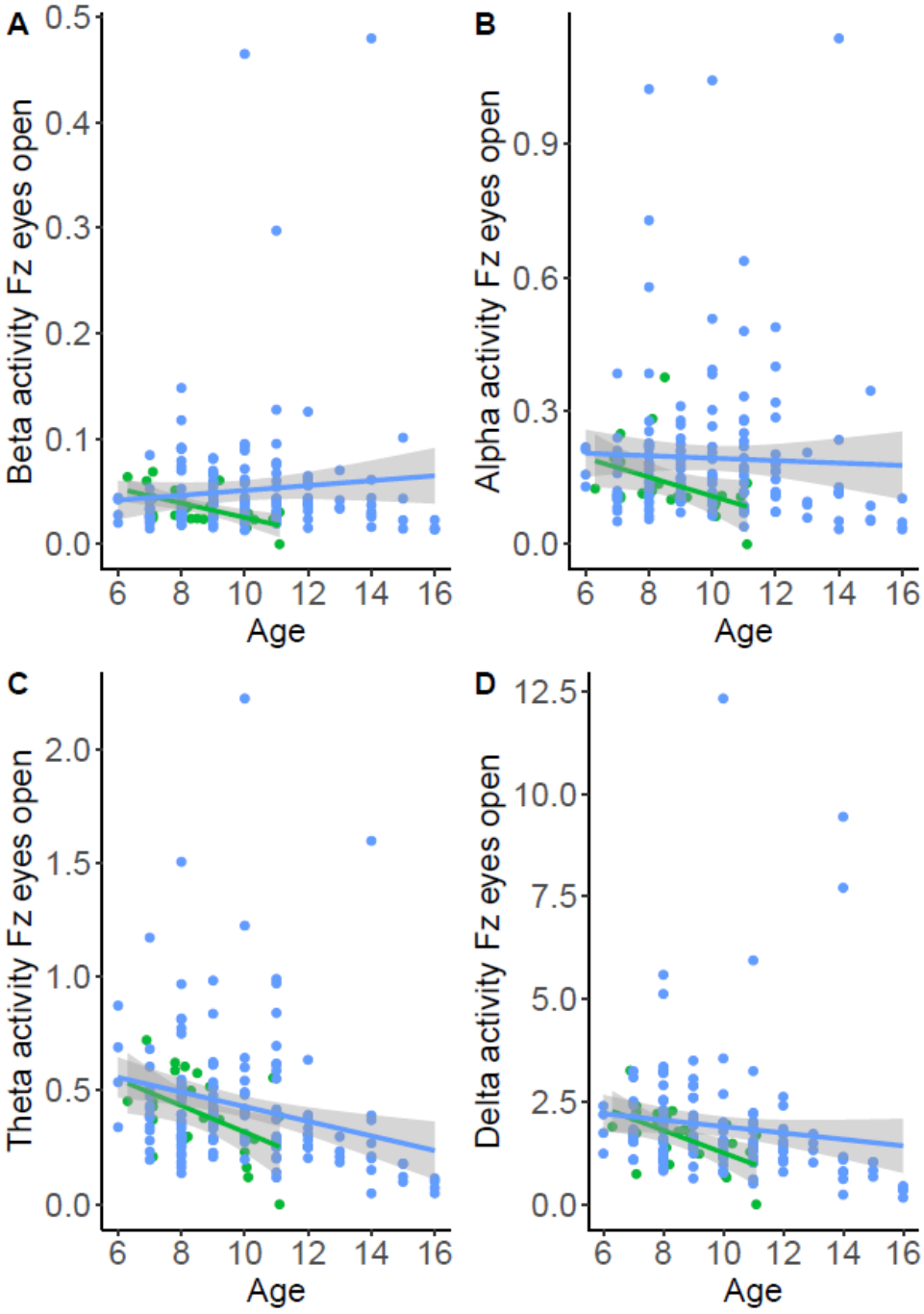

Figure A11. Association between age and spectral power in beta (**A**), alpha (**B**), theta (**C**), and delta (**D**) frequency bands for eyes open data at electrode position Fz for ADHD (blue) and non-ADHD (green) children and adolescents <16 years of age.

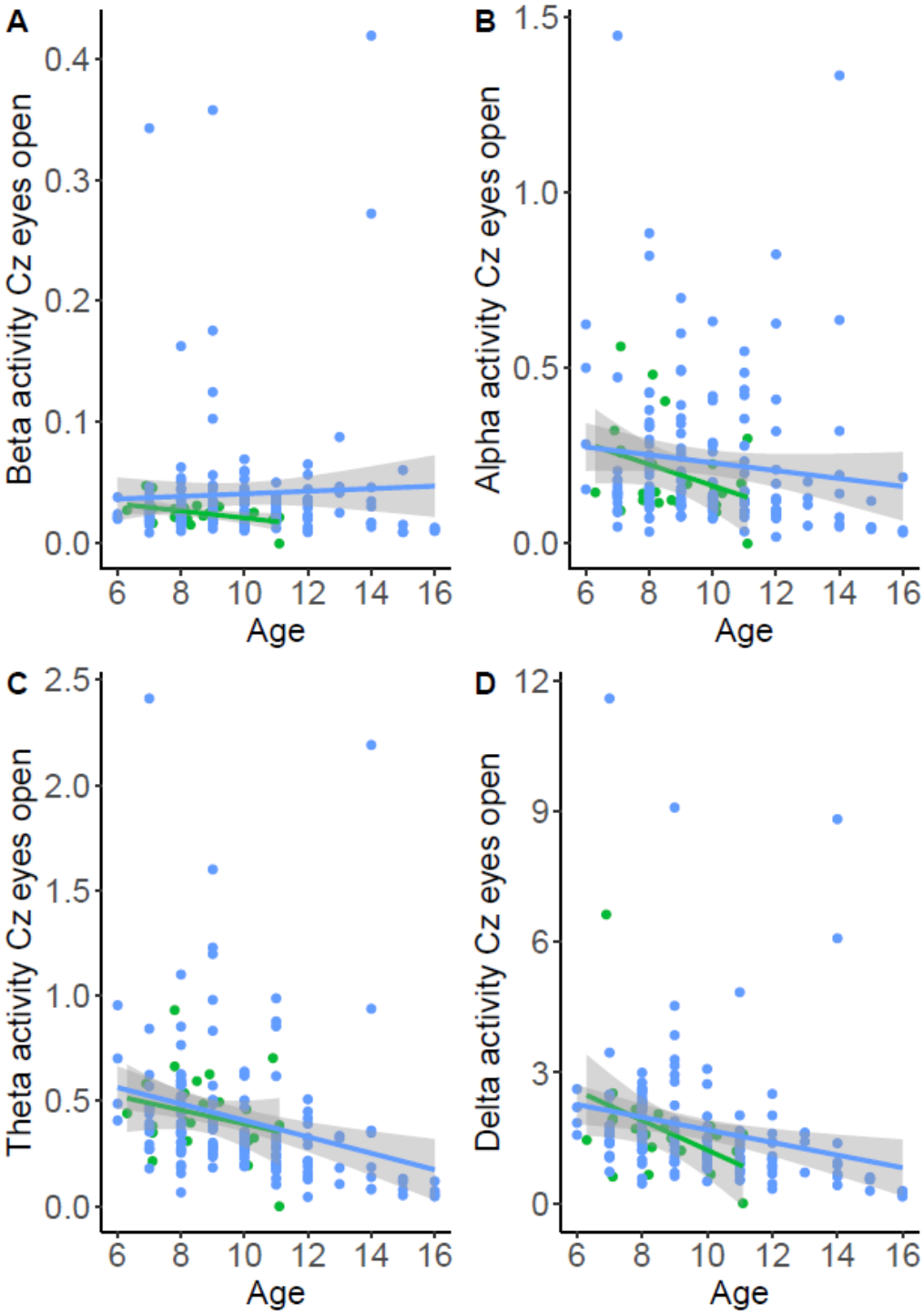

Figure A12. Association between age and spectral power in beta (**A**), alpha (**B**), theta (**C**), and delta (**D**) frequency bands for eyes open data at electrode position Cz for ADHD (blue) and non-ADHD (green) children and adolescents <16 years of age.

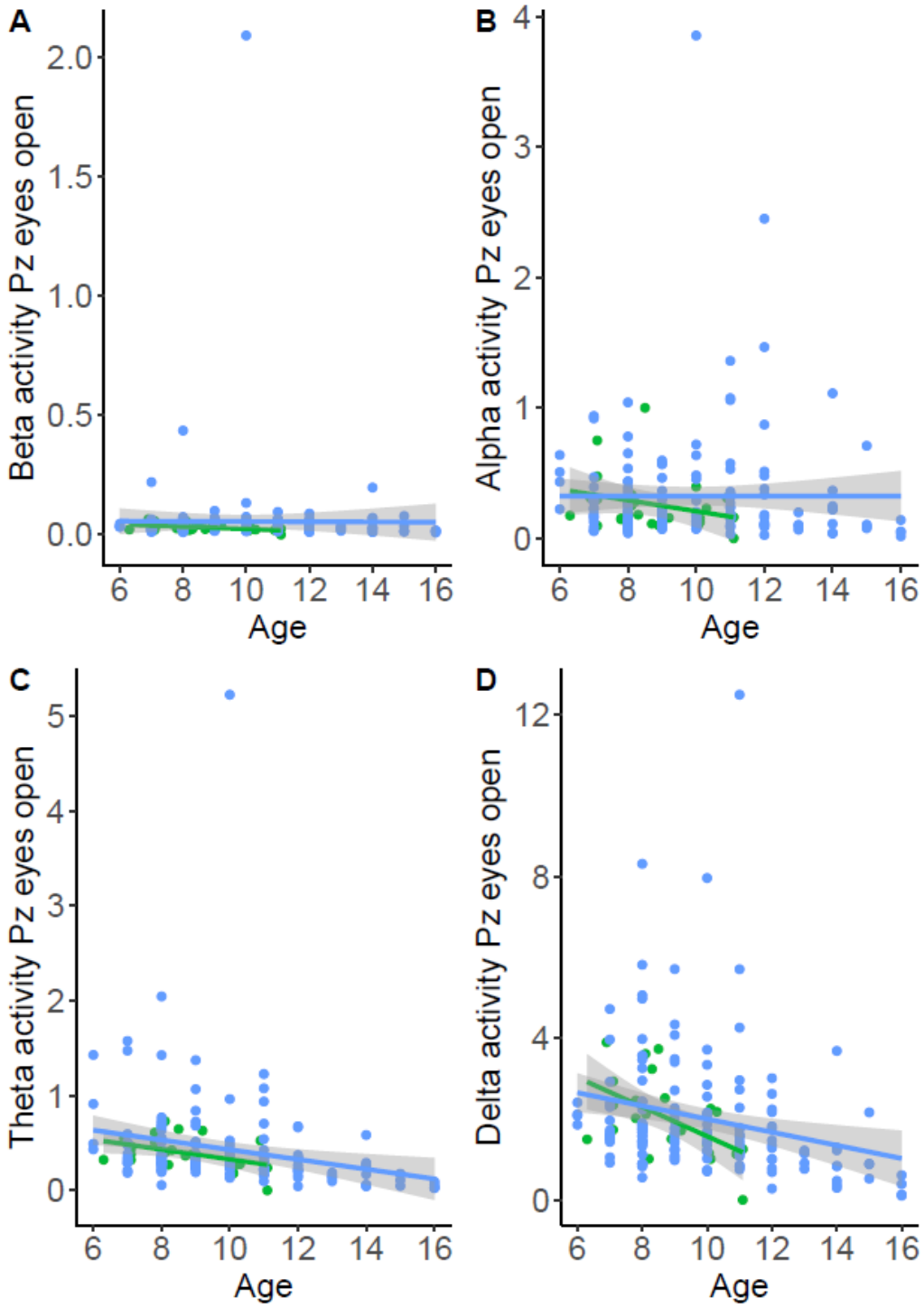

Figure A13. Association between age and spectral power in beta (**A**), alpha (**B**), theta (**C**), and delta (**D**) frequency bands for eyes open data at electrode position Pz for ADHD (blue) and non-ADHD (green) children and adolescents <16 years of age.

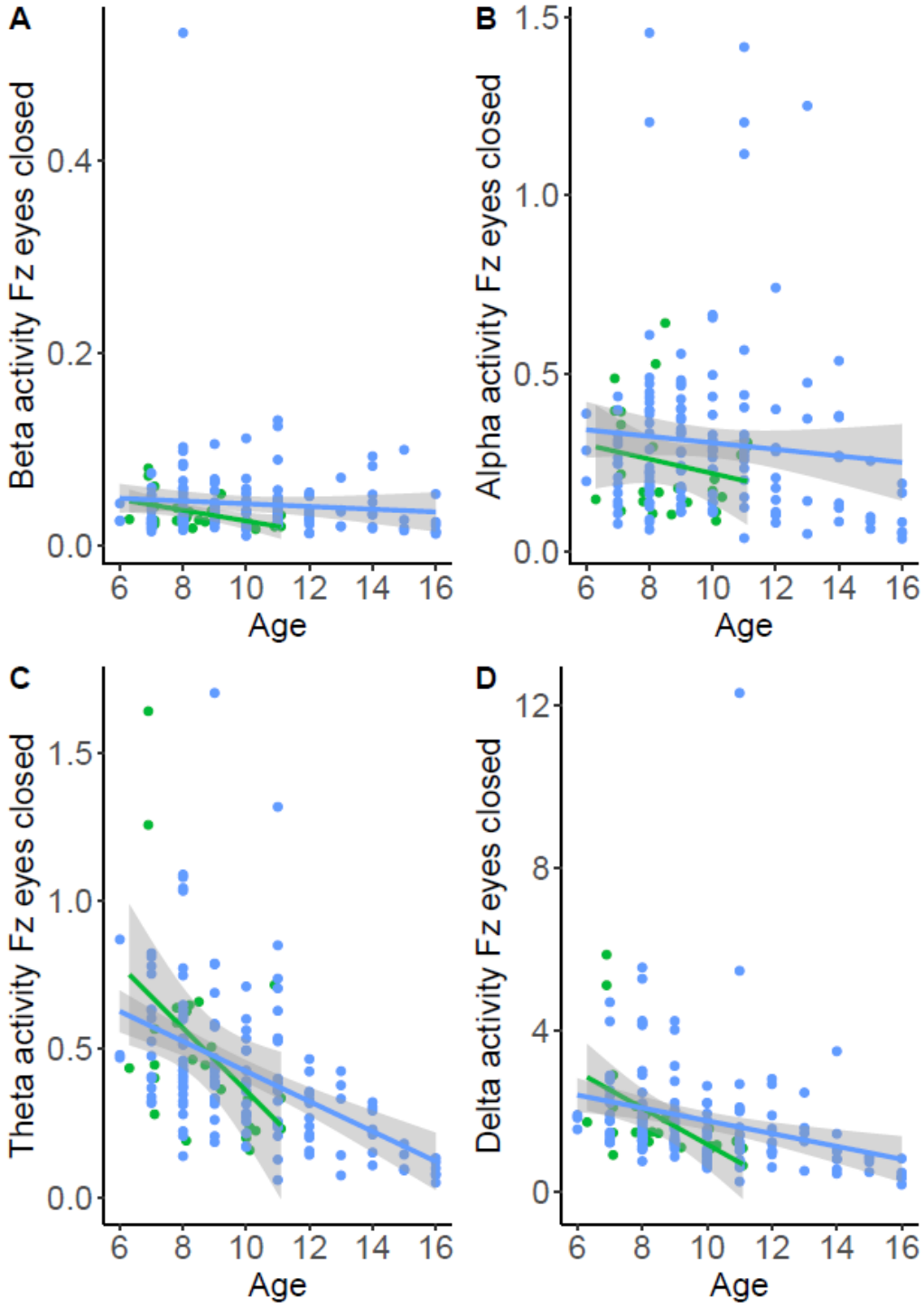

Figure A14. Association between age and spectral power in beta (**A**), alpha (**B**), theta (**C**), and delta (**D**) frequency bands for eyes closed data at electrode position Fz for ADHD (blue) and non-ADHD (green) children and adolescents <16 years of age.

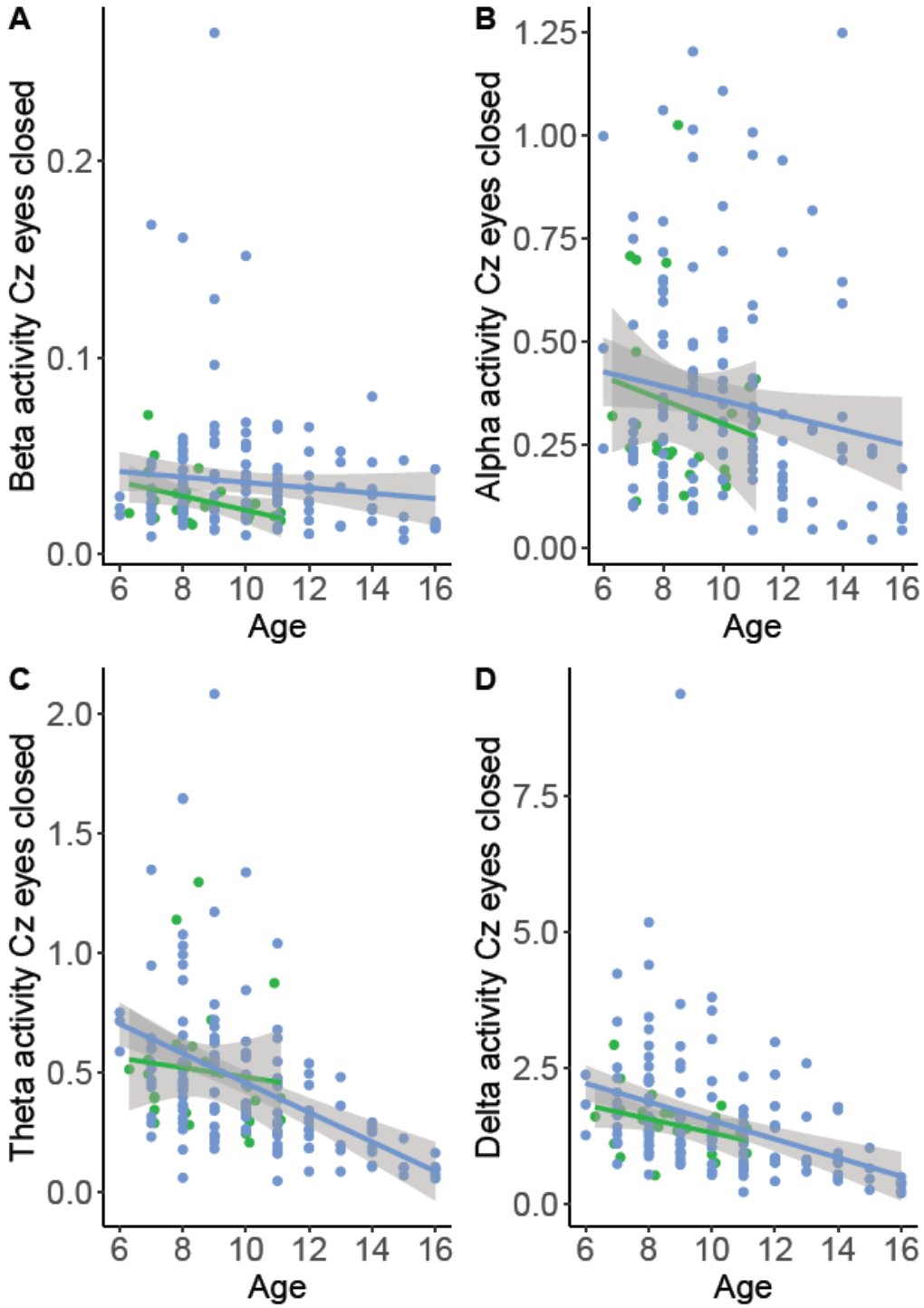

Figure A15. Association between age and spectral power in beta (**A**), alpha (**B**), theta (**C**), and delta (**D**) frequency bands for eyes closed data at electrode position Cz for ADHD (blue) and non-ADHD (green) children and adolescents <16 years of age.

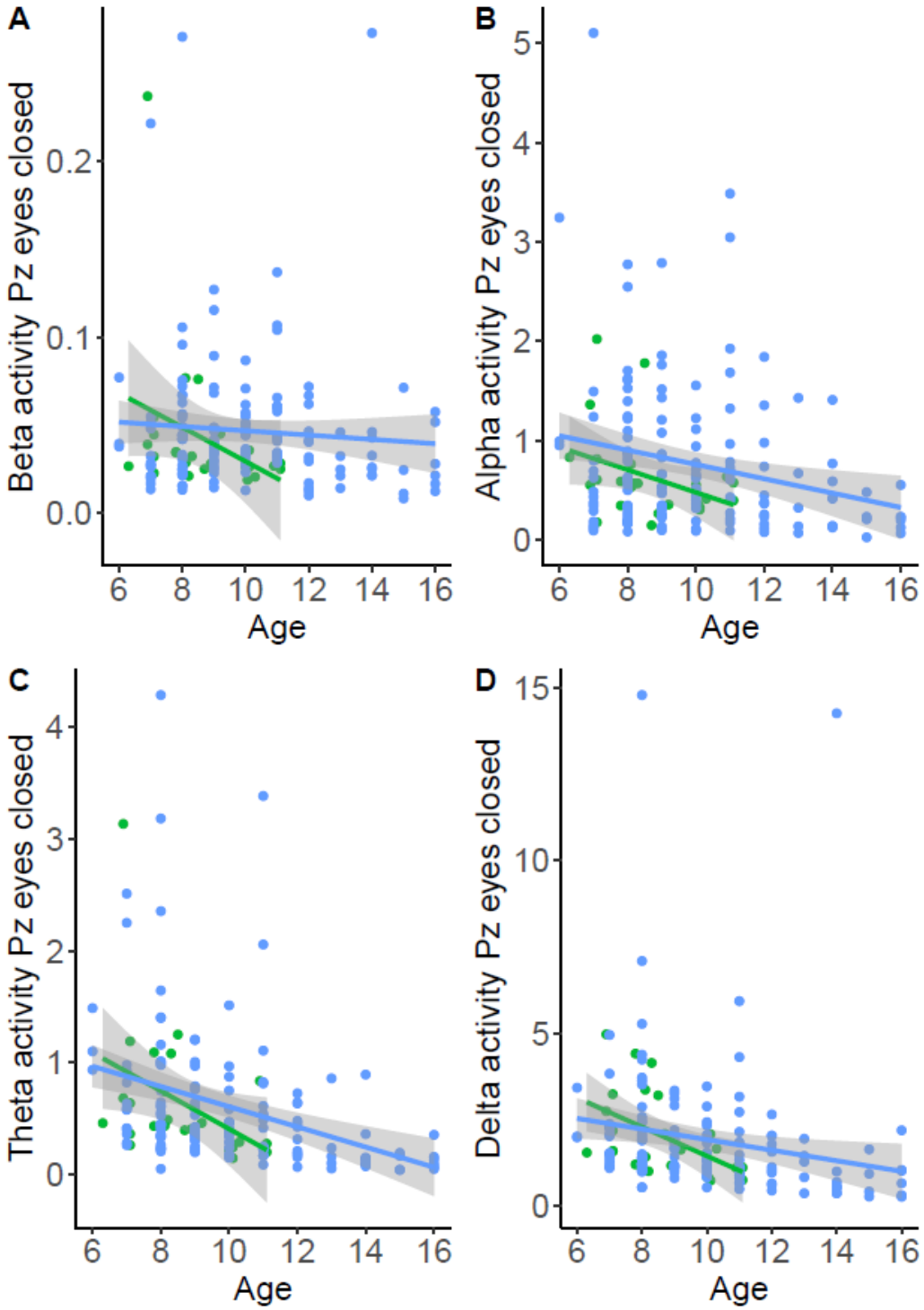

Figure A16. Association between age and spectral power in beta (**A**), alpha (**B**), theta (**C**), and delta (**D**) frequency bands for eyes closed data at electrode position Pz for ADHD (blue) and non-ADHD (green) children and adolescents <16 years of age.

Appendix E

Table A5. Results from stepwise regression models for eyes open alpha activity at electrode Fz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.005	0.001	−0.291	<0.0001	0.085	0.085	200.23	<0.0001
	Age	−0.005	0.001	−0.301	<0.0001				
2	Inattention	0.013	0.010	0.100	0.196	0.109	0.024	8.83	<0.0001
	Hyperactivity/impulsivity	0.010	0.010	0.076	0.321				
	Age	−0.004	0.001	−0.273	<0.0001				
3	Inattention	0.011	0.010	0.083	0.273	0.152	0.043	9.66	<0.0001
	Hyp/imp	0.006	0.010	0.046	0.549				
	Data quality	−0.001	0.000	−0.213	0.001				

N = 220. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A6. Results from stepwise regression models for eyes open alpha activity at electrode Cz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.007	0.001	−0.295	<0.0001	0.087	0.087	200.94	<0.0001
	Age	−0.007	0.001	−0.313	<0.0001				
2	Inattention	0.030	0.014	0.163	0.036	0.109	0.022	8.84	<0.0001
	Hyp/imp	−0.028	0.015	−0.147	0.057				
	Age	−0.006	0.001	−0.291	<0.0001				
3	Inattention	0.028	0.014	0.150	0.052	0.135	0.027	8.46	<0.0001
	Hyp/imp	−0.032	0.014	−0.172	0.026				
	Data quality	−0.001	0.000	−0.168	0.011				

N = 220. . Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A7. Results from stepwise regression models for eyes open alpha activity at electrode Pz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.007	0.003	−0.156	0.020	0.024	0.024	50.49	0.020
	Age	−0.007	0.003	−0.167	0.014				
2	Inattention	0.037	0.029	0.102	0.203	0.042	0.018	3.18	0.025
	Hyp/imp	0.017	0.029	0.046	0.567				
	Age	−0.007	0.003	−0.151	0.026				
3	Inattention	0.034	0.029	0.092	0.249	0.057	0.015	3.25	0.013
	Hyp/imp	0.010	0.030	0.028	0.730				
	Data quality	−0.001	0.001	−0.125	0.067				

N = 220. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A8. Results from stepwise regression models for eyes open beta activity at electrode Fz.

		Unstandardized coefficients		Standardized coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.001	0.000	−0.155	0.021	0.024	0.024	5.38	0.021
	Age	−0.001	0.000	−0.164	0.015				
2	Inattention	0.004	0.003	0.091	0.257	0.048	0.024	3.66	0.013
	Hyp/imp	0.003	0.003	0.086	0.282				
	Age	−0.001	0.000	−0.139	0.037				
3	Inattention	0.003	0.003	0.075	0.339	0.083	0.035	4.88	0.001
	Hyp/imp	0.002	0.003	0.058	0.463				
	Data quality	0.000	0.000	−0.192	0.005				

N = 220. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A9. Results from stepwise regression models for eyes open beta activity at electrode Cz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	0.000	0.000	−0.092	0.173	0.008	0.008	1.87	0.173
	Age	−0.001	0.000	−0.104	0.127				
2	Inattention	0.005	0.004	0.111	0.174	0.019	0.011	1.42	0.239
	Hyp/imp	−0.005	0.004	−0.109	0.177				
	Age	0.000	0.000	−0.066	0.313				
3	Inattention	0.004	0.003	0.087	0.265	0.099	0.080	5.93	<0.0001
	Hyp/imp	−0.007	0.003	−0.152	0.054				
	Data quality	0.000	0.000	−0.290	0.000				

N = 220. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A10. Results from stepwise regression models for eyes open beta activity at electrode Pz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.001	0.001	−0.059	0.384	0.003	0.003	0.76	0.384
	Age	−0.001	0.001	−0.065	0.341				
2	Inattention	0.008	0.011	0.061	0.456	0.018	0.015	1.36	0.256
	Hyp/imp	0.011	0.011	0.078	0.333				
	Age	−0.001	0.001	−0.048	0.479				
3	Inattention	0.007	0.011	0.050	0.535	0.034	0.015	1.89	0.114
	Hyp/imp	0.008	0.011	0.060	0.460				
	Data quality	−0.001	0.000	−0.127	0.066				

N = 220. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A11. Results from stepwise regression models for eyes open theta activity at electrode Fz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.015	0.002	−0.480	<0.0001	0.230	0.230	65.51	<0.0001
	Age	−0.015	0.002	−0.485	<0.0001				
2	Inattention	0.014	0.019	0.053	0.462	0.239	0.009	22.74	<0.0001
	Hyp/imp	0.015	0.019	0.055	0.439				
	Age	−0.014	0.002	−0.460	<0.0001				
3	Inattention	0.010	0.018	0.037	0.597	0.274	0.035	20.43	<0.0001
	Hyp/imp	0.007	0.019	0.027	0.700				
	Data quality	−0.002	0.000	−0.193	0.001				

N = 220. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A12. Results from stepwise regression models for eyes open theta activity at electrode Cz.

		Unstandardized coefficients		Standardized coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.016	0.002	−0.456	<0.0001	0.208	0.208	57.59	<0.0001
	Age	−0.017	0.002	−0.461	<0.0001				
2	Inattention	0.012	0.022	0.039	0.587	0.215	0.006	19.77	<0.0001
	Hyp/imp	−0.029	0.022	−0.095	0.191				
	Age	−0.016	0.002	−0.438	<0.0001				
3	Inattention	0.008	0.022	0.025	0.723	0.243	0.029	17.36	<0.0001
	Hyp/imp	−0.037	0.022	−0.120	0.095				
	Data quality	−0.002	0.001	−0.174	0.005				

N = 220. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A13. Results from stepwise regression models for eyes open theta activity at electrode Pz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.017	0.003	−0.325	<0.0001	0.106	0.106	25.93	<0.0001
	Age	−0.017	0.003	−0.331	<0.0001				
2	Inattention	0.023	0.033	0.054	0.487	0.119	0.013	9.75	<0.0001
	Hyp/imp	0.033	0.033	0.075	0.327				
	Age	−0.016	0.003	−0.314	<0.0001				
3	Inattention	0.018	0.033	0.043	0.574	0.135	0.016	8.42	<0.0001
	Hyp/imp	0.024	0.033	0.056	0.464				
	Data quality	−0.002	0.001	−0.130	0.047				

N = 220. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A14. Results from stepwise regression models for eyes open delta activity at electrode Fz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.061	0.009	−0.415	<0.0001	0.172	0.172	44.98	<0.0001
	Age	−0.061	0.009	−0.416	<0.0001				
2	Inattention	0.021	0.092	0.017	0.820	0.181	0.009	15.78	<0.0001
	Hyp/imp	0.104	0.093	0.083	0.266				
	Age	−0.057	0.009	−0.389	<0.0001				
3	Inattention	0.005	0.089	0.004	0.954	0.233	0.051	16.13	<0.0001
	Hyp/imp	0.053	0.091	0.042	0.565				
	Data quality	−0.009	0.002	−0.233	< 0.0001				

N = 217. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A15. Results from stepwise regression models for eyes open delta activity at electrode Cz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.065	0.010	−0.415	<0.0001	0.172	0.172	45.34	<0.0001
	Age	−0.066	0.010	−0.418	<0.0001				
2	Inattention	0.028	0.098	0.022	0.774	0.174	0.001	15.13	<0.0001
	Hyp/imp	−0.061	0.099	−0.046	0.538				
	Age	−0.061	0.010	−0.387	<0.0001				
3	Inattention	0.003	0.095	0.002	0.976	0.233	0.059	16.34	<0.0001
	Hyp/imp	−0.112	0.097	−0.084	0.249				
	Data quality	−0.010	0.003	−0.251	< 0.0001				

N = 219. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A16. Results from stepwise regression models for eyes open delta activity at electrode Pz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.071	0.011	−0.410	<0.0001	0.168	0.168	44.25	<0.0001
	Age	−0.072	0.011	−0.417	<0.0001				
2	Inattention	0.104	0.108	0.072	0.337	0.172	0.004	15.107	<0.0001
	Hyp/imp	−0.016	0.108	−0.011	0.886				
	Age	−0.066	0.010	−0.384	<0.0001				
3	Inattention	0.074	0.104	0.051	0.479	0.236	0.063	16.64	<0.0001
	Hyp/imp	−0.070	0.105	−0.048	0.504				
	Data quality	−0.102	0.003	−0.258	< 0.0001				

N = 220. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A17. Results from stepwise regression models for eyes closed alpha activity at electrode Fz.

		Unstandardized coefficients		Standardized coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.006	0.002	−0.209	0.002	0.044	0.044	9.50	0.002
	Age	−0.006	0.002	−0.216	0.002				
2	Inattention	0.012	0.017	0.057	0.483	0.065	0.021	4.72	0.003
	Hyp/imp	0.023	0.018	0.105	0.196				
	Age	−0.005	0.002	−0.185	0.010				
3	Inattention	0.011	0.017	0.053	0.515	0.075	0.011	4.15	0.003
	Hyp/imp	0.018	0.018	0.079	0.339				
	Data quality	−0.001	0.000	−0.111	0.128				

N = 208. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A18. Results from stepwise regression models for eyes closed alpha activity at electrode Cz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.009	0.002	−0.306	<0.0001	0.094	0.094	21.37	<0.0001
	Age	−0.010	0.002	−0.324	<0.0001				
2	Inattention	0.034	0.019	0.144	0.072	0.109	0.015	8.33	<0.0001
	Hyp/impy	−0.012	0.020	−0.050	0.528				
	Age	−0.009	0.002	−0.292	<0.0001				
3	Inattention	0.033	0.019	0.140	0.080	0.120	0.012	6.97	<0.0001
	Hyp/imp	−0.019	0.020	−0.077	0.339				
	Data quality	−0.001	0.001	−0.116	0.102				

N = 208. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A19. Results from stepwise regression models for eyes closed alpha activity at electrode Pz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.022	0.006	−0.268	<0.0001	0.072	0.072	16.03	<0.0001
	Age	−0.023	0.006	−0.276	<0.0001				
2	Inattention	0.043	0.054	0.065	0.423	0.085	0.013	6.31	<0.0001
	Hyp/imp	0.044	0.055	−0.064	0.427				
	Age	−0.021	0.006	−0.254	<0.0001				
3	Inattention	0.041	0.054	0.062	0.444	0.090	0.005	5.03	0.001
	Hyp/imp	0.031	0.056	0.046	0.578				
	Data quality	−0.002	0.001	−0.077	0.285				

N = 208. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A20. Results from stepwise regression models for eyes closed beta activity at electrode Fz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.001	0.000	−0.151	0.029	0.023	0.023	14.81	0.029
	Age	−0.001	0.000	−0.164	0.019				
2	Inattention	0.004	0.003	0.112	0.176	0.037	0.014	2.63	0.052
	Hyp/imp	0.001	0.003	0.014	0.867				
	Age	−0.001	0.000	−0.117	0.104				
3	Inattention	0.004	0.003	0.106	0.198	0.063	0.026	3.41	0.010
	Hyp/imp	−0.001	0.003	−0.027	0.749				
	Data quality	0.000	0.000	−0.173	0.019				

N = 208. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A21. Results from stepwise regression models for eyes closed beta activity at electrode Cz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	0.000	0.000	−0.123	0.076	0.015	0.015	3.19	0.076
	Age	−0.001	0.000	−0.141	0.045				
2	Inattention	0.004	0.002	0.137	0.102	0.028	0.013	1.97	0.120
	Hyp/imp	−0.002	0.002	−0.072	0.385				
	Age	0.000	0.000	−0.060	0.390				
3	Inattention	0.004	0.002	0.125	0.120	0.102	0.074	5.77	<0.0001
	Hyp/imp	−0.004	0.002	−0.140	0.086				
	Data quality	0.000	0.000	−0.293	<0.0001				

N = 208. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A22. Results from stepwise regression models for eyes closed beta activity at electrode Pz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.001	0.000	−0.170	0.014	0.029	0.029	6.17	0.014
	Age	−0.001	0.000	−0.190	0.006				
2	Inattention	0.006	0.003	0.156	0.060	0.047	0.018	3.36	0.020
	Hyp/imp	−0.005	0.003	−0.121	0.141				
	Age	0.000	0.000	−0.106	0.125				
3	Inattention	0.005	0.003	0.144	0.070	0.128	0.081	7.46	<0.0001
	Hyp/imp	−0.007	0.003	−0.192	0.017				
	Data quality	0.000	0.000	−0.306	<0.0001				

N = 208. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A23. Results from stepwise regression models for eyes closed theta activity at electrode Fz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.017	0.002	−0.520	<0.0001	0.271	0.271	76.82	<0.0001
	Age	−0.016	0.002	−0.514	<0.0001				
2	Inattention	−0.013	0.018	−0.051	0.482	0.273	0.002	25.60	<0.0001
	Hyp/imp	0.010	0.019	0.037	0.604				
	Age	−0.014	0.002	−0.446	<0.0001				
3	Inattention	−0.015	0.018	−0.060	0.388	0.325	0.052	24.52	<0.0001
	Hyp/imp	−0.005	0.019	−0.020	0.772				
	Data quality	−0.002	0.000	−0.246	<0.0001				

N = 208. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A24. Results from stepwise regression models for eyes closed theta activity at electrode Cz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.018	0.002	−0.472	<0.0001	0.223	0.223	59.48	<0.0001
	Age	−0.018	0.002	−0.469	<0.0001				
2	Inattention	−0.008	0.023	−0.027	0.718	0.224	0.001	19.74	<0.0001
	Hyp/imp	0.011	0.024	0.035	0.640				
	Age	−0.016	0.002	−0.403	<0.0001				
3	Inattention	−0.011	0.022	−0.036	0.618	0.273	0.049	19.15	<0.0001
	Hyp/imp	−0.007	0.024	−0.021	0.772				
	Data quality	−0.002	0.001	−0.238	<0.0001				

N = 208. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A25. Results from stepwise regression models for eyes closed theta activity at electrode Pz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.027	0.005	−0.383	<0.0001	0.147	0.147	35.67	<0.0001
	Age	−0.027	0.005	−0.380	<0.0001				
2	Inattention	−0.014	0.044	−0.024	0.757	0.152	0.005	12.28	<0.0001
	Hyp/imp	0.049	0.045	0.084	0.279				
	Age	−0.023	0.005	−0.321	<0.0001				
3	Inattention	−0.018	0.043	−0.032	0.671	0.191	0.039	12.07	<0.0001
	Hyp/imp	0.020	0.045	0.034	0.661				
	Data quality	−0.004	0.001	−0.213	0.002				

N = 208. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A26. Results from stepwise regression models for eyes closed delta activity at electrode Fz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.063	0.010	−0.383	<0.0001	0.165	0.165	40.67	<0.0001
	Age	−0.062	0.010	−0.380	<0.0001				
2	Inattention	−0.031	0.096	−0.024	0.748	0.165	0.000	13.47	<0.0001
	Hyp/imp	0.025	0.099	0.084	0.799				
	Age	−0.049	0.010	−0.321	<0.0001				
3	Inattention	−0.047	0.091	−0.032	0.604	0.247	0.082	16.66	<0.0001
	Hyp/imp	−0.064	0.096	0.034	0.504				
	Data quality	−0.012	0.003	−0.213	<0.0001				

N = 207. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A27. Results from stepwise regression models for eyes closed delta activity at electrode Fz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.057	0.008	−0.451	<0.0001	0.203	0.203	52.61	<0.0001
	Age	−0.056	0.008	−0.448	<0.0001				
2	Inattention	−0.025	0.077	−0.024	0.747	0.206	0.003	17.69	<0.0001
	Hyp/imp	0.068	0.079	0.065	0.389				
	Age	−0.046	0.008	−0.365	<0.0001				
3	Inattention	−0.042	0.073	−0.041	0.570	0.285	0.078	20.21	<0.0001
	Hyp/imp	0.000	0.077	0.000	0.995				
	Data quality	−0.010	0.002	−0.301	<0.0001				

N = 207. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

Table A28. Results from stepwise regression models for eyes closed delta activity at electrode Pz.

		Unstandardized Coefficients		Standardized Coefficients					
Step	**Predictor**	**B**	**SE**	**β**	***p***	**R^2**	**ΔR^2**	**F**	***p***
1	Age	−0.077	0.013	−0.382	<0.0001	0.146	0.146	35.43	<0.0001
	Age	−0.077	0.013	−0.386	<0.0001				
2	Inattention	0.041	0.125	0.026	0.742	0.147	0.000	11.74	<0.0001
	Hyp/imp	−0.032	0.129	−0.019	0.802				
	Age	−0.060	0.013	−0.301	<0.0001				
3	Inattention	0.022	0.119	0.014	0.853	0.229	0.082	15.12	<0.0001
	Hyp/imp	−0.153	0.126	−0.091	0.226				
	Data quality	−0.015	0.003	−0.309	<0.0001				

N = 208. Hyp/imp = Hyperactivity/impulsivity. SE = standard error of B.

6.3 SUPPLEMENT STUDY 3: A developmental perspective on impulsivity-facets and brain-activity correlates from adolescence to adulthood

Supplement A

Assessment of impulsivity

Trait impulsivity

The NEO-PI-R has been shown to provide a valid measurement for broad dimensions of personality [1] that is based on the Five-Factor Model of Personality. The SURPS measures lower-order personality trait dimensions related to psychopathology as well as different levels of personality risk factors for psychopathology (e.g. hopelessness, anxiety, impulsivity). Finally, the TCI-R was used as a third indicator of trait impulsivity to assess lower-order personality traits specifically linked to disinhibitory psychopathology.

Choice impulsivity: temporal discounting

The KIRBY provides a measure of delay discounting by assessing the preference of immediate lower over delayed higher monetary rewards. This questionnaire asks for the relative preference of one sum compared to another sum rather than asking for decisions about absolute amounts of money.

Choice impulsivity: probabilistic discounting

The CGT was developed to assess decision-making and risk-taking behavior. It is part of the Cambridge Neuropsychological Test Automated Battery (CANTAB) providing sensitive and objective measures of cognitive functioning [2]. Information is presented to the subjects without any need to learn or retrieve information over consecutive trials afterwards. On each trial, the subject is presented with a row of ten boxes across the top of the screen. Some of these boxes are red, others are blue. At the bottom of the screen are rectangles containing the words 'Red' and 'Blue'. The participants are instructed to guess whether a yellow token is hidden in a red or a blue box. In the gambling stages, participants start with a number of points displayed on the screen. They can select a proportion of these points, shown in either rising or falling order in a second box on the screen to gamble on their confidence. A

stake box on the screen displays the current amount of the bet. The participants are instructed to accumulate as many points as possible. For the current modified version, the time between stakes is reduced from 5s to 2s to make the task shorter and more interesting. Stakes are displayed in ascending order first.

Supplement B

Assessment of brain activity – fMRI paradigms

The Stop Signal Task (SST; [3])

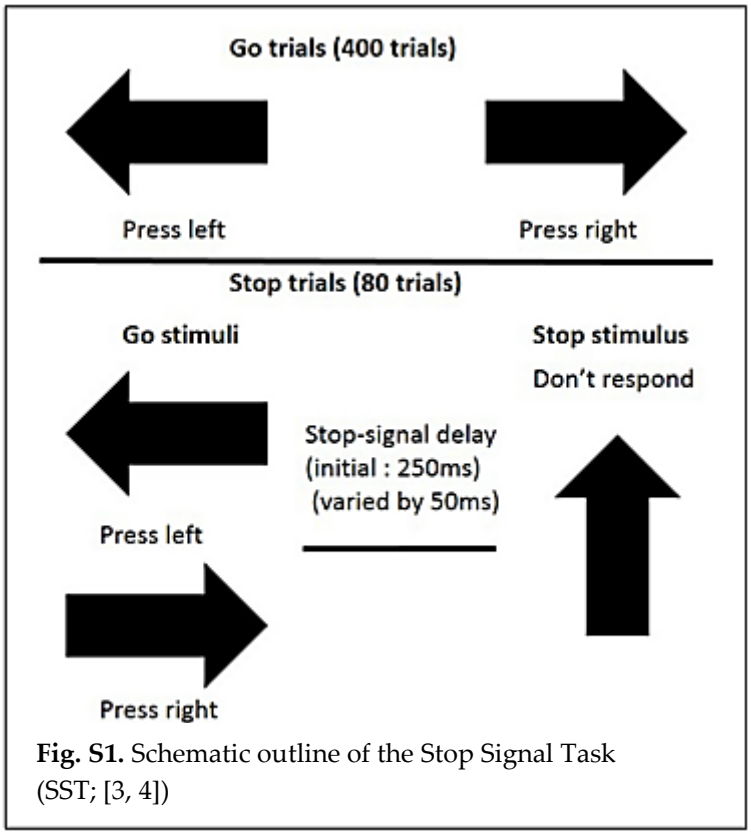

Fig. S1. Schematic outline of the Stop Signal Task (SST; [3, 4])

During the SST, participants are presented with arrows in the center of a computer screen that point either to the left or right (go signal). Subjects are instructed to indicate the direction of the arrow by pressing either the left or right button as quickly and accurately as possible. On 20% of the trials, the go signal is followed by the stop signal (arrow pointing upwards) and subjects are instructed to withhold their response. To manipulate stopping difficulty across trials, the onset of the stop signal after the go signal (stop signal delay) was varied (for algorithm, see [3]). Consequently, subjects successfully stopped on 50% of trials. The total task contained 400 go trials with a stimulus-duration of 1000 ms each, and, furthermore,

80 stop trials with a stimulus duration varying between 0-900 ms (initial delay of 250 ms). A practice session was implemented prior to scanning to familiarize subjects with the task. Thereby, 60 trials were performed during 2 minutes.

The Monetary Incentive Delay Task (MID; [5])

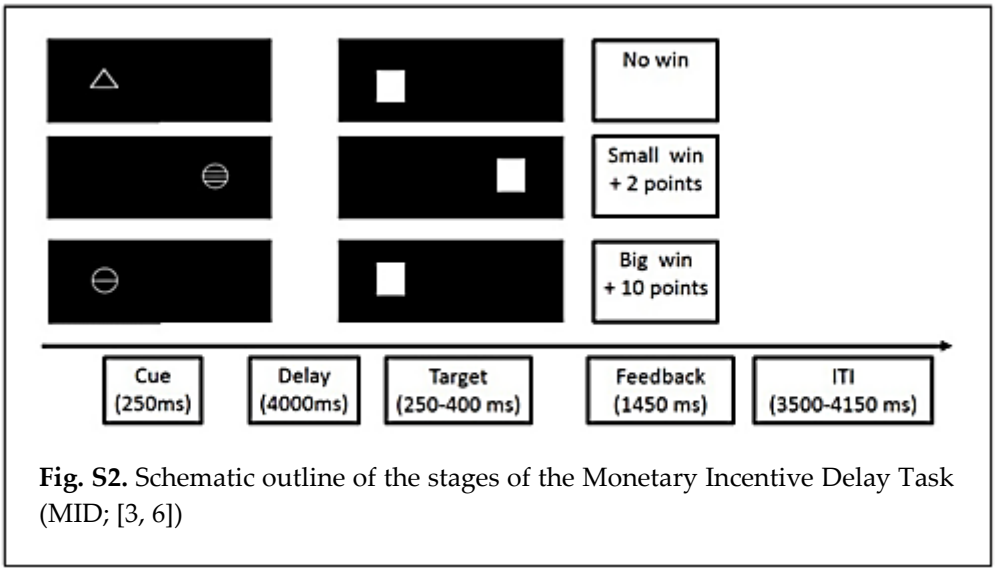

Fig. S2. Schematic outline of the stages of the Monetary Incentive Delay Task (MID; [3, 6])

On each trial of the MID task, participants are presented with one of three cues: a triangle, a circle with a line through it, or a circle with three lines through it. Each cue is presented for 250 ms, either on the left or on the right of the screen. The type of cue, and the cue's location predict the reward value (possibility of winning 0, 2, or 10 points when responding correctly), and the location (left or right side of the screen) of a subsequently presented target (a white square). The cue stimulus is followed by a fixation cross (4500 ms), which in turn is followed by the presentation of the target stimulus for a varied duration (between 250–400 ms). Subjects were told that they could win the predicted reward if they correctly indicate the location of the target by pressing a button with the index finger. If participants responded too early or too late they did not receive any reward. Feedback on reward points was given following the presentation of the target. In order to increase motivation, participants received a single sweet for every five points that they won. Task difficulty was varied using an algorithm that ensured that participants were successful on 66% of trials, and that they did not win more than 200 points. There were 22 trials per condition

(no win, small win, big win). Total task duration was 11 min. Participants were familiarized with the task during a practice session for 3 min prior to scanning. In the scanner, participants were reminded of the instructions.

Supplement C

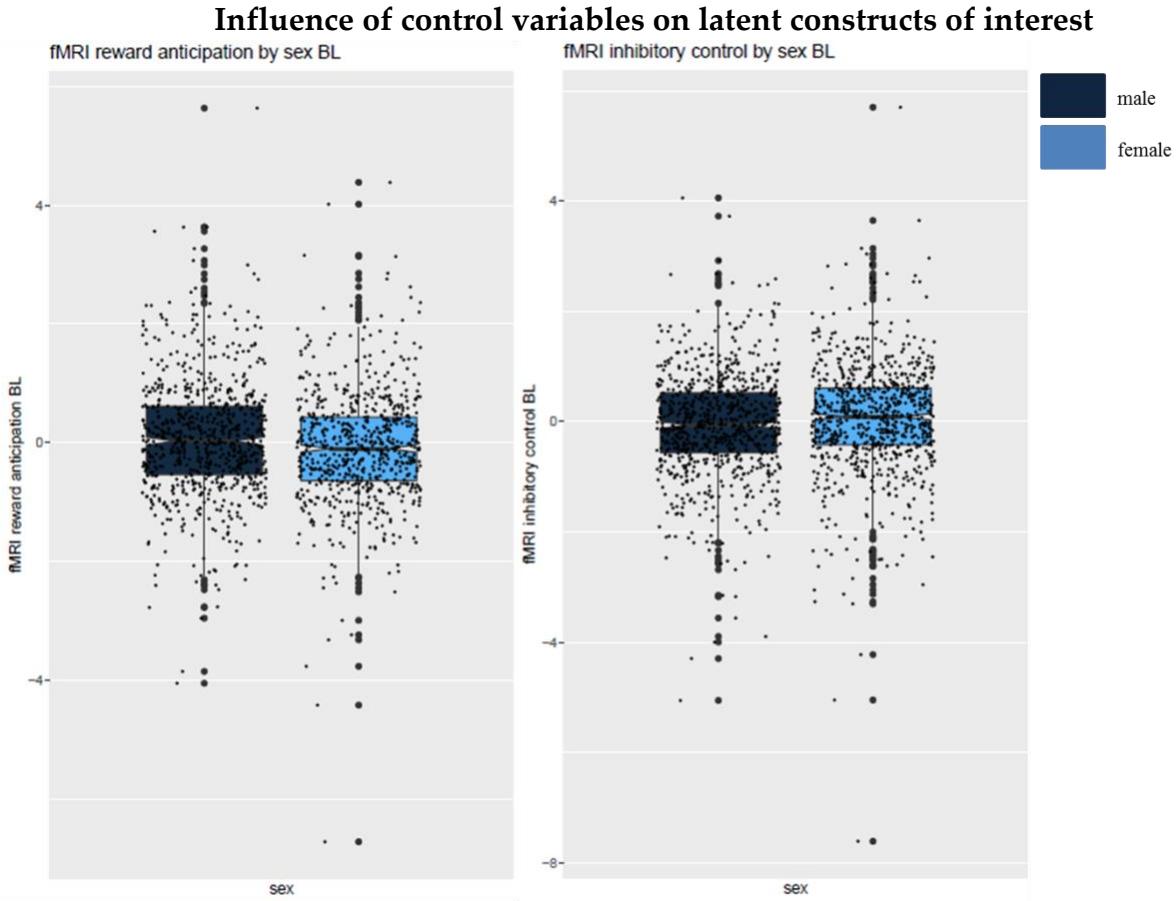

Fig. S3. Sex differences for fMRI reward anticipation and fMRI inhibitory control at baseline.

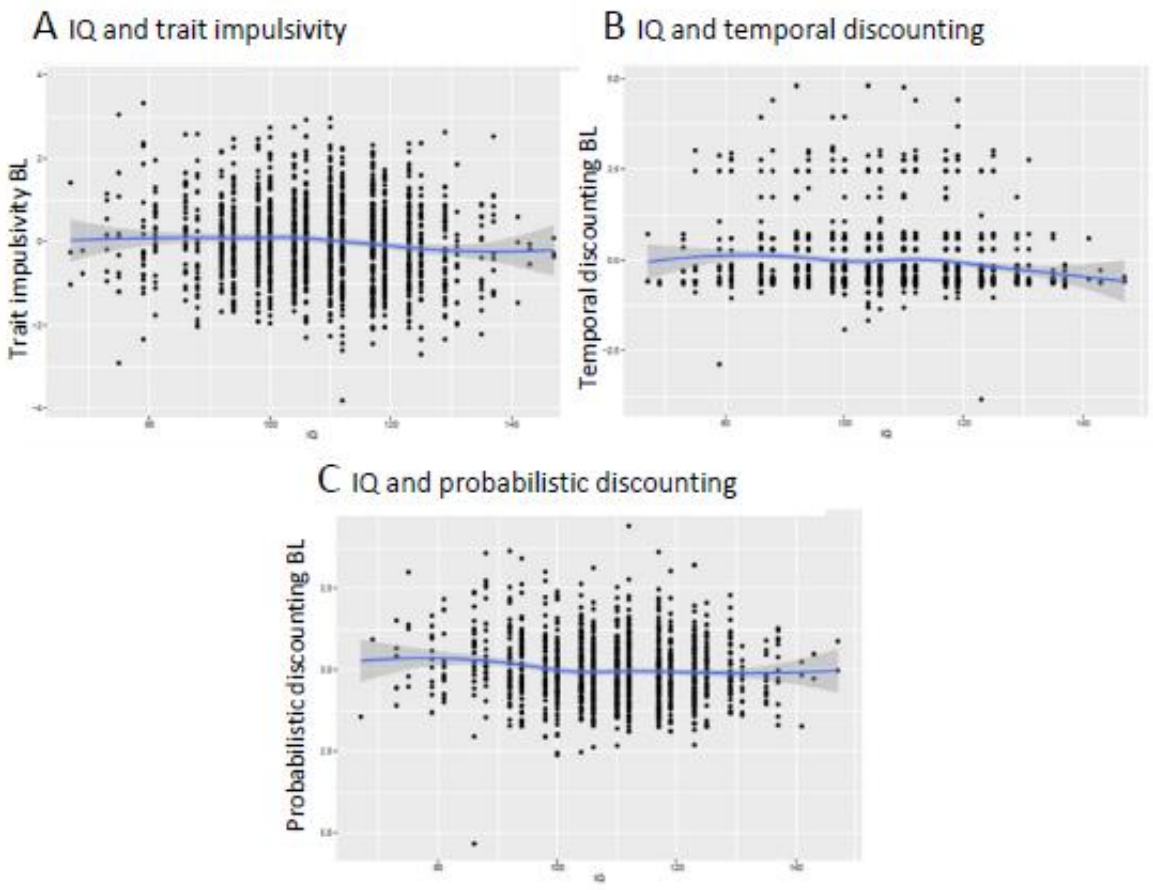

Fig. S4. IQ effects on trait and decisional forms of impulsivity at baseline. A Trait impulsivity. B Temporal discounting. C Probabilistic discounting.

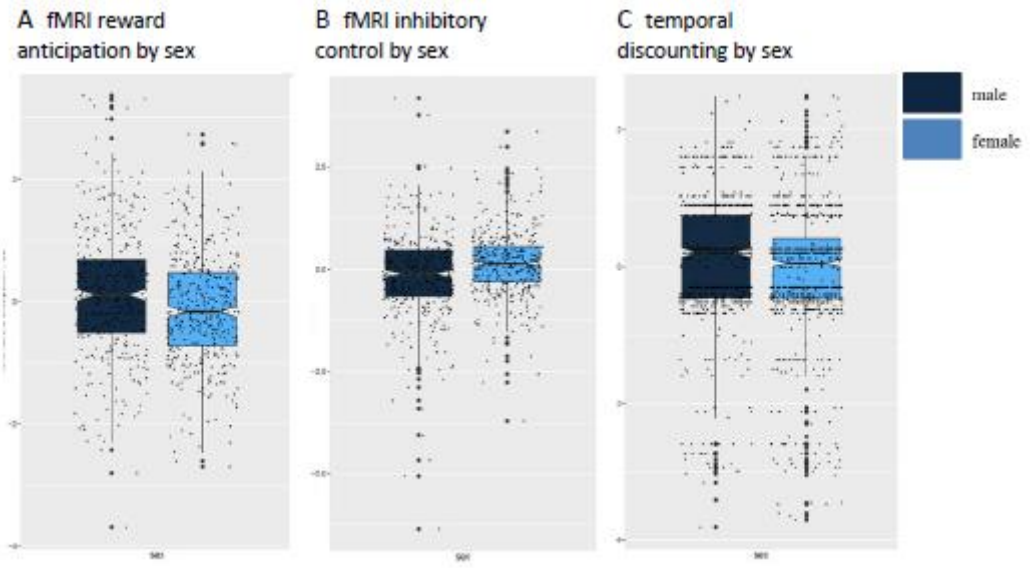

Fig. S5. Significant sex differences for fMRI paradigms and for temporal discounting as a form of decisional impulsivity at follow-up.

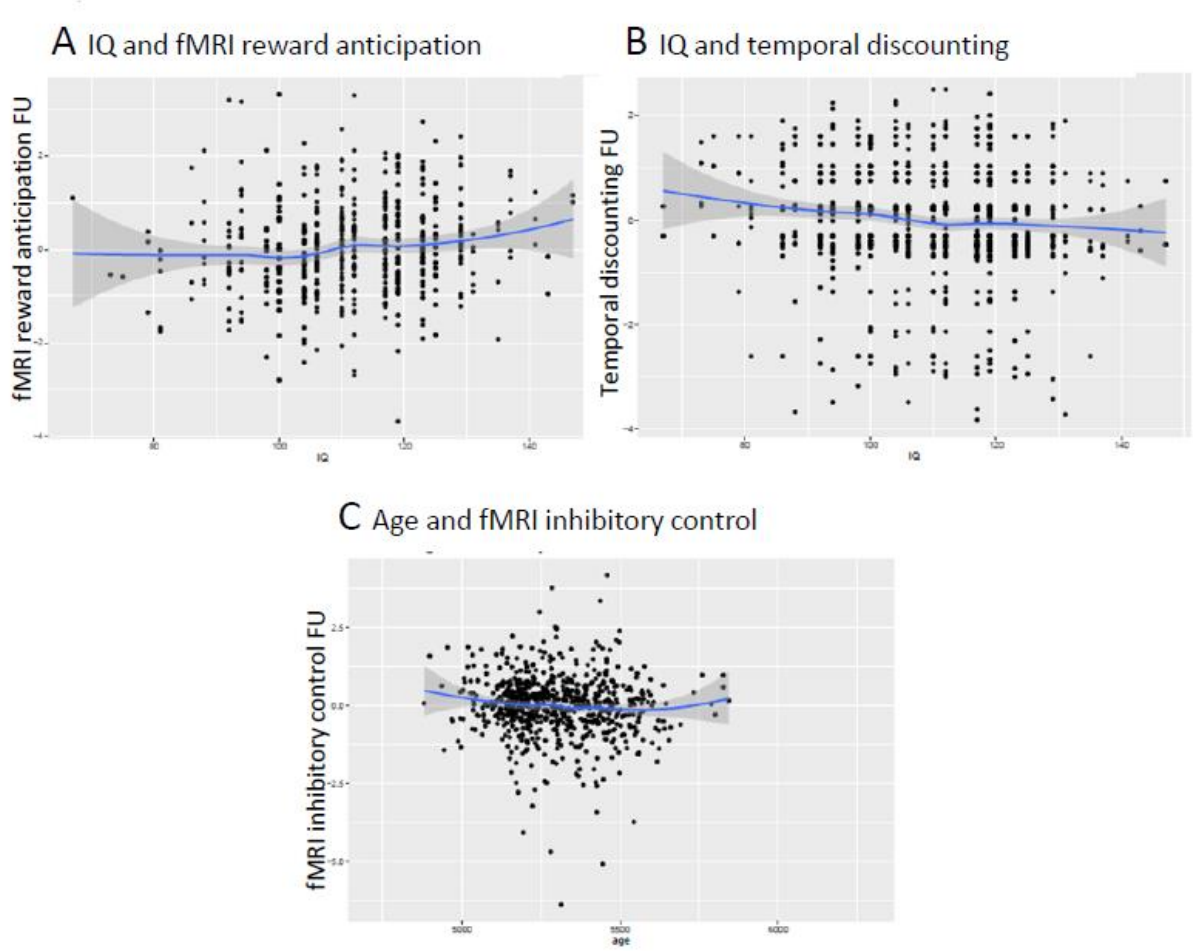

Fig. S6. Significant IQ and age effects on fMRI paradigms and temporal discounting as one form of decisional impulsivity at follow-up. *Note.* Age in days.

Supplement D

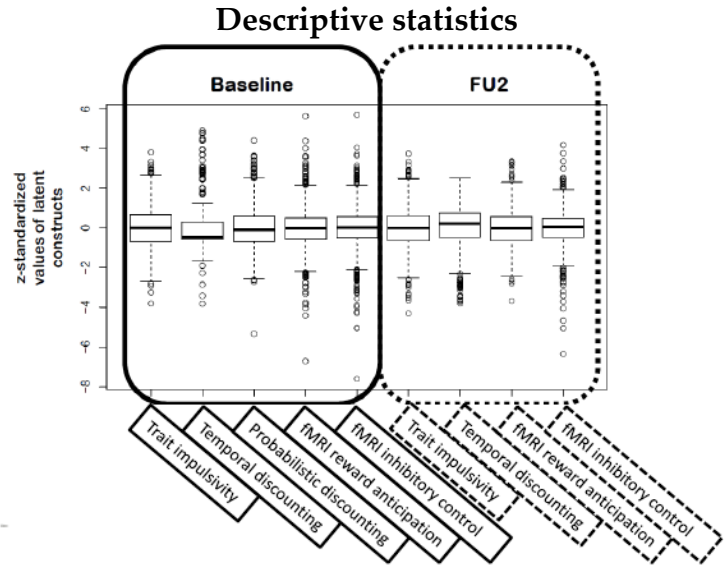

Fig. S7. Distribution of z-standardized (predicted) values for trait and decisional forms of impulsivity and for fMRI brain responsivity to proximate and distant constructs.

Supplement E

Associations between all constructs of interest

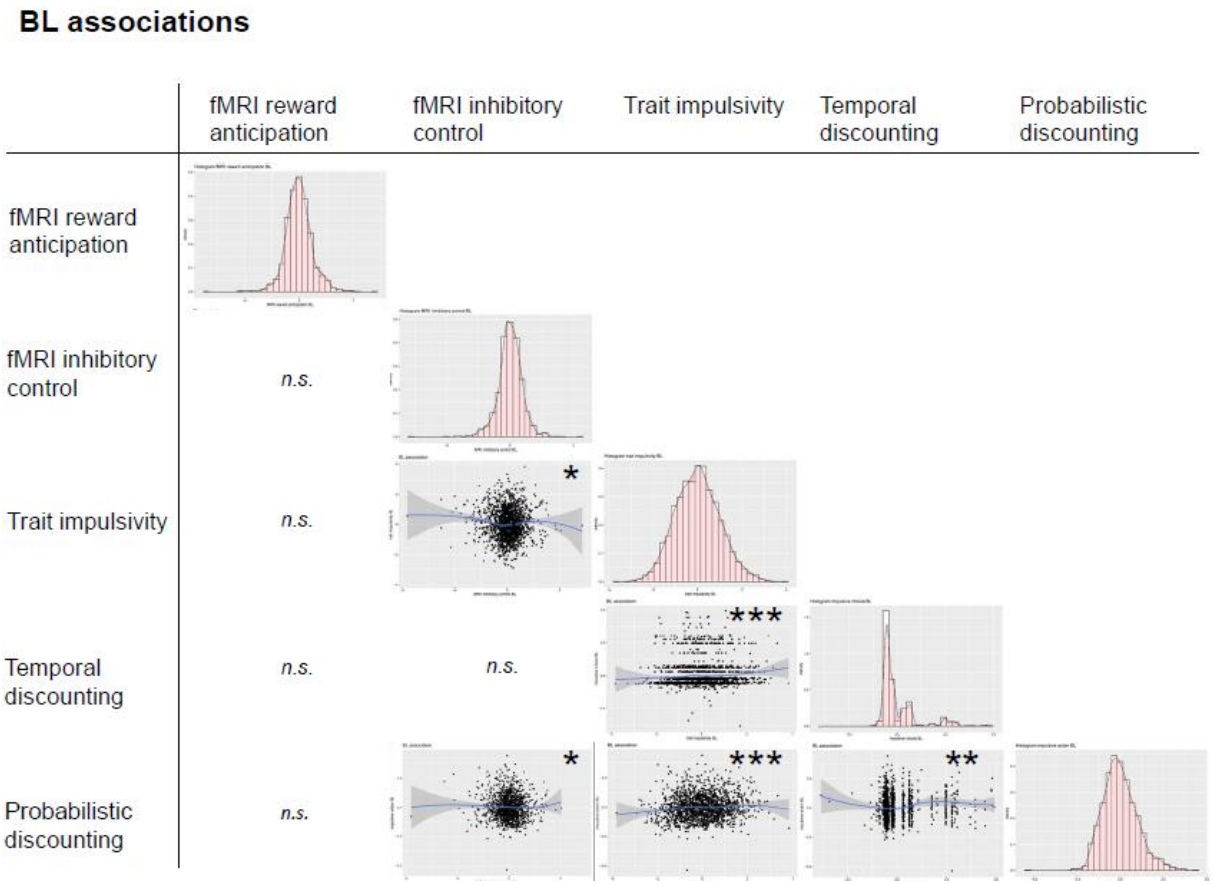

Fig. S8. Baseline associations between all constructs of interest. *Note.* ° $p \leq .10$, * $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$, uncorrected. fMRI reward anticipation represents mean ROI activity in VS. fMRI inhibitory control reflects weighted mean ROI activity (CFA) in pre-SMA and IFG. Impulsive choice represents mean of distinct categorical scores from KIRBY (K1-K3).

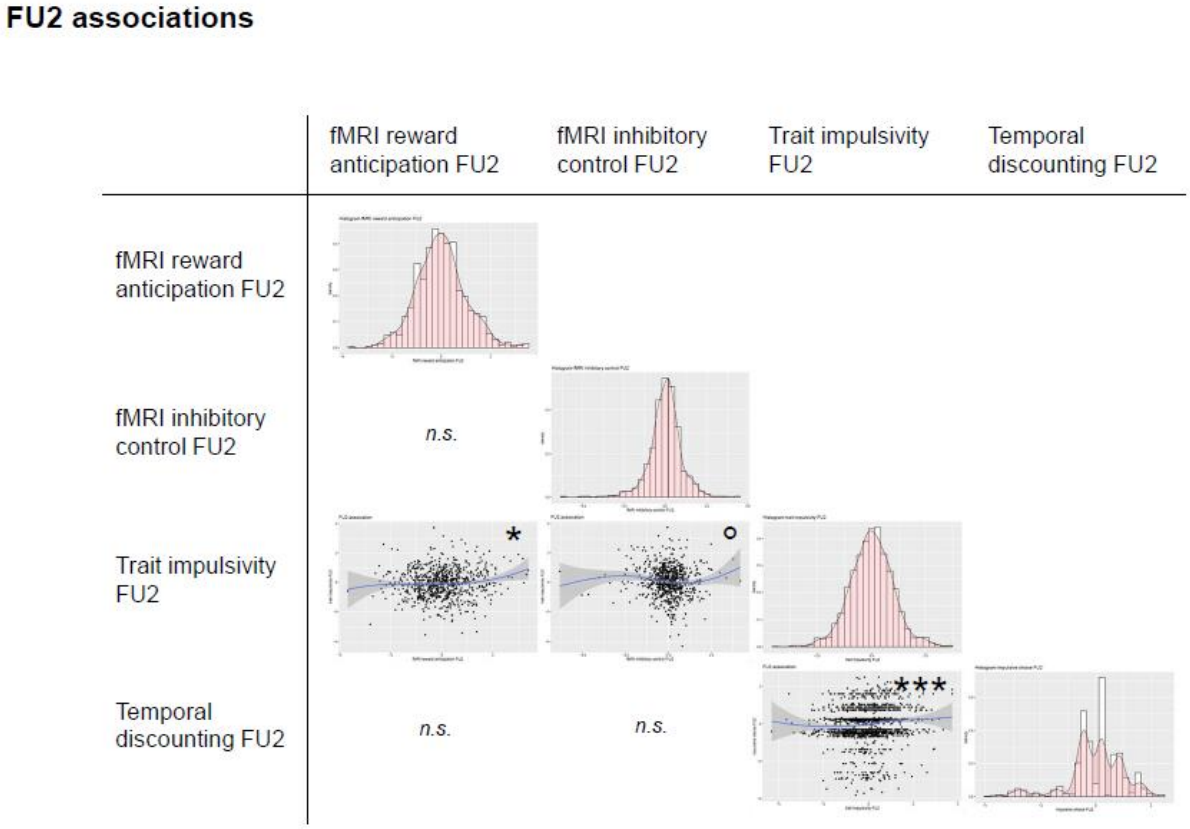

Fig. S9. Follow-up associations between all constructs of interest. *Note.* ° $p \leq .10$, * $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$, uncorrected. fMRI reward anticipation represents mean ROI activity in VS. fMRI inhibitory control reflects weighted mean ROI activity (CFA) in pre-SMA and IFG. Impulsive choice represents mean of distinct categorical scores from KIRBY (K1-K3).

Supplement F

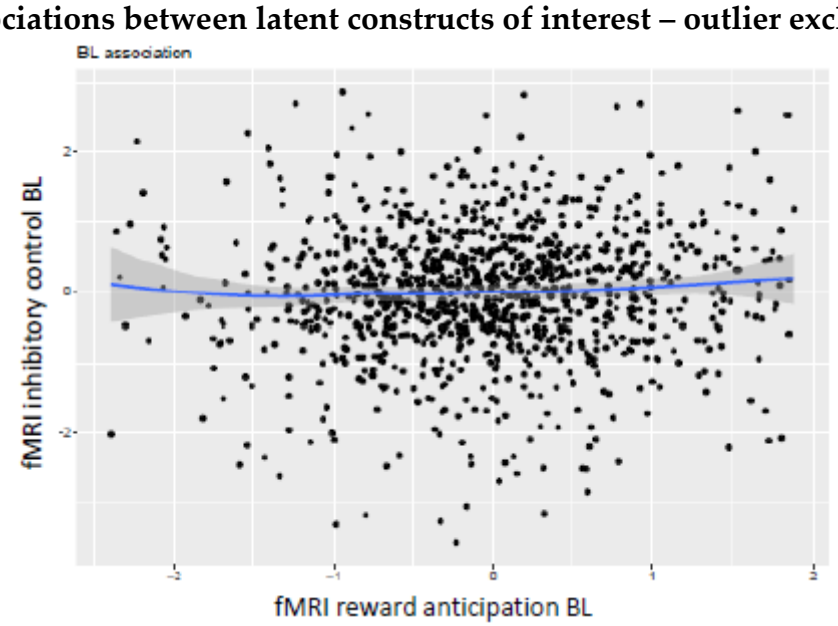

Fig. S10. Relationship between fMRI reward anticipation and fMRI inhibitory control activity in adolescence; extreme values excluded; *p*=0.048.

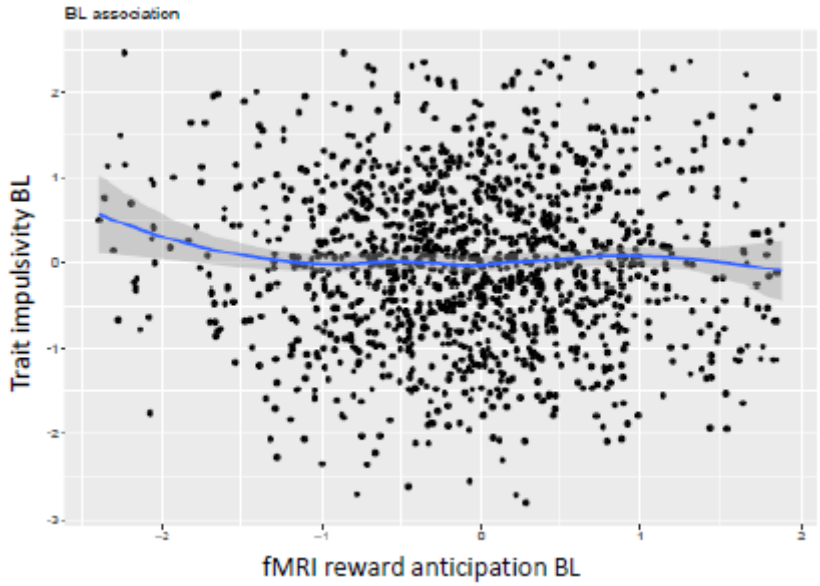

Fig. S11. Relationship between fMRI reward anticipation activity and trait impulsivity in adolescence; extreme values excluded; *p*=0.551.

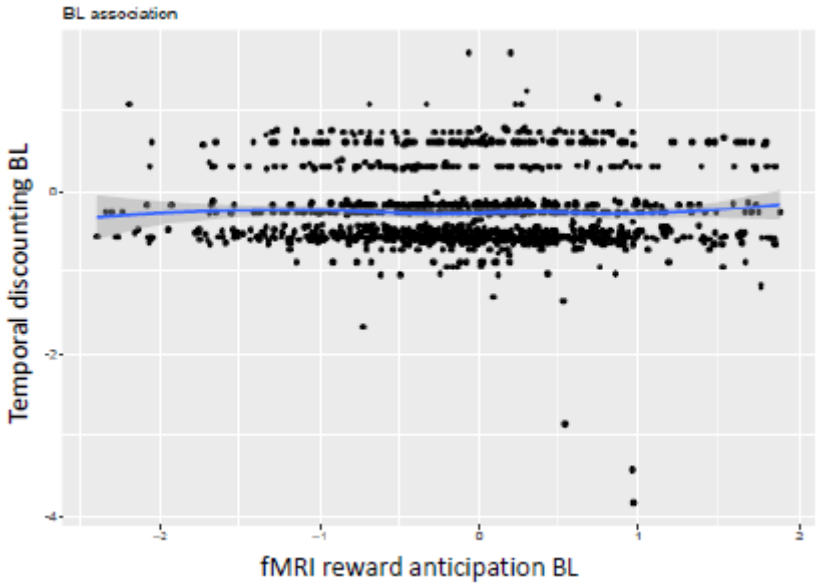

Fig. S12. Relationship between fMRI reward anticipation activity and temporal discounting in adolescence; extreme values excluded; *p*=0.810.

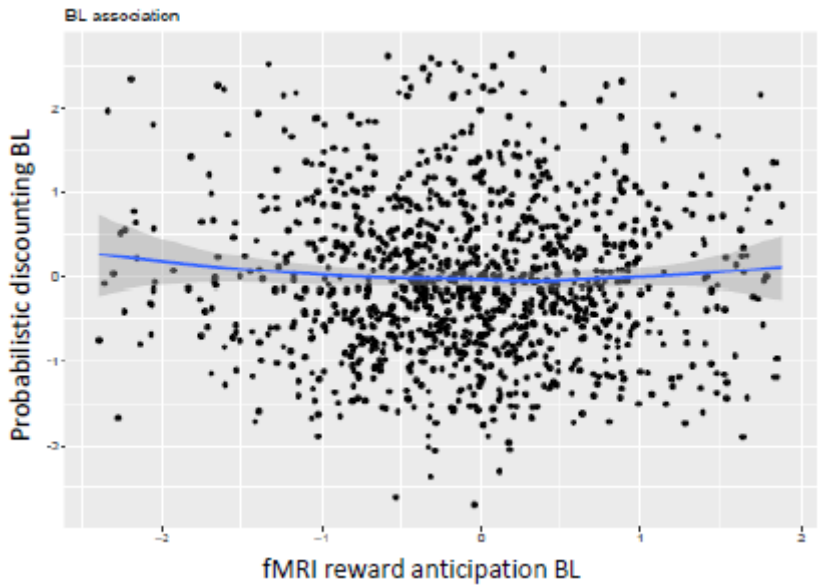

Fig. S13. Relationship between fMRI reward anticipation activity and probabilistic discounting in adolescence; extreme values excluded; *p*=0.576.

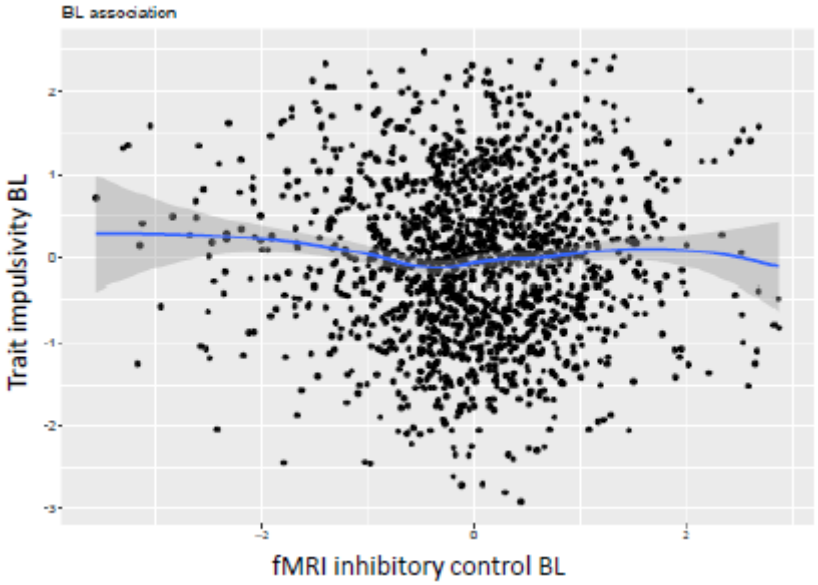

Fig. S14. Relationship between fMRI inhibitory control activity and trait impulsivity in adolescence; extreme values excluded; p=0.043.

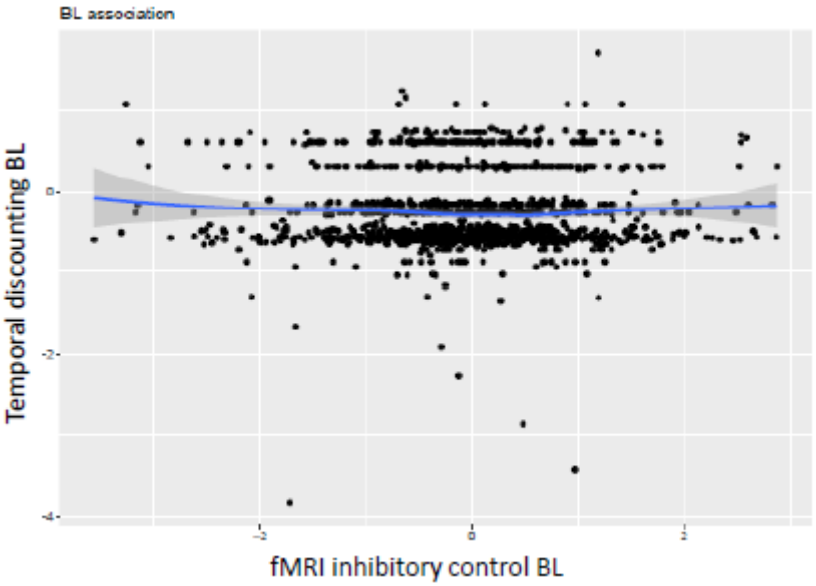

Fig. S15. Relationship between fMRI inhibitory control activity and temporal discounting in adolescence; extreme values excluded; p=0.765.

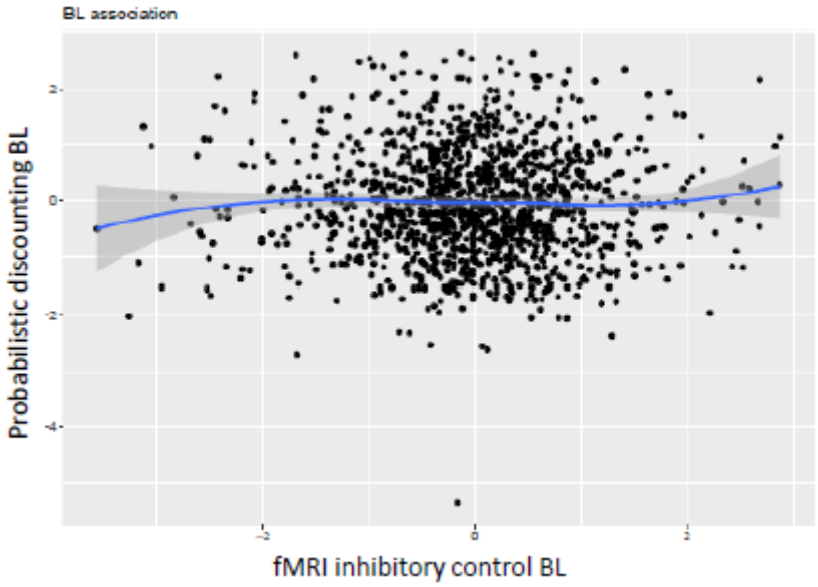

Fig. S16. Relationship between fMRI inhibitory control activity and probabilistic discounting in adolescence; extreme values excluded; p=0.163.

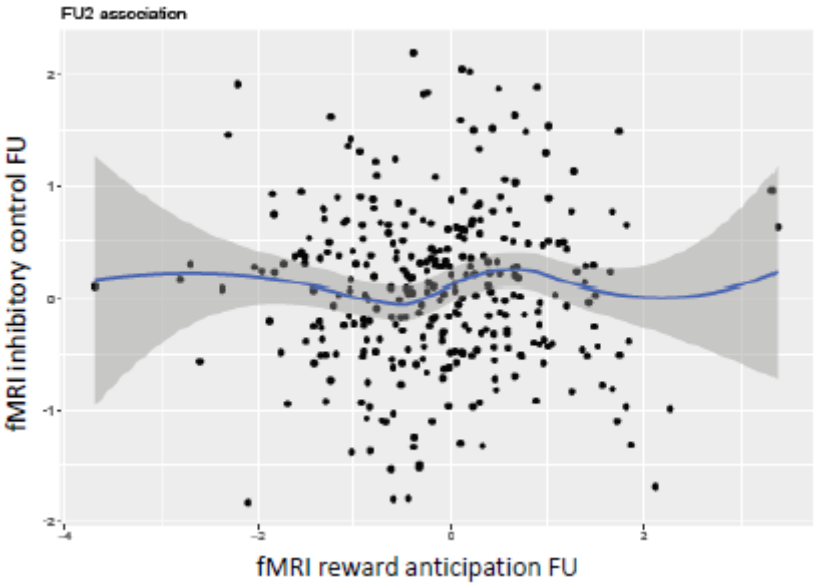

Fig. S17. Relationship between fMRI reward anticipation and fMRI inhibitory control activity in young adulthood; extreme values excluded; p=0.739.

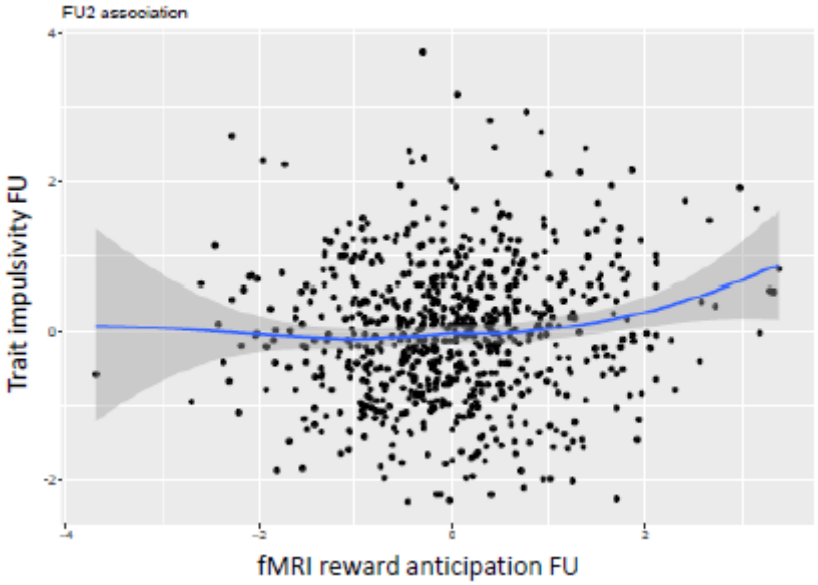

Fig. S18. Relationship between fMRI reward anticipation activity and trait impulsivity in young adulthood; extreme values excluded; *p*=0.073.

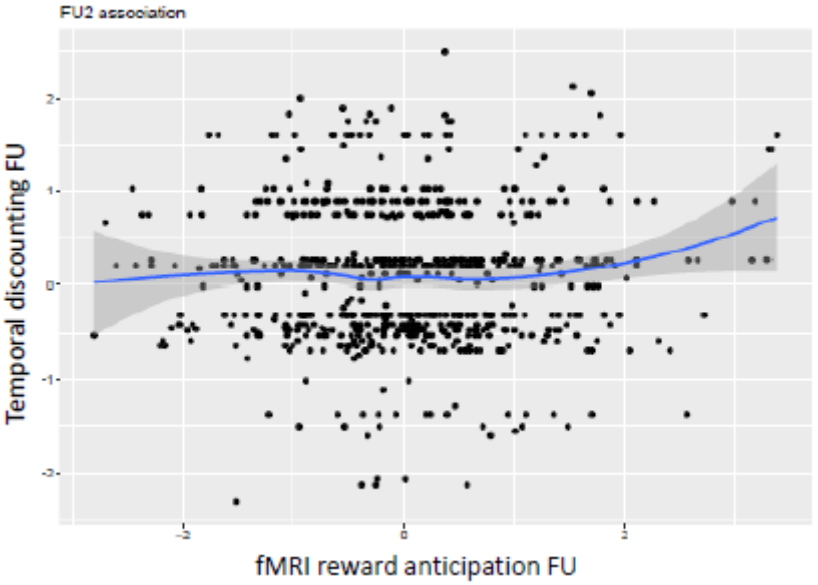

Fig. S19. Relationship between fMRI reward anticipation activity and temporal discounting in young adulthood; extreme values excluded; *p*=0.766.

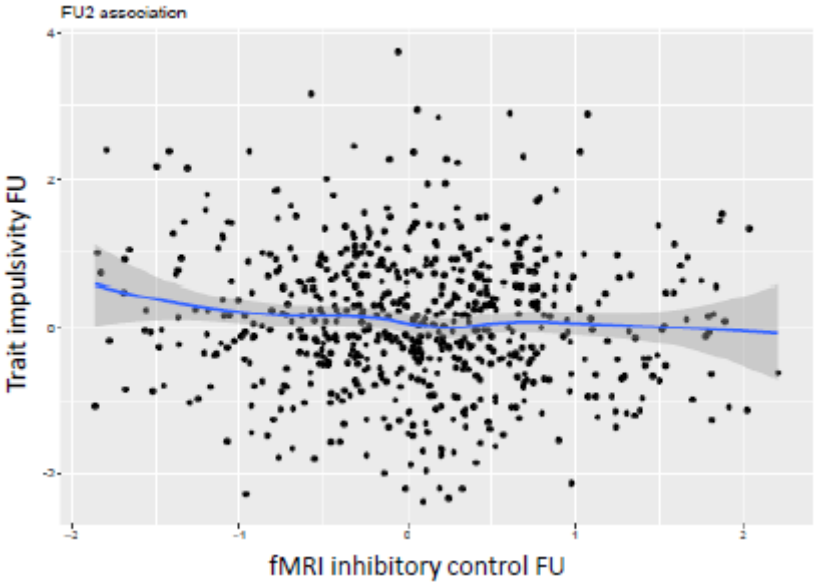

Fig. S20. Relationship between fMRI inhibitory control activity and trait impulsivity in young adulthood; extreme values excluded; p=0.026.

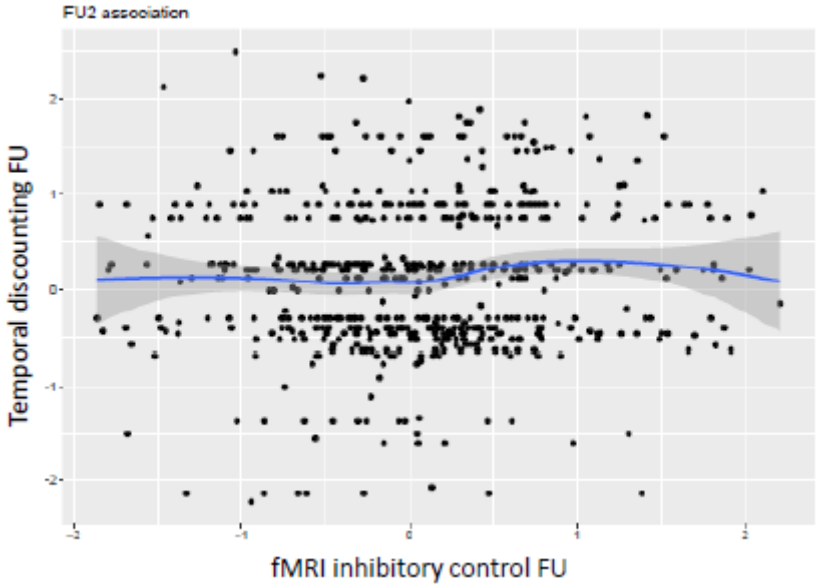

Fig. S21. Relationship between fMRI inhibitory control activity and temporal discounting in young adulthood; extreme values excluded; p=0.235.

Supplement G

Plots of residuals and plots of random effects for mixed-effects models addressing changes in brain responsivity-impulsivity relationships

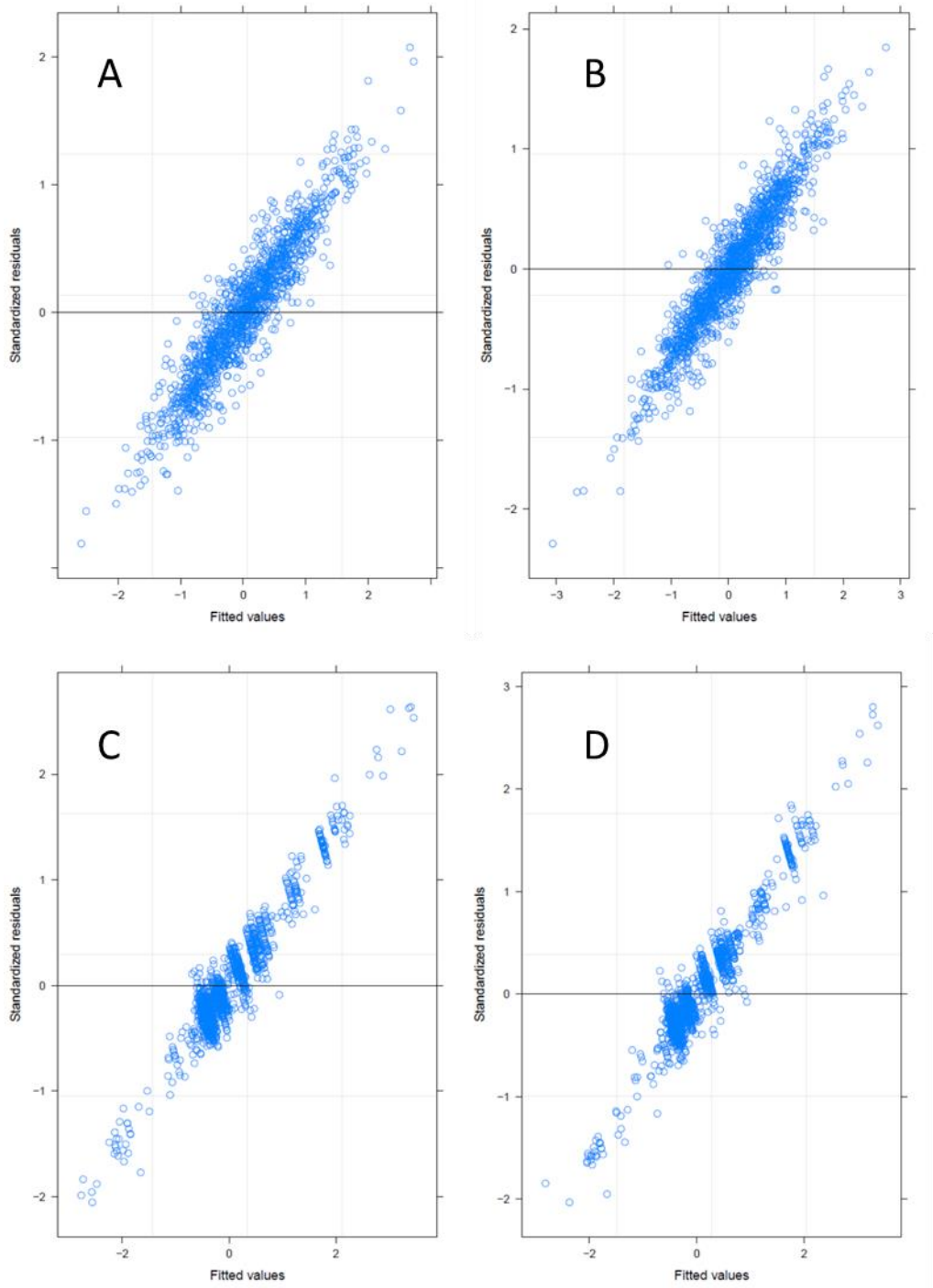

Fig. S22. Plots of residuals for mixed-effects models: change in brain responsivity-impulsivity relationships from baseline to follow-up. *Note.* A - changes in association between trait impulsivity and reward anticipation; B - changes in association between trait impulsivity and inhibitory control; C - changes in association between temporal discounting and reward anticipation; D - changes in association between temporal discounting and inhibitory control.

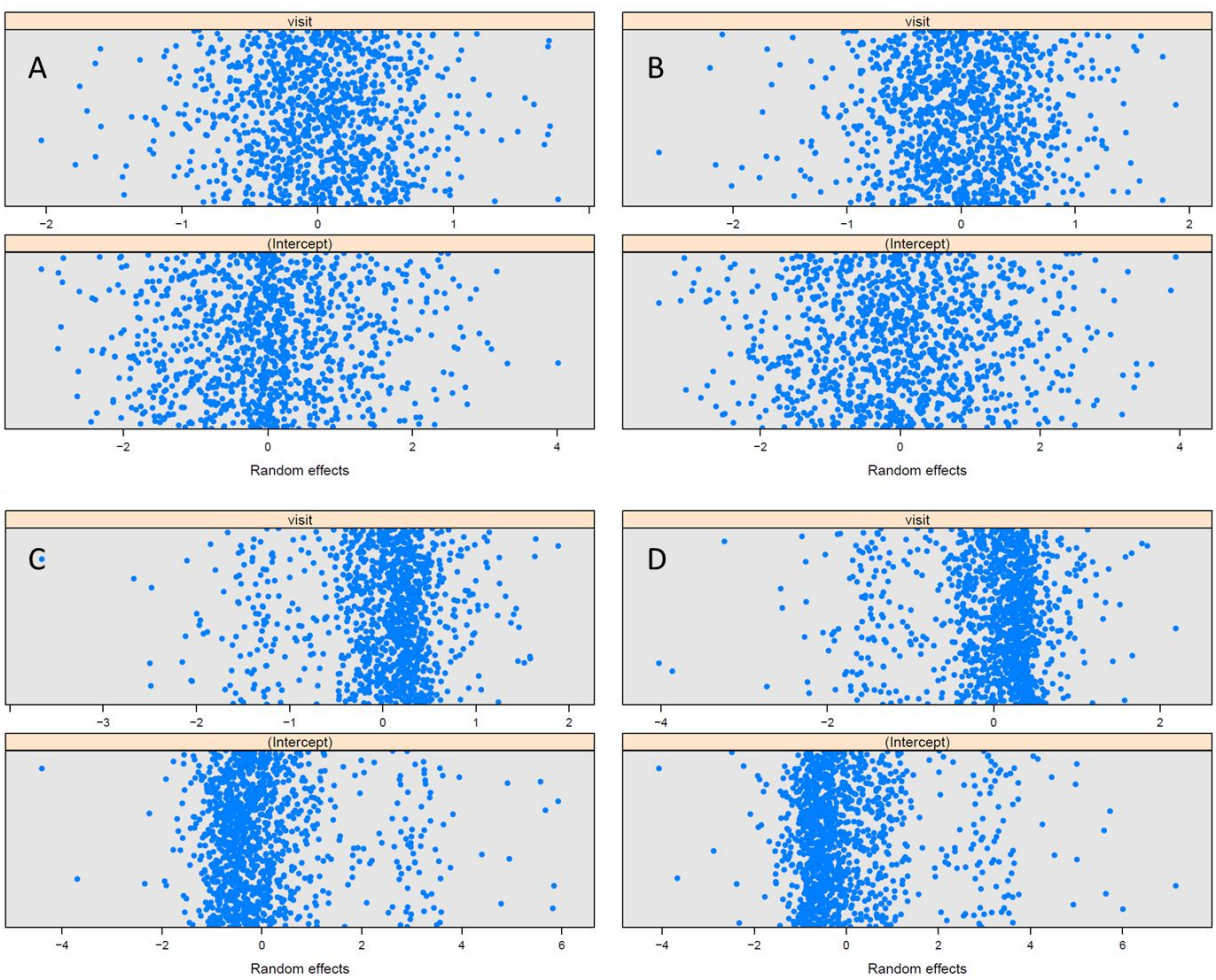

Fig. S23. Plots of random effects for visit in mixed-effects models: change in brain responsivity-impulsivity relationships from baseline to follow-up. *Note.* A - changes in association between trait impulsivity and reward anticipation; B - changes in association between trait impulsivity and inhibitory control; C - changes in association between temporal discounting and reward anticipation; D - changes in association between temporal discounting and inhibitory control.

Appendix H

Post-hoc analyses

Significant correlations were obtained for the latent dimensions of impulsivity (trait impulsivity: $r_{partial}$=.334, p<.001; temporal discounting: $r_{partial}$=.148, p<.001). Non-significant associations were found for fMRI data (reward anticipation: $r_{partial}$=.030, *n.s.*; inhibitory control: $r_{partial}$=.078, *n.s.*) indicating substantial developmental changes in neural processing from adolescence to young adulthood. Figure S24 below presents plots of changes for latent constructs of interest from adolescence to young adulthood on an individual level.

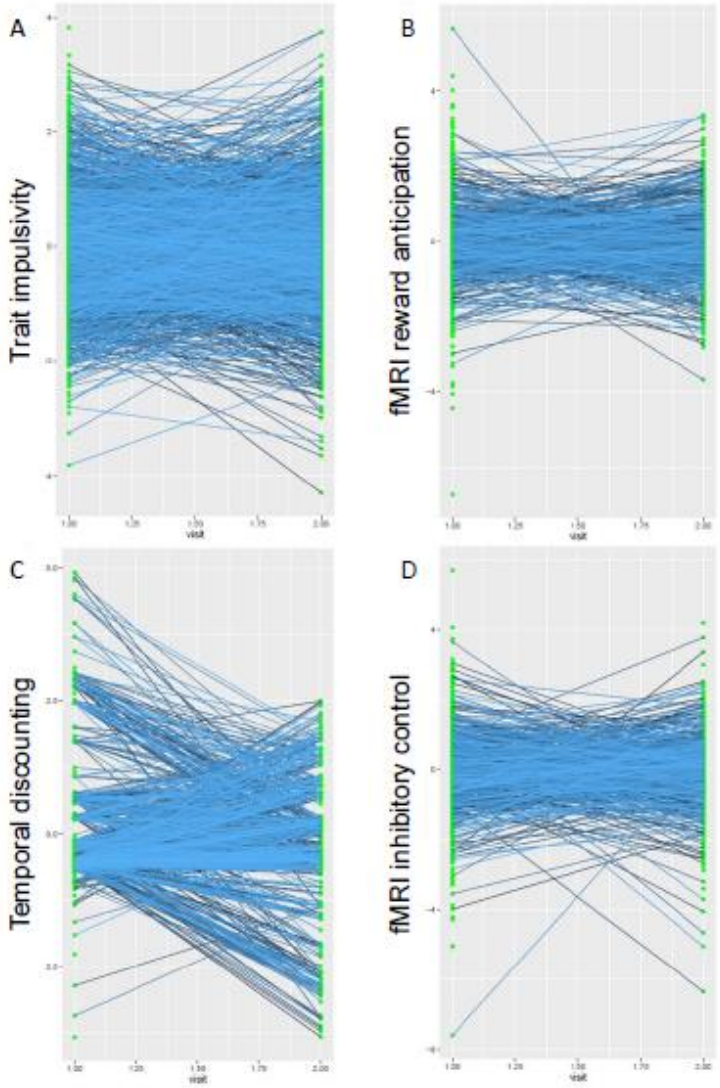

Fig. S24. Plots of changes for latent constructs of interest from baseline to follow-up. *Note.* A - trait impulsivity; B - fMRI reward anticipation activity; C – temporal discounting; D - fMRI inhibitory control activity.

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7 CURRICULUM VITAE AND PUBLICATIONS

Curriculum Vitae

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- Multimodal characterization of brain function using electroencephalography/event-related potentials (EEG/ERPs), magnetoencephalography (MEG), and (functional) magnetic-resonance imaging ((f)MRI)
- Non-pharmacological, regulation-based therapy options targeting neuromodulation (neurofeedback, slow-cortical potentials (SCP)-training)

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09/2011 – 08/2014	**University of Mannheim** Bachelor of Science (B. Sc.) psychology (grade: 1.6; date: 2nd of July 2014)
09/2003 – 05/2011	**St. Raphael Gymnasium**, Heidelberg Secondary school, Abitur/Hochschulzugangsberechtigung (grade: 1.3, date: 30th of May 2011)

Publication list

First author:

Kaiser, A., Aggensteiner, P. M., Baumeister, S., Holz, N. E., Banaschewski, T., & Brandeis, D. (2020). Earlier versus later cognitive event-related potentials (ERPs) in Attention-Deficit/Hyperactivity Disorder (ADHD): A meta-analysis. *Neuroscience & Biobehavioral Reviews, 112*, 117-134. doi:10.1016/j.neubiorev.2020.01.019

Kaiser, A., Aggensteiner, P.-M., Holtmann, M., Fallgatter, A., Romanos, M., Abenova, K., Alm, B., Becker, K., Döpfner, M., Ethofer, T., Freitag, C. M., Geissler, J., Hebebrand, J., Huss, M., Jans, T., Jendreizik, L. T., Ketter, J., Legenbauer, T., Philipsen, A., Poustka, L., Renner, T., Retz, W., Rösler, M., Thome, J., Uebel-von Sandersleben, H., von Wirth, E., Zinnow, T., Hohmann, S, Millenet, S., Holz, N. E., Banaschewski, T., Brandeis, D., and the ESCAlife-consortium (2021). EEG Data quality: Determinants and impact in a multicenter study of children, adolescents, and adults with Attention-Deficit/Hyperactivity Disorder (ADHD). *Brain Sciences, 11*(2), 214. doi: 10.3390/brainsci11020214

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Co-author:

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8 ACKNOWLEDGMENTS (DANKSAGUNGEN)

Da eine solche Arbeit nur mit der Unterstützung anderer Menschen entstehen kann, gibt es eine ganze Reihe von Personen, denen ich gerne danken möchte.

Allen voran möchte ich mich bei meinen Professoren Dr. Daniel Brandeis und Dr. Dr. Tobias Banaschewski bedanken, die eine Entstehung dieser Arbeit überhaupt erst möglich gemacht haben und deren Rat und Unterstützung ich mir zu jedem Zeitpunkt sicher sein konnte. Außerdem möchte ich Prof. Dr. Frauke Nees danken, die dazu beigetragen hat, dass noch ein weiteres Paper in diese Dissertation Eingang finden konnte.

Weiterhin möchte ich meinen wundervollen Kollegen aus den Arbeitsgruppen Klinische Neurophysiologie des Kindes- und Jugendalters und Entwicklungsneurowissenschaften in der Psychiatrie danken: Dr. Nathalie E. Holz, Dr. Sarah Baumeister, Dr. Pascal-M. Aggensteiner, Max Monninger und Tania Pollok, auf deren Beistand ich mich immer verlassen konnte und die mir ein tolles und motivierendes Arbeitsklima geschaffen haben. Ein ganz besonderes Dankeschön geht natürlich auch an Sibylle Heinzel, die mit ihrer positiven, ehrlichen und direkten Art in jeder Lebenslage – beruflich wie privat – genau die richtigen Worte findet. Außerdem gilt mein Dank Dr. Sabina Millenet, Brigitta Gehrig, Matthias Winkler, Karina Abenova, Mirjam Ziegler und den anderen lieben Mädels aus der Arbeitsgruppe Aufmerksamkeits-Defizit/Hyperaktivitätsstörung des Kindes- und Jugendalters. Ein großes Dankeschön geht natürlich auch an alle Studienteilnehmenden - ohne die ich keine Grundlage für mein Arbeiten gehabt hätte.

Ich danke selbstverständlich auch meinen Freunden. Besonders danken möchte ich meinen Mädels, Maren, Kira, Svenja und Cathi – dafür, dass ihr mich in regelmäßigen Abständen aus meiner Komfortzone lockt und mich anschließend genau wieder dorthin zurück bringt. Und natürlich danke ich Julia, die mich schon mein Leben lang begleitet, für ihre Ehrlichkeit und Offenheit und dafür, dass sie mir so oft eine ganz andere Perspektive gibt.

Ein besonderes Dankeschön geht an meinen Freund Matthias, dafür, dass er immer an meiner Seite ist und ich mich immer auf ihn verlassen kann.

Mein größter Dank geht natürlich an meine Eltern. Ich danke meinem Papa, für seine ewige Energie und Ausdauer, wodurch auch mein Engagement angeregt wird; und ich danke Ute, die hier eine Balance schafft, und immer wieder die ruhigen und entspannten Seiten des Lebens betont. Bernd danke ich für seine Neugier und dafür, dass er mich immer wieder aufs Neue herausfordert und damit anspornt. Meiner Mama danke ich für ihr Verständnis und ihr Feingefühl, sich in mich und andere hineinzuversetzen, die richtigen Worte zu finden und einem das Gefühl zu geben, dass immer alles gut wird. Ihr alle schafft es so, mir stets den Rücken freizuhalten und das Leben leichter zu machen. Danke, dass ihr immer für mich da seid!

Zuletzt geht mein innigster Dank an meine Großeltern. Ich danke meinem Opa für sein Interesse an mir und an der Welt um uns herum, das mir viele Türen geöffnet hat. Und meiner Oma für ganz viel Mut und die Selbstsicherheit, auch in schwierigen Lebenslagen immer an mich und das, was ich tue, zu glauben. Ich habe euch immer bei mir – „reich mir die Hand, mein Leben“ (Oper *Don Giovanni*, Wolfgang Amadeus Mozart; deutscher Verleihtitel des österreichischen Films *Mozart* von 1955).