Executive functions and ERP biomarkers in children and adolescents with ADHD and Autism

Linda Angelica Häger Krabberød

Gillberg Neuropsychiatry Centre
Institute of Neuroscience and Physiology
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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linda.angelica.hager@gu.se

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ABSTRACT

Executive Functions (EF) refer to skills that help us initiate, organize and evaluate activities. Problems with EF are associated with neurodevelopmental disorders such as Attention Deficit Hyperactivity Disorder (ADHD) and autism spectrum disorder (ASD). In the present project, we use parent ratings, scores from an attention test (a cued visual continuous performance test [VCPT]) and Event Related Potentials (ERPs) to examine EF. The **overarching aim** of this thesis has been to learn more about the underlying neurocognitive bases of ADHD, ASD, EF, and to explore the possibilities of using ERPs and VCPT scores as supplementary diagnostic tools. **In study 1**, we studied correlations of d*i*fferent measures of EF in 59 ADHD patients. We found that the correlations between the EF measures were different among children (9-12 years) and adolescents (13-17 years), indicating developmental dynamics. The overall conclusion of the study was that the different measures of EF are complementary, each contributing unique knowledge. **In study 2**, the goal was to develop and evaluate a diagnostic ADHD index by combining data from ERP assessments and scores from the VCPT. Initially, sixty-one children with ADHD and 69 "typically developing children" (TDC) participated. The calculated index discriminated between the ADHD and the TDC groups with a large effect size (d=1.47). In a replication sample, d was 3.03. **In study 3**, we compared ERPs and test scores for 63 adolescents with ASD and 60 TDC. We found no significant group differences in behavioral test scores. However, several visual ERP components differed with largest difference seen in ERP component Visual Negativity (vN) which is assumed to reflect visual preparation. This finding is in accordance with theories claiming that predictive mechanisms are altered in ASD. **Study 4** was a comprehensive case study of a boy with ADHD, mathematical disability and nonverbal learning disability, illustrating how clinical information from several methods, including EPR-data, can be integrated. **In summary,** it is argued that ERPs can contribute to diagnostic conclusions and increased understanding of EF problems related to ADHD and ASD.

Keywords: Supplementary biomarkers, child psychiatry, ADHD, autism, executive function, neuropsychological tests, event related potentials, EEG

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SAMMANFATTNING PÅ SVENSKA

Förekomsten av ADHD bland barn och unga uppges vara 3-7 %, och för autism ca. 1%. Kunskapen om de neuropsykologiska nedsättningarna vid ADHD och autism är fortfarande relativt begränsad och det finns ett behov av att komplettera befintliga diagnostiska metoder med mer objektiva data. Vid både ADHD och autism är exekutiva funktioner (EF) ofta nedsatta. EF är en samlingsbeteckning för övergripande psykologiska regleringsfunktioner vilka omfattar bland annat planering, organisation, fokusering, inhibering och monitorering. EF har stor inverkan på individens funktion i vardagen och är därför ett viktigt område för insatser när det gäller stöd.

Vid kartläggning av EF är det vanligt att använda frågeformulär och/eller neuropsykologiska tester. En tredje metod, som främst används inom forskning, är kognitiva ”event-related potentials” (ERP). ERP baseras på avläsning av hjärnans elektriska aktivitet (EEG) under tiden en person arbetar med olika uppgifter. Genom speciella tekniker kan information erhållas som visar hur hjärnan bearbetar information i olika faser av en uppgift. Det kan handla om att registrera stimuli, tolka dessa, förbereda ett svar, svara eller inhibera en sådan plan, beroende på vilka stimuli som uppstår i testet. Trots att metoden har en begränsad förmåga att med säkerhet lokalisera var i hjärnan de olika ERP-komponenterna genereras, har ERP-metoderna en styrka genom att de kan användas för att studera sensoriska, perceptuella och kognitiva händelser i hjärnan på en millisekundsskala. Detta är en av få metoder där det är möjligt att studera hjärnans aktivitet samtidigt som man utför uppgifter.

Det övergripande syftet med denna avhandling har varit att utveckla ny kunskap om den underliggande neurokognitiva basen för ADHD, autism, EF, och att utpröva möjligheten att använda ERP:er och neuropsykologiska testpoäng (ett så kallad VCPT [visual continuous performance test]) som kompletterande diagnostiska instrument. Tillsammans med mina handledare och andra kollegor har fyra delstudier genomförts.

I studie 1 studerade vi associationerna mellan olika mått på EF (skattningar, VCPT poäng och ERP:er) hos 59 ADHD-patienter. Vi fann att korrelationerna mellan EF-måtten var olika bland barn (9-12 år) och ungdomar (13-17 år), vilket tyder på att associationerna mellan dessa mått kan variera med utveckling. Den övergripande slutsatsen av studien var att föräldraskattningar, testpoäng från VCPT och kognitiva ERP:er kompletterar varandra, och att var och en bidrar med potentiellt unik information.

I studie 2 var syftet att utveckla och utvärdera ett diagnostiskt ADHD-index genom att kombinera data från ERP-bedömningar och poäng från det neuropsykologiskt test. I en utprövningsstudie deltog 61 barn med ADHD och 69 "typiskt utvecklande barn" (TUB). Det beräknade indexet diskriminerade mellan ADHD- och TUB-grupperna med en stor effektstorlek (d=1,47). I en replikationsstudie (20 ADHD, 21 TDC) var d 3,03.

I studie 3 jämförde vi ERP och testresultat för 63 ungdomar med autism och 60 TUB. Vi hittade inga signifikanta skillnader i resultat på VCPT. Vi fann dock att flera visuella ERP-komponenter skilde sig signifikant mellan grupperna, där amplituderna var mindre hos autismgruppen. Den största skillnaden sågs i en ERP-komponent som kallas Visual Negativity (vN) som antas spegla visuell förberedelse/förutsägelse. Detta fynd ligger i linje med teorier som säger att i synnerhet top-down, prediktionsmekanismer är annorlunda i autism.

Studie 4 var en fallstudie av en pojke med ADHD, matematiksvårigheter funktionsnedsättning och icke-verbala inlärningssvårigheter som illustrerar hur klinisk information från flera metoder, inklusive EPR-data, kan integreras vid diagnostiska överväganden. Bland annat användes det diagnostiska ADHD-indexet som utvecklades i studie 2 och vi fann att pojken hade ett högt indexpoäng. Vi fann också att en ERP-komponent som kallas Cue P3-komponenten var väldigt svag hos den här pojken. Cue P3 antas spegla "visuell identifiering" och kan möjligen ses som en markör för icke-verbala inlärningssvårigheter och räknesvårigheter, vilket behöver studeras mer systematiskt i fortsatt forskning.

Sammanfattningsvis visar avhandlingen att ERP och testresultat från VCPT kan bidra till diagnostiska slutsatser och ökad förståelse för exekutiva problem relaterade till ADHD och autism.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Häger, L. A., Øgrim, G., Danielsen, M., Billstedt, E., Gillberg, C., & Johnels, J. Å. (2020). Indexing Executive Functions with Test Scores, Parent Ratings and ERPs: How Do the Measures Relate in Children versus Adolescents with ADHD? *Neuropsychiatric Disease and Treatment*, *16*, 465.

II Häger, L. A., Johnels, J. Å., Kropotov, J. D., Weidle, B., Hollup, S., Zehentbauer, P. G. & Øgrim, G. (2021). Biomarker support for ADHD diagnosis based on Event-Related Potentials and scores from an attention test. *Psychiatry Research*, *300*, 113879.

III. Häger L.A, Høyland Anne L. Kropotov J.D., Åsberg Johnels J., Weidle B., Hollup S., Øgrim G. (submitted 2023). Is visual prediction impaired in adolescents with autism spectrum disorder? Event-Related Potentials in a cued visual GO/NOGO task.

IV. Åsberg Johnels, J, Häger, L., Billstedt, E., Hagberg, B., Øgrim, G & Gillberg, C. (manuscript). Integrating psychoeducational and EEG-based data in neurodevelopmental assessment: Case study of a child with attentional, mathematical and nonverbal learning difficulties.

CONTENTS

ABBREVIATIONS

ADHD	Attention-Deficit/Hyperactivity Disorder
ASD	Autism Spectrum Disorder
CNV	Contingent Negative Variation
CPT	Continuous Performance Tests
ICA	Independent Component Analysis
BRIEF	Behavior Rating Inventory of Executive Functions
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE)
LD	Learning disabilities
EC	Effortful Control
EEG	Electroencephalography
EF	Executive Function
fMRI	Functional magnetic resonance imaging
GNC	Gillberg Neuropsychiatry Centre
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, Third Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

ICD-8	International statistical Classification of Diseases and Related Health Problems, 8th revision
ICD-9	International statistical Classification of Diseases and Related Health Problems, 9th revision
ICD-10	International statistical Classification of Diseases and Related Health Problems, 10th revision
IQ	Intelligence Quotient
GEC	Global Executive Composite
MEG	Magnetoencephalography
ODD	Oppositional Defiant Disorder
QEEG	Quantitative Electroencephalogram
SAS	Supervisory Attention System
VCPT	Visual Continuous Performance Test
ERP	Event-Related Potentials
TDC	Typically Developing Children
Vn	Visual Negativity
WISC-IV	Wechsler Scales of Intelligence (WISC) version IV
RT	Reaction time
ROC	Receiver Operating Characteristic
GAF	Grand-Average Files

1 INTRODUCTION

1.1 CLINICAL CHARACTERISTICS, DIAGNOSTIC CRITERIA AND PREVALENCE OF ADHD

Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by impairing problems with attention, hyperactivity and impulsivity. In school-aged children, the prevalence of ADHD is approximately 3–7% (Kessler et al., 2006; Willcutt, 2012) and is relatively consistent across class, culture and ethnic groups (Polanczyk et al., 2007). One of the first scientific descriptions of ADHD-like symptoms (attention and hyperactivity/impulsivity) was presented by Still (1902). A total of twenty children from his clinic were described as having deficits in inhibition and moral control. Since then, diagnostic names have changed and criteria have been developed and revised several times (Barkley, 1997). The term ADHD is used in DSM-IV (1994) and DSM-V (American Psychiatric, 2013). In DSM-5, the ADHD diagnosis was moved from the category of disruptive behaviour to the neurodevelopmental disorder category. In the DSM-V the clinician also needs to classify the symptoms as mild, moderate or severe.

In the DSM-V, there were slight revisions made concerning age of onset (from prior to 7 to prior to 12). Also, the number of symptoms necessary in older adolescents and adults were reduced according to the notion that older individuals with ADHD do not necessarily present with all symptoms, although still live with impairment (Association, 2010; Cortese & Coghill, 2018).

Boys, more of often than girls, are referred clinically with a ratio of approx. 3:1. This could highlight questions if a higher number of girls with ADHD remain undiagnosed (Young et al., 2020). It is still quite unclear whether there are differences between boys and girls with ADHD in terms of course and long-term prognosis (Greven et al., 2018).

According to the DSM-5, ADHD has three presentations. The *combined presentation* has 6 or more symptoms of hyperactivity /impulsivity and 6 or more symptoms of inattention from a list of 9 symptoms in each category. The *predominantly inattentive presentation* requires 6 or more symptoms of

inattention, and less than 6 symptoms hyperactivity/impulsivity. For people over 17 years, 5 symptoms from each category are required. The *hyperactive /impulsive presentation* presents with 6 or more symptoms of hyperactivity/impulsivity, but less than 6 symptoms of inattention. It is not uncommon to change presentation throughout a lifespan. For this reason, the DSM-IV term "subtype" of ADHD was replaced by "presentation". The symptoms of ADHD are presented in the table below.

Table 1: ADHD Symptoms

Symptoms of inattention
- Fails to give close attention to details or makes careless mistakes
- Has difficulty sustaining attention
- Does not appear to listen
- Struggles to follow through on instructions
- Has difficulty with organisation
- Avoids or dislikes tasks requiring a lot of thinking
- Loses things
- Is easily distracted
- Is forgetful in daily activities
Symptoms of hyperactivity/impulsivity
- Fidgets with hands or feet or squirms in chair
- Has difficulty remaining seated
- Runs about or climbs excessively in children/extreme restlessness in adults
- Difficulty in engaging in activities quietly
- Acts as if driven by a motor

- Talks excessively

- Difficulty waiting or taking turns

Studies have confirmed that ADHD runs in families (Deater-Deckard, 2017) and twin and adoption studies have concluded that this is to a large extent (at least 70%) due to genetic liabilities shared in families (Faraone & Larsson, 2019). Environmental factors are believed to account for about 10-30% of the variance, although causal relationships with such environmental factors have been shown difficult to prove (e.g., prematurity, maternal smoking), since such factors can in themselves be "caused" by genetic ADHD liability (Sciberras et al., 2017).

The symptoms of ADHD are not completely specific for the diagnosis, and diagnosing can therefore sometimes be challenging. For instance, the symptom "forgetfulness in everyday activities" may be common not only in ADHD, but also in people with learning difficulties, depression, or sleep problems. Assessment of ADHD is based on clinical interviews, rating scales, observations and developmental history. Medical examinations are carried out to exclude somatic etiologies such as metabolic and neurological disorders. Reale et al. found that in an ADHD population, 34% had ADHD only, whereas 66% had at least one additional comorbid psychiatric diagnosis (sleep disorders, learning disorders, anxiety disorders and oppositional defiant disorder (ODD) (Reale et al., 2017). Similarly, Gillberg et al. summarized research that ADHD has a very high frequency of coexistence with other child neuropsychiatric/neurodevelopmental disorders (Gillberg et al., 2004; Kadesjö & Gillberg, 2001).

The symptoms of ADHD very often lead to significant impairments in different domains of life, including in school performance, family life and social relationships (e.g., Frazier et al., 2007; Ros & Graziano, 2018). Diagnosis and treatment as early as possible have shown to be beneficial, and is believed to reduce the high burden of ADHD throughout life (Sonuga-Barke et al., 2011). Currently, in terms of intervention, psychoeducational support is of paramount importance. In Norway, about 80% of children and adolescents diagnosed with ADHD try stimulant medication, mainly composed of Methylphenidate or Dextroamphetamine (Rajeh et al., 2017). These medications seem to be helpful in about 70% of the cases for reducing symptom load and increasing adaptive functioning in everyday life (Aasen et al., 2018; Johnson et al., 2021; Lichtenstein et al., 2012; Miklós et al., 2019).

1.2 CLINICAL CHARACTERISTICS, DIAGNOSTIC CRITERIA AND PREVALENCE OF AUTISM

Autism Spectrum Disorder (ASD) is characterised by marked problems in the development of social relations and communication, accompanied by restricted and repetitive interests and behaviours (Mirkovic & Gérardin, 2019). In 1943, Leo Kanner presented one of the first descriptions of "infantile autism". The case series described 11 children that had severe problems in social interaction, a strong insistence on sameness and a reluctance to change. Kanner's descriptions also included echolalia, pronoun reversal and unusual prosody (Rosen et al., 2021). In 1944, Hans Asperger described a group of boys with unusually intense special interests, significant social difficulties and with strong verbal skills (Hosseini & Molla, 2022). In the early diagnostic manuals, e.g. DSM-I (1952), autistic behaviour was classified as childhood schizophrenia (Kita & Hosokawa, 2011) whereas from DSM-III and ICD-8 onwards described autism as a developmental disorder. The association to schizophrenia most probably originated from Kanner's description and the use of the word autism, which means "self-centred thinking" and reminds us of Eugen Bleuler's description of schizophrenia (Moskowitz & Heim, 2011). In ICD-10 (1999), Asperger syndrome was a defined category, but in 2013 was removed from the DSM-5 (along with other subtypes of autism) – thus, there is currently only one diagnosis that is formally coded: Autism Spectrum Disorder (ASD). In the diagnostic process, the clinician must specify intellectual impairment, language impairment and if the ASD diagnosis is associated with a known medical or genetic condition (Volkmar & McPartland, 2014). The severity level is also specified on a scale of 1 to 3, where level 3 means considerable need of support. The classical triad of symptoms (Wing 1979) (Leekam et al., 2002; Leekam et al., 2007) in DSM-5 is reduced to two symptoms categories – social communication/interaction and restrictive repetitive behaviour (American Psychiatric, 2013). Assessment of ASD is, like ADHD, based on clinical interviews, rating scales, observations and developmental history. Medical examinations are carried out and there is often a high rate of comorbid problems, somatic, cognitive and psychiatric, that need medical attention and treatment, such as epilepsy (Gillberg, 2010). Table 2 presents the diagnostic criteria.

DSM-5 AUTISM DIAGNOSTIC CRITERIA

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive, see text):

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity: Severity is based on social communication impairments and restricted repetitive patterns of behavior. (See table below.)

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g, strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior. (See table below.)

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if:

- **With or without accompanying intellectual impairment**
- **With or without accompanying language impairment**
    - (Coding note: Use additional code to identify the associated medical or genetic condition.)
- **Associated with another neurodevelopmental, mental, or behavioral disorder**
    - (Coding note: Use additional code[s] to identify the associated neurodevelopmental, mental, or behavioral disorder[s].)
- **With catatonia**
- **Associated with a known medical or genetic condition or environmental factor**

(American Psychiatric, 2013).

The prevalence of ASD is thought to be 0.5% to 1.5% in the childhood population (Atladottir et al., 2015; Baird et al., 2006; Fombonne, 2009; Lai et al., 2014; Nydén et al., 1999; Nygren et al., 2012). The importance of early diagnosis has been emphasized in the literature (Baird et al., 2003; Johnson & Myers, 2007; Lai et al., 2019). Furthermore, research has shown that the

prevalence of autism has increased, and the meaning and causes of this rise is a topic of research and much discussion (Arvidsson et al., 2018; Gillberg et al., 2006).

In most cases, ASD affects quality of life and adaptive skills (Bishop-Fitzpatrick et al., 2016; Meyer et al., 2018). There are no available medications for the core symptoms of ASD; instead, treatment lies in adapting the environment and communication to the person's specific challenges and needs. Psychoeducational support for parent and school is of paramount importance.

1.3 ESSENCE

ADHD and ASD are developmental disorders, changing in expression during the lifespan, although symptoms usually persist into adulthood. There is a considerable comorbidity between autism and ADHD. Studies show that 30-80% of individuals with ASD also have ADHD (Lau-Zhu et al., 2019) and 20-50% of the ADHD population also present with ASD or marked traits thereof (van der Meer et al., 2012). Thus, it is also common that there are symptoms of the other disorder, but below the threshold for a full diagnosis (Gillberg, 2010; Ronald et al., 2014). In addition, other "comorbid" disorders (specific learning disabilities such as dyslexia or dyscalculia, borderline intellectual functioning or intellectual disability, motor coordination problems, anxiety, depression, eating disorders, tic disorders, etc.) are rather the rule than the exception in ADHD and autism - which is illustrated by the concept of ESSENCE coined by Christopher Gillberg (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) (Gillberg, 2010). ESSENCE means that the presence of one neurodevelopmental condition often signals that there are other coexisting neurodevelopmental conditions or symptoms, a fact with important consequences for research, diagnostic procedures and for the organization of healthcare and systems of support provision. The symptoms of atypical brain development manifest early in life and often lead to a neuropsychiatric/neurodevelopmental evaluation of some sort, and the need for support throughout life might change but is unlikely to completely go away.

1.4 BIOMARKERS IN PSYCHIATRY

In somatic medicine, biomarkers are often used as criteria for diagnosis and/or treatment selection. In psychiatry, there has been a long search for possible biomarkers (Rush & Ibrahim, 2018). A biomarker can be a chemical,

biological, genetical, physical, physiological, cognitive, or psychological measure (Page et al., 2018). Biomarkers in psychiatry may be potentially helpful for supplementing behaviorally based diagnostic practices, predicting medication response as well as long term prediction (Faraone & Larsson, 2019). In addition, biomarkers based on measures of brain function, such as EEG and ERPs, could also eventually lead to a subtyping that is more closely related to prognoses and treatment selection. As for now, there are no agreed upon, stable biomarkers for psychiatric conditions (Scarr et al., 2015), but there is an ongoing research, with more focus on identifying biotypes (groups within the group) or bio-correlates of symptomatic dimensions (Drysdale et al., 2017). The heterogeneity within the psychiatric diagnostic categories complicates this search. Some benchmarks have been developed for biomarker evaluation, that is, in order to qualify as a biomarker it should be reliable, specific, sensitive, reproducible, validated across independent data sets and clinically relevant (Drucker & Krapfenbauer, 2013; Kim et al., 2020; Kim et al., 2019).

According to Faraone and Larsson (2019), however, the neural and biological mechanisms behind behaviorally defined symptoms like impulsivity, inattention, sensory sensitivity, or communication problems may differ from person to person, which reduces the likelihood for finding biomarkers closely related to behavior. Arguably, the likelihood for finding biomarkers that are specific for one diagnosis, and sensitive across all individuals within that diagnostic category, is therefore small. At the same time, the benefits of trying to isolate biomarkers are potentially helpful for diagnosing, predicting medication response and long term prediction (Faraone & Larsson, 2019). In this thesis we argue that *combining* biomarkers that discriminate significantly between groups with at least a moderate effect size into a diagnostic index score can be a clinically useful supplement in formal diagnostic procedures.

1.5 EXECUTIVE FUNCTION

Executive function (EF) is a neurocognitive term for a set of separate, but interrelated, cognitive skills, including focusing, working memory, inhibition, planning, monitoring, and attentional flexibility. It is a set of abilities that can guide human behaviour toward goals. Luria (1973) described three frontal processes that exist in behaviour towards a goal: programming, regulating and verifying (Ashbrook, 1984). As a concept, EF was first introduced in 1973 by Pribram, Baddely and Hitch (Pribram & Luria, 2013), and later specified by Lezak (Lezak, 1982).

Patients with acquired brain damage to the frontal lobes usually show impaired EF. There is a close relationship between attention and EF. To avoid overstimulation in the brain, attention filters and selects information (Lachter et al., 2004). There are several theoretical models of EF and EF development (Davidson et al., 2006; Diamond, 2006; Hughes, 2002). In an early, still influential, theoretical framework, Norman and Shallice described the importance of attention for action control (Norman & Shallice, 1986). They distinguished between two systems: contention scheduling and the supervisory attention system (SAS). The first system is responsible for routine behaviours where minimal attention is needed, whereas the SAS system can override automatic responses, and create new schemas in novel situations where flexibility is needed. Building on this account, it has been shown that certain parts of the brain, including lateral prefrontal cortex, are crucial for learning something new, or when acting strategically and flexibly in novel tasks and environments is needed (Duncan & Owen, 2000). During well-known activities, the top-down EF control is not always necessary for efficient action and may indeed be hindering (Chein & Schneider, 2005; H. Garavan et al., 1999; Roepstorff & Frith, 2004). In a recent account of EF (Doebel, 2020), the development of EF is best understood as the emergence of skills "in using control in the service of specific goals" (p 1). It has been shown that EF development takes place over a long period of time. Taking different aspect into account when forming goal-based actions is indeed challenging throughout life (See fig 1). At the individual level, EF is considered to be developing up until the early 20s (Anderson, 2002).

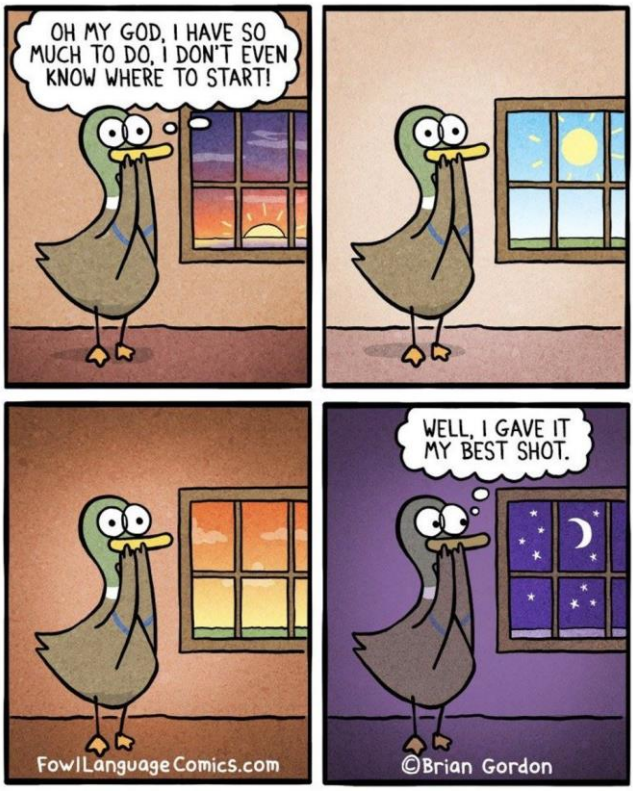

Figure 1: printed with kind permission from Brian Gordon; followlanguagecomics.com

1.6 NEUROPSYCHOLOGICAL TESTS AND RATINGS OF EF

Assessment of EF is often carried out in clinics, since it has been shown that EF is known to be related to academic and occupational achievement. Indeed, EF can be a target for intervention (Biederman et al., 2004; Biederman et al., 2006; Preston et al., 2009). Conventionally, EF has been evaluated by rating-based questionnaires and neuropsychological performance tests. Rating scale measures represent an averaged impression over time. The Behavior Rating Inventory of Executive Functions (BRIEF) (Gioia et al., 2000) is one of the most frequently used questionnaires for rating EF in children and adolescents. Here, the parent or the teacher answer to what extent, for example, the

child/adolescent "manages to start on his/her own", "interrupts others", "leaves the room in a mess" or needs an adult to "keep track of the assignment". The rater answers "never ", "sometimes" or "often". Studies on the BRIEF report show significant problems for the ASD group and the ADHD group alike (G. A. Gioia et al., 2002).

Yet, there are several methodological concerns associated with rating scales, such as negative halo effects, source effects and temporal instability (Burns et al., 2003; Pelham et al., 2005; Stevens & Quittner, 1998). Therefore, neuropsychological tests are also used for measuring EF in children and adolescents. Neuropsychological tests are carried out in the clinic/lab and results in performance-based scores. Go/no go tests, or continuous performance tasks (CPTs) are among the most common methods to evaluate attention and executive function (Piani et al., 2022; Roebuck et al., 2016; Shalev et al., 2011). The term VCPT simply means visual CPT, i.e. the "go" and "no go" consist of visual (rather than auditory) stimuli. In the current thesis, the terms VCPT and go/no go test are used interchangeably. Luria used a manual version of VCPT in 1966, and today there are many computerised versions of the test (H Garavan et al., 1999). In short, the task for the participants is to respond by pressing a button when presented with a "go" signal, and not respond when they see a "no go" signal. To activate EF, the test includes a cue for preparation or inhibition of a response to the go or the no go stimuli; thus, for successful completion the person must activate attentional control, and not only routine behaviour, hence the term cued go/no go test. The go/no go test often reports on hit rate time and variability, omissions (i.e. the number of instances where the person fails to respond to the "go signal") and commissions (i.e. the number of instances where the person incorrectly responds) (Kenworthy et al., 2008; Roth et al., 2014). Similar to all neuropsychological tests, cued go/no go tests are performed in highly structured settings. Sometimes concerns have been raised that the neuropsychological tests lack ecological validity (Spooner & Pachana, 2006).

Research literature has shown that performance-based neuropsychological tests and ratings of EF (questionnaires) have only a weak or no correlation (Krieger & Amador-Campos, 2018; Stern et al., 2017). This can at first appear surprising. A study of the comprehensive literature can however lead to the conclusion that these measures reflect different aspects of EF, at different levels (Toplak et al., 2009). While the tests seem to measure an individual's *optimal* performance in an adjusted environment, the rating scale seem to reflect the individual's *typical* function (Krieger & Amador-Campos, 2018; Toplak et al., 2009; Toplak et al., 2013). Thus, it is often recommended that

both ratings and test scores are collected in order to assess EF more comprehensively (Toplak et al., 2013).

1.7 EEG AND EVENT RELATED POTENTIALS

In addition to neuropsychological tests and rating scales, different neurophysiological techniques (e.g. fMRI, MEG, electroencephalography (EEG), and Event-related Potentials (ERPs)) are increasingly used for studying neurodevelopmental conditions and EF (Bridwell et al., 2015; J. F. Brunner et al., 2015; Grane et al., 2016; I. U. D. Kropotov, 2016; Luck, 2014; Ogrim et al., 2014) although their use in clinical settings are still rare. The use of EEG in psychiatry research has, however, a long history. In 1938, EEG was used in one study including children with behavioural problems (probably including what we today call ADHD), with results showing slower EEG in frontal and central areas (Jasper et al., 1938; Loo & Makeig, 2012).

To secure comparable EEG recordings from different people, the electrodes are placed according to the so-called international 10-20 system. A 19 sites cap (Fig.2) is widely used, but in high-density EEG more than 100 or even 200 channels are utilised (Chu, 2015). High-density EEG is important for improved source localization and for analysis of connectivity patterns (Luck, 2014). However, the improved accuracy of high-density EEG setups comes with other costs, as the preparation (i.e., putting all the sensors and channels in place) might take up to 90 minutes per individual, who needs to be seated, which is clearly difficult for children in general, and especially so for children with ESSENCE.

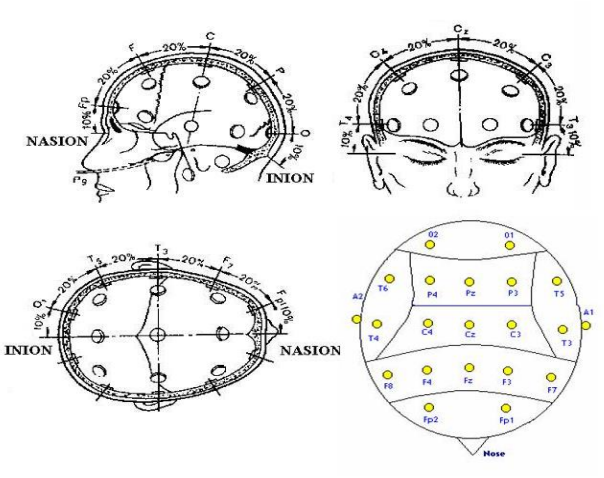

Figure 2: The international 10-20 system for electrode placement (printed with permission from Øgrim and Kropotov 2020)

It has been shown that EEG patterns are affected by psychological state (e.g., being sleepy) and the intake of some medications, but still EEG shows acceptable test-retest stability when testing is performed under standard conditions. The normal patterns are the same across cultures and ethnicities, and some distinct patterns seem to run in families (Eischen et al., 1995). A correspondence between mental states and EEG patterns has been described: an increase or dominance of delta activity (1-3Hz) is associated with sleep. A high level of theta activity (4-7Hz) is associated with drowsiness or an under-activated mental state. Alfa (8-12 Hz) has been described as an introvert, although alert, mental state. Low beta (13-20 Hz) increases when we are attentive and actively focusing on something externally. Excess of high beta (21-30 Hz) may reflect over-activation, stress and ruminations (Sawant & Jalali, 2010).

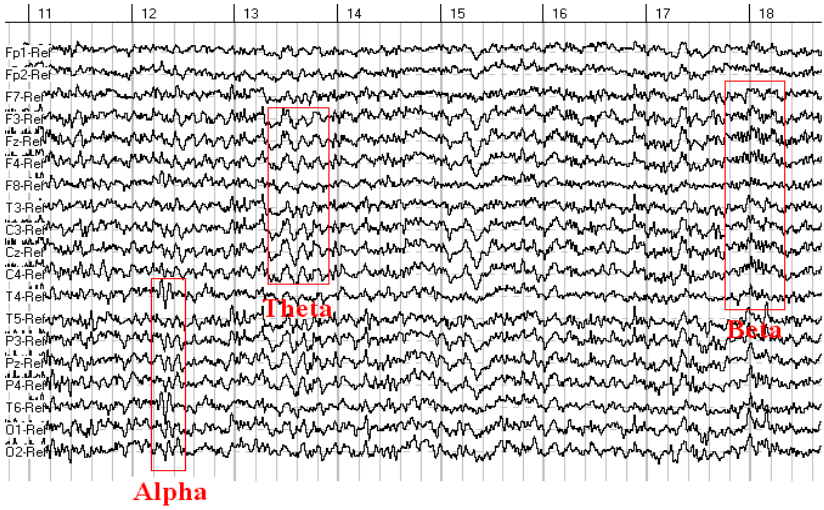

Figure 3: The figure shows 7 seconds of raw EEG registered from 19 sites. Examples of theta, alpha and beta waves are shown.

The EEG potential fluctuations are measured on the scalp and are the sums of cortical potentials that originate from synchronous firing of neurons. EEG data has a very good time resolution but a relatively poor spatial resolution. Electrical source potentials must be highly synchronous or spatially consistent to be recorded (Loo & Makeig, 2012).

Event-related potentials (ERPs) are extracted from EEG. An ERP is a direct response to an "event". The event can be a sensory, cognitive or a motor event. Kropotov (2016) offers the following definition of ERP: "Event-related potentials (ERPs) are scalp-recorded voltage fluctuations that are time-locked to an event" (page 59). The event can be elicited in a neuropsychological test, such as a go/no go test. The ERP is the averaged fluctuations over trials of the same event. The different ERPs reflects different stages of information processing in the brain (Kropotov, 2010; J. D. Kropotov, 2016). The usual way of describing an ERP component is by latency, amplitude, polarity, and scalp distribution. Research has revealed that amplitude measures tend to have higher reliabilities compared with latency measures (Harper et al., 2014; Kompatsiari et al., 2016). The ERPs are named by their polarity – e.g., a positive peak occurring 200 ms. post stimulus onset is called P200 or P2 (Smith et al., 2003). Also reported is their voltage as a function of time related to stimulus.

As mentioned, ERP components can be elicited in cued go/no go test paradigms. Roughly speaking, early components, appearing from 0 ms. to about 200 ms. after stimulus presentation, are thought to represent sensory and perceptual processes. Later components are thought to reflect EF processes. The most common ERPs in this area of research include Cue P3, the CNV, the P3 go, the N2 no go, and the P3 no go (Jan Ferenc Brunner et al., 2015; I. U. D. Kropotov, 2016). The Cue P3 is probably associated with classification of a stimulus. The CNV appears between a cue and the next stimuli, indicating response preparation. (Ahmadian et al., 2013). Visual Negativity (vN) is seen most clearly at a parietal position, in the time interval from 800-1100 ms after presentation of a visual stimulus and is proposed to reflect visual readiness (Di Russo et al., 2019). The P3 appears at approximately 300 ms. after the go signal and is associated to selection of responses (Bledowski et al., 2004). The P3 can also be subdivided into an early fronto-central component (P3a) and a later, posterior component (P3b, in our paradigm called P3 go). P3a is thought to reflect the attention to a newly detected object, whereas P3b is assumed to be related to target identification and response selection (Verleger, 2020), though this distinction is far from always made in research (Haig & Gordon, 1998; Harper et al., 2014; Kiiski et al., 2011; Smart et al., 2014). Although the functional meaning of the P3 is still debated it is agreed upon that the P3 reflects information processing that is elicited during tasks demanding attention and problem solving (Polich, 2012). The N2 no go is a frontal negative deflection appearing immediately before the P3 no go component. The N2 no go is sometimes named “template update” reflecting that the expected go-stimulus did not appear, and, hence, the planned response needs to be changed.

1.8 ERP:S, NEUROPSYCHOLOGICAL TESTS AND RATING SCALES

Rating scales, neuropsychological tests (e.g. go/no go tests) and cognitive ERPs are all used to assess EF (Ozonoff, 1997). Some, but not very many, studies have systematically explored how individual differences in EF-related ERPs correlate with performance measures or with rating scores of EF in school-age children and adolescents. In one study by Wiersema and Roeyers (2009), it was found that lower scores on ratings of effortful control (EC) were correlated with more commission errors in the go/no go task that was used, and also to smaller N2 no go and P3 no go amplitudes. Both components are considered to be connected to executive networks. Moreover, children with a

high degree of ADHD symptoms scored low on the EC ratings and had more commission errors and a smaller P3 no go amplitude (Wiersema & Roeyers, 2009). One study from 2012 showed a smaller N2 amplitude in preschool age children who performed better on the executive test Dimensional Change Card Sort. The authors concluded that the N2 even in young children may be seen as a marker of executive function (Espinet et al., 2012). In addition to informing our theoretical understanding of EF, the literature suggests that ERPs can be seen as markers of neural development (Riggins & Scott, 2020). In the 1970s, studies on the P3 started to emerge with a focus on the development of the ERPs throughout life. A review of the research on the development of the P3 from infancy to adolescence suggests that in infancy there is a lack of the P3 component and the electrophysiological response to stimuli that are unexpected is different from that in children, adolescents and adults (Riggins & Scott, 2020). The P3 seems to appear in children about 5 years of age and has been argued to reflect similar cognitive processes as in adults. P3 amplitude increases from early childhood to an adult level in about 12 years (Mueller et al., 2008).

1.9 EXECUTIVE FUNCTIONS AND ERP:S IN ADHD AND ASD

Many studies have shown that deficits of EF is strongly associated with ADHD (Kessler et al., 2006; Nigg et al., 2017; Pliszka, 2007; Willcutt et al., 2005) although EF deficits are not completely synonymous with ADHD (Roth et al., 2014; Toplak et al., 2009; Toplak et al., 2005). Regarding neuropsychological test data, go/no go test scores have been shown to be moderately effective in discriminating between cases with ADHD from cases with other neurodevelopmental/ESSENCE disorders (Craig et al., 2016; Hult et al., 2018). Also, ratings of broad everyday EF deficits are very often found in ADHD samples of various ages (Gerard A Gioia et al., 2002). Problems in everyday life function, closely related to problems in executive functions, are common in the autism group as well (Rosenthal et al., 2013). According to Frith (Frith, 1996), EF deficits also lie at the core of the repetitive and restricted behaviours that partly define ASD, and other authors also assume that many of the autism symptoms may be caused by EF problems (Ozonoff, 1997). An article from 2014 (Sinha et al., 2014) presents a hypothesis that an important aspect of autism may be found in an impaired ability to predict, which will lead to a an experience of the world where events will happen more unexpectedly

and to a greater extent lack causality. This brings to mind the concept of Bayesian inference theory, which is based on the principles of probability theory. Bayesian reasoning refers to how our representations of (aspects of) the world is formed probabilistically and with beliefs being updated as we gain new experiences (Palmer et al., 2017). The idea of an alteration in this domain is potentially clinically meaningful since it could potentially contribute to explain the need for routines and sameness typically seen among people with ASD. Fairly little empirical evidence is available for the theory at date, but potentially, preparatory and predictive capacities can be formally assessed using ERPs, such as vN.

According to a review by Hill (2004), children with ADHD show more difficulties in go/no-go tests than children with ASD, however mild impairment compared with typically developing samples has also been observed in autism (Geurts et al., 2014; Goldstein et al., 2001). In a study by Nydén et al. (1999), few differences were in fact observed in EF difficulties when comparing children (all boys) with ADHD (n = 10) and ASD (n = 10) (Nydén et al., 1999). Pennington and Ozonoff also examined executive functions in children with ADHD and ASD and found that while EF deficits were common in both groups, they presented themselves differently in ADHD compared with in ASD (Pennington & Ozonoff, 1996). Participants with ADHD had more difficulties with inhibition whilst the ASD-group showed more difficulties concerning mental flexibility and verbal working memory. Compared to typically developing controls, Corbett et al. found that children with ADHD group had difficulties in vigilance, inhibition and working memory (B. A. Corbett et al., 2009). Goldstein et al. found that individuals with ASD had more difficulties performing tasks that require mental flexibility and processing speed, but not severe difficulties with sustained attention, which by contrast are commonly reported problems in ADHD (Goldstein et al., 2001).

Thus, current findings regarding the nature of EF deficits in ADHD and ASD are not fully consistent. Here we must bear in mind the common coexistence of ADHD and ASD which very likely affects the outcome of research on executive difficulties. In particular, how studies handle comorbidities (did they include or exclude “comorbid” cases?) are often inconsistent and sometimes not addressed at all (where the participants comprehensively assessed/screened?). To add further complexity, other comorbidities very likely affect the manifestation of EF deficits in ADHD and autism. In particular, comorbid learning disabilities in the ADHD group, such as language learning disorders, non-verbal learning disability, dyslexia and/or dyscalculia, are common and seem to have additive effects (Luoni et al., 2022; Semrud-

Clikeman & Bledsoe, 2011; Åsberg Johnels et al., 2014). Given the high degree of symptom overlap between disorders, an ESSENCE perspective is considered crucial for accurate clinical characterisation in general, and for revealing underlying neuropsychological problems linked with behavioural and symptomatic profiles. In addition, and as mentioned, there are several different possible procedures available for assessing EF.

The literature on VCPT derived (cued go/no go) ERPs involving children with ADHD is quite extensive (Aasen et al., 2018; Høyland, Øgrim, et al., 2017; Johnstone et al., 2013; Kropotov et al., 2019), whereas in the case of ASD or comorbid ADHD + ASD relatively less is known (Høyland, Nærland, et al., 2017). For ADHD, several ERPs, mentioned above, have shown to be different in ADHD, specifically Cue P3, the CNV, the P3 go, N2 no go, and the P3 no go (Johnstone et al., 2013). A meta-analysis (Kaiser et al., 2020) summarised literature from 52 relevant articles on cognitive ERPs in ADHD, including in 1576 individuals with ADHD and 1794 non-ADHD participants, smaller group differences were found in earlier components compared with later, cognitive/EF, components in ADHD individuals. Overall, individuals with ADHD had smaller Cue P3 amplitudes, longer P3 go latencies, smaller P3 no go amplitudes, longer P3 no go latencies, and smaller CNV amplitudes. The meta-analysis identified moderate group differences for the later ERPs ($-0.32<d<-0.57$). The authors conclude, however, that substantial heterogeneity was found between studies, and highlight that only moderate effect sizes were observed ($d<0.6$) which limits the use of these ERPs clinically (Kaiser et al., 2020). When it comes more specifically to using ERPs as a diagnostic tool for ADHD, i.e. to classify individuals rather than separating groups on average scores, an extensive review of the literature for diagnostic-based ERPs only found 7 studies that met the inclusion criteria in reporting sensitivity and specificity for discriminating ADHD from healthy controls (Gamma & Kara, 2020). They point to the problem of lack of standardised procedures for ERP methods and paradigms (Gamma & Kara, 2020). It is also noteworthy that most studies attempting to evaluate ERPs for ADHD identification have relied on a single ERP component. As proposed by (Lenartowicz & Loo, 2014), it might not be possible to identify ADHD by a single neurophysiological variable, in view of the fact that ADHD is known to be a heterogeneous condition. Therefore, Lenartowicz and Loo (2014) suggested that statistically combining different ERPs might increase the classification accuracy. Moreover, very little is currently known about improved classification accuracy by combining different assessments of EF, e.g. neuropsychological test scores and EF-related ERPs.

In a meta-analysis of P3 ERPs in ASD, Cui et al found some indications of a reduced P3b amplitude in participants with ASD as compared to typically developed children (Cui et al., 2017), confirming the existence of EF alterations, at least subtle, in this group as well. Still, some researchers suggest that the pattern of ERPs on some key EF-related ERPs look normal in the ASD group – whereas earlier components – presumed to reflect sensory and perceptual rather than cognitive processing – by contrast tend to show clearer differences compared to typically developing controls (Hoyland et al., 2017). For example, studies have shown increased N1 latency in ASD, and it has further been suggested that there are connectivity alterations in visual processing networks in ASD which might contribute to social communication problems (Jeste & Nelson, 2009). In another study, the ASD group showed stronger cortical responses than controls to task irrelevant stimuli during early visual processing (Baruth et al., 2010). Yet another ERP study reports a smaller P1 amplitude in a group with ASD group as compared to typically developing controls (Kovarski et al., 2019). The authors conclude that ASD is characterised by "atypical visual perception both in the social and nonsocial domain" (p 3377), which might not necessarily reflect EF specifically, but broader aspects of perception.

A few studies have directly compared ASD and ADHD groups. A study from 2013 using a flankered cued continuous performance test in groups of boys aged 8-13 years with ASD (n = 19), ADHD (n = 18), co-morbid ASD + ADHD (n = 29) and typically developing controls (TD; n = 26) showed that the combined ASD+ADHD and the ADHD group made more omission errors, had an increased variability in reaction time and reduced Cue P3 amplitude and P3 no go compared to the TD group and the ASD-only group. All in all, the authors conclude that the children with ASD + ADHD show deficits associated with both disorders. The authors further conclude that ERPs that reflect attention and inhibition could be useful for guiding clinical assessment (Tye et al., 2014). Again, however, variances in paradigms and participants might also contribute to divergence in study results.

2 AIM

The overall aim of this thesis is to contribute to increased knowledge regarding EF, and, in particular, learn more about VCPT-derived ERPs and how they can inform paediatric ADHD and ASD assessment. To achieve this aim, I will address the following research questions and topics:

1. How do different measures of EF – assessed with parent ratings (BRIEF), VCPT-derived test scores, and ERP amplitudes – correlate among children and among adolescents with ADHD, and how do the profiles and associations differ with age? (study 1)

2. Is it possible to distinguish between children, aged 9-12 years, with ADHD and an age- and sex-matched group of children without neurodevelopmental/psychiatric disorders using a combined index of test results and ERPs amplitudes derived from a VCPT? (study 2)

3. With a main focus on visual processing: Do adolescents, aged 13-17 years, with autism differ from an age- and sex-matched group of children without neurodevelopmental or psychiatric disorders on VCPT-derived test scores and ERPs? (study 3)

4. How can VCPT-derived ERP measures and performance scores be integrated as an information source and be used in clinical practice to understand the needs and strengths of an individual child with complex ESSENCE presentation including ADHD? (study 4)

3 METHODS

3.1 PARTICIPANTS

Patients aged between 9 and 18 years were invited to participate in the studies. Most of the participants came from the Åsebråten child and adolescent psychiatric clinic, where they had been referred for possible ADHD or ASD. The children provided assent and their guardians gave written consent, as did adolescents above 16 years. In all studies, exclusion criteria were IQ below 70, diagnosed traumatic brain injury or epilepsy. In addition, anonymous patients from previous studies (in our own clinic, Åsebråten, in Norway) were included in parts of the study (REK 2016/1453).

Participants received a standard diagnostic evaluation according to clinical guidelines (American Psychiatric, 2013; santé et al., 1992). The examination of the child consisted of medical screening, collection of developmental history, clinical interview, rating scales, direct observation in clinic, school and home as needed, and cognitive assessment. For autism, comprehensive parent interviews and direct observations of the child (e.g. ADOS (Lord et al., 1999) and ADI-R (Rutter et al., 2003) were used, depending on clinical judgement. Screening for comorbid disorders (specific and general learning disabilities, language disorders, developmental coordination disorder, oppositional defiant disorder, Tourette syndrome, depression, anxiety disorders, attachment disorder, etc.) was completed according to standard clinical procedures.

The comparison groups (typically developed children, TDC) consisted of children and adolescents aged 9-17 years without any known or diagnosed neurodevelopmental, psychiatric or brain disorder. The gender ratio of the patients was about 2:1 (male/female), which is also the ratio of the controls. About half of the controls were recruited at schools from two Norwegian sites (Fredrikstad and Trondheim), and the rest were drawn from the HBi database (www.hbi.med.com), with no systematic selection other than age and gender. Most of the latter were tested in Switzerland in 2003 with similar equipment as the other controls and the patients. (Test scores and ERP amplitudes are not markedly affected by testing at different sites when similar equipment is used according to Mitzar-medical.com). The inclusion criteria in HBi are identical to the inclusion criteria for the TDC group described above.

In study 1, the participants were 59 patients diagnosed with ADHD (age 9-17). To examine ERP differences related to age, we subdivided the sample based on cut off of 12 years, in line with Johnstone (2013). We did not exclude

participants with common comorbidities, like behavioural and emotional disorders, learning disabilities, Tic/Tourette syndrome, or ASD since that would impact the generalisability. However, as mentioned, children with intellectual disabilities and/or epilepsy were not included.

In study 2, 61 children (age 9-12 years) diagnosed with ADHD and common comorbidities, and 69 age- and sex-matched typically developing children (TDC) participated. The inclusion and exclusion criteria were the same as in study 1. A replication sample of another 20 children with ADHD and 21 TDC were also included.

In study 3, 63 adolescents with autism spectrum disorders (ASD) and a sex- and age-matched group of 60 TDC participated. ASD patients with comorbid ADHD were not included.

In study 4, a follow up description of a 9–10-year-old boy was conducted.

An overview of participants and research designs in the different studies are reported in the table 3 below.

STUDY	DESIGN	PARTICIPANTS	AGE	SEX
I	Correlational study	28 young ADHD 31 older ADHD	9-12y 13-17y	18m,10f 19m, 12f
II	Case-control study	61+20 ADHD 69+21 TDC	9-12y 9-12y	37+12m, 24+8f 42+12m ,27+9f
III	Case-control study	63 ASD 60 TDC	12-17y 12-17	34m, 29f 19m, 41f
IV	Case study	1 ESSENCE	9 years	1m

TABLE 3. ADHD: PATIENTS DIAGNOSED WITH ADHD. TDC: TYPICALLY DEVELOPING CONTROLS (SEX- AND AGE-MATCHED). ASD: PATIENTS DIAGNOSED WITH ASD. ESSENCE, HERE: DIAGNOSED WITH SEVERAL NEURODEVELOPMENTAL DISORDERS.

3.2 PROCEDURES

In all studies, the participants were tested with the WinEEG system to obtain EEG, VCPT test scores and ERPs.

To obtain the EEG and ERP data, the WinEEG program from Mitsar-medical.com was applied. Figure 4 shows the ERP/EEG setup and test paradigm.

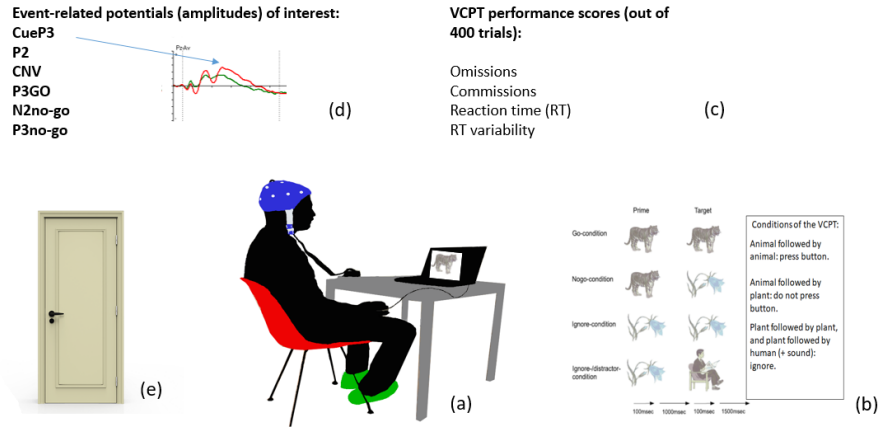

Figure 4: Overall illustration of a) the physical setup, b) description of the VCPT, c) the neuropsychological test scores, d) the main ERPs of interest and e) which is a metaphor for the level of executive functioning displayed by the participants/patients outside the lab

This equipment is presently used at the three Norwegian sites and was also available at the Gillberg Neuropsychiatric Centre (GNC), Sweden, in 2017. The personnel doing the registrations were fully trained to ensure that the registrations were completed as they should be. The exchange of data was completed according to regional ethics committee procedures. The scoring of EEG data was done by the PhD student and/or supervisor GØ.

EEG recordings are sensitive to artifacts. The curves may be greatly influenced by eye blinking and lateral eye movements, muscle tensions, movements and external electrical noise etc.; thus, artifact correction is needed. Our system (WinEEG) is to a larger extent based on automatic artifact correction compared with traditional manual artifact corrections. The raw EEG data are submitted to independent component analysis (ICA), and components representing artifacts, or a high portion of artifacts, can be removed. In addition, strong signals, outside the natural range of EEG, are automatically removed. The process of artifact correction ends with a visual inspection of the curves and cutting off obvious artifacts still left. It has been shown that similar results are obtained by comparing manual and automatic artifact correction (Kropotov, 2010). As mentioned, a Mitsar 201 19-channel EEG system (www.mitsar-medical.com) was used for recording. A total of three conditions were used in the registrations: a 3 minute long eyes-closed resting condition, a 3 minutes eyes-opened resting condition, and 20 minutes for the cued go/no-go task.

In the VCPT task, pictures of animals (*a*), plants (*p*) and humans (*h*) are shown in pairs, with 1000 ms. interval between pictures in a pair, and a 3000 ms. interval between pairs. The four trial categories are: *a-a, a-p, p-p, and p-h*, with 100 trials in each category. Patients and controls were instructed to respond (press mouse button) only to *a-a* trials, and to reply be accurately and quickly. The overall luminance and the image sizes of animals and plants were about equal in all pairs and did not differ between the clinics doing the registrations. Sounds were presented along with human images in the *p-h* trials. These sounds produced the novelty ERP wave.

As mentioned, the go/ no go task generates scores of omissions (number of go-responses omitted), commissions (number of responses in no go condition), reaction time in milliseconds in the go condition, and reaction time variability (standard error of reaction time in go condition).

Before the recording started, all participants had the chance to practice the task. Participants were seated in a comfortable chair in front of a 17-inch computer screen placed at a distance of approx. 1.5 meter. A correct response was registered when pressing the button to *a-a* pairs within 200–1000 ms. after presentation of the second stimulus. If the participants did not respond to *a-a* pairs within this interval an omission error was registered. Impulsive hit responses to *a-p* pairs were scored as commission errors. Two short breaks during the task were given.

Input signals were referenced to earlobe electrodes, filtered between 0.5 Hz and 50 Hz, and digitised at a sampling rate of 250 Hz (500 Hz at St. Olav's) with impedance kept below 5 kΩ for all 19 electrodes. We used an electrode cap with tin electrodes (Electro-cap International, Eaton OH, USA). Electrode placement was done in accordance with the international 10–20 system. EEG data were re-referenced offline to the common average montage prior to data processing. Eye-blink artifacts were corrected using Independent Component Analysis and epochs with outlier amplitudes (100 μV) and/or excessively fast (35 μV in 20–35 Hz band) and slow (50 μV in 0–1 Hz band) frequency activities are automatically excluded from analysis.

In all studies, ERPs were analysed manually. (A supplementary method, called cluster-based permutation test, was used in Study 3. This method is described in the manuscript for study 3). The manual method is described here. The amplitudes of the local ERP components were measured individually. The sites of registration were based on the grand average files (GAFs) of the total group, i.e., patients and controls. The sites showing the largest GAF amplitudes were chosen. The amplitude of a local peak is the highest microvolt value within the defined time window. To avoid registration of the offset of a preceding component or the onset of the next component, the peak must be surrounded on both sides by lower voltages (Luck 2014).

The ERP waves, sites, and time intervals after stimulus 1 were as follows. Cue P3 amplitude at site Pz: 400-600 ms. (In Study 2: site P3). Visual Negativity (vN) at site P3: The strongest negativity in time interval 800-1100 ms. CNV at site Cz or Pz: The strongest negativity in time interval 1000–1100 ms. (The site with the strongest CNV amplitude of the participant was used). P2 at sites T5 and T6: The strongest peak in time interval 200-400 ms. and the latency of this peak. The ERP waves, sites, and time intervals after stimulus 2 were as follows.

P1 latency: The latency of this peak. Go amplitude: The strongest amplitude at site Pz in time interval 200-450 ms. Go latency: The latency of this peak. N2 no go amplitude at site Fz: The strongest negative peak in time interval 200-330 ms. N2 no go latency: The latency of this peak. P3 no go amplitude at Cz: The peak amplitude in time interval 250-500 ms. P3 no go latency: The latency

of this peak. Auditory N1 amplitude at site Cz: The negative peak in time interval 100-200 ms. in *p-h* condition. Auditory P2 (P3a) amplitude: The amplitude at Cz in time interval 160-250 ms.

In study 1, a parent (in most cases the mother) of the participant filled out The Behavior Rating Inventory of Executive Functions (BRIEF) in addition to the QEEG/VCPT/ERP testing. BRIEF consists of 86 items organised in subscales (Roth et al., 2014) that are converted to a summary score, the Global Executive Composite (GEC). We included only the GEC score in study 1, in order to reduce the number of correlations and the risk of type 1 error. The BRIEF ratings were electronically scored, and expressed in norm-referenced T-scores (around the normative mean of 50, SD = 10).

In study 4, the participating boy was assessed at two times points, as part of standard clinical practice, with a broad battery of psychological and educational assessments, including the Wechsler Scales of Intelligence (WISC) version IV (Wechsler, 2007) assessments of math and numeric skills (Adler, 2007; Nosworthy et al., 2013; Prodér Kampesveen & Verner, 2018) and reading and reading-related skills (Elwér et al., 2016). The primary assessments were conducted at two time points on two separate days and 1.5 years later by the same child and adolescent psychiatrist, a neuropsychologist and an educational specialist. As part of a research project, the boy also performed EEG/ERP assessment using the same WinEEG system as above.

3.3 ETHICAL CONSIDERATIONS

The Norwegian part of the project was approved by the regional committee for medical and health research ethics (REK 2016/1453). The Swedish part of the project was approved by the regional committee in Västra Götaland (REK 441-17) with amendments (2022-05731-02). All parents and patients received oral and written information about this research project and signed a written consent to participate. Including anonymous participants from previous studies was approved by REK 2016/1453. Some of the TDC (controls) come from the international HBi database. In 2003, written consent was given that the anonymous scores can be used for clinical and research purposes.

There are several ethical issues that need consideration in the project. The EEG/ERP examination is not part of a standard evaluation. However, most of the patients completed this test as part of an extended neuropsychiatric evaluation and all gave written consent that the test results can be used for

specified research purposes. For patients and controls, the test requires an extra visit to the clinic and takes about one hour. From an ethical point of view, there might be a risk that the child will worry that something is wrong with his/her brain considering the use of a cap with electrodes to investigate brain activity. To counteract this, we always take the time to explain to the child what the procedure does and what it does not measure. No pain or danger is involved, there are no known side effects, and we are very explicit with the participants that we are not able to read anyone's mind, but that our focus is on how the brain works when it relaxes and when it concentrates. In our experience, most children find the test exciting and are intrigued by having the chance to "look" at their own brain waves on the computer screen. If a child feels anxious about the testing, a parent can be present for as long as needed, and a test session is discontinued if the child does not feel comfortable. The PhD student and other test leaders are all experienced clinicians. The test can potentially give us important information about different aspects of information processing and contribute to decisions about treatment (as has been shown earlier) and thus the approach is considered ethically defensible.

3.4 STATISTICAL ANALYSIS

Different statistical methods were used for the specific purposes of the studies.

In study 1, several steps were taken. To compare the EF scores (BRIEF parent ratings, VCPT test scores and ERPs) between children and adolescents, the data were first checked for confounding variables (not included in the analyses). The distribution of ADHD subtypes and the proportion of comorbid disorders did not differ between the groups. Mean IQs were slightly lower in the adolescent group, but the variables of interest were not significantly correlated with IQ.

The following variables were included in the analysis: GEC (the global BRIEF score), the amplitudes of three ERPs (Cue P3, P3 go, P3 no go), and four test scores from VCPT (number of omissions and commissions, reaction time (RT) and RT variability.

To compare the differences in EF scores between the groups the non-parametric Mann-Whitney U-test was applied. To compute the correlations between EF measures, Spearman's rank order correlations was used. These correlations were computed for children and adolescents separately as per the age cut off used by Johnstone (2013).

In study 2, a classification approach was developed and evaluated. First, we compared the two groups on each outcome measure using independent samples t-tests and calculations of Cohen's *d*. Variables that differed significantly between groups with an effect size $d > .50$ were used in the computation of the diagnostic index. The significant ERPs were: P2, Cue P3, CNV, P3 go, N2 no go and P3 no go. Three test scores from the VCPT were also included: Number of omission and commission errors and RT variability. None of these nine variables correlated +/- 0.7 or more, which implies that each of them contributes to the index. Then, the individual scores on these variables were converted to percentile scores based on the TDC group. Score 1 was set for all scores within the interval 1-80 percentile. Score 2: 80-90 percentile; score 3: 90-95 percentile; score 4: 95-98 percentile and score 5: 98-100 percentile. Percentiles are helpful when scores are not normally distributed, which was the case in our study. In addition, a five-point percentile-based scale is, we believe, also clinically meaning- and helpful since it makes it possible to grasp and communicate diverging scores in a manner that is more known by clinicians and parents. Next, we calculated each individual's final score by multiplying the percentile (P) score by the effect size (*d*) of each scale. (If the P score was 3 and $d = 0.4$, the final score was 1.2). Finally, these final scores were summed for each individual in order to determine the diagnostic index score.

Since, the diagnostic index score was not normally distributed, we applied a Log10 correction that resulted in a normal distribution. The effect size (*d*) of the diagnostic index was based on the Log10 correction.

A receiver operating characteristic curve (ROC curve) was also applied to the data. In this accuracy calculation, sensitivity and specificity were equally weighted. Finally, we explored how rigorous the classification accuracy was in an independent replication sample.

In study 3, we compared groups on the ERPs using standard and more novel, sophisticated statistical techniques. The ERP variables selected for statistical analyses in SPSS were based on comparisons of Grand-Average Files (GAFs) in WinEEG (ASD vs. TDC). Individual scores on variables that differed significantly between the groups were exported to SPSS. The files were checked for outliers. The few outliers, about equally distributed in the two groups, were moved to the "nearest neighbour" in line with common practice. Independent samples t-test was used to compare the two groups.

In addition, a cluster-based permutation test was applied to the ERP components. ERPs for all conditions separately (such as Cue continue [stimulus 1 is an animal] and Cue-ignore [stimulus 1 is a plant], go and no go) were compared between the groups using a cluster-based permutation test (Eric Maris & Robert Oostenveld, 2007) implemented in WinEEG. This procedure solved the problem of multiple comparisons by clustering the data based on temporal and spatial proximity. The cluster-based analysis procedure was very similar to the one implemented in the FieldTrip MATLAB toolbox for M/EEG analysis. Specifically, samples with statistics corresponding to p-values $p < 0.05$ were clustered together based on temporal and spatial adjacency. We considered that the sensors located at the border of the electrode grid had 3 neighbours (closely spaced electrodes), while the others had 4 neighbours. Cluster-level statistics were calculated by taking the sum of the z-scores within every cluster. Then n data permutations ($n = 1000$) were performed by shuffling the ASD and control labels, and for each permutation, clustering was performed, and cluster-level statistics were calculated. Finally, the permutation distribution of the maximum cluster-level statistics was used in order to determine the cluster-corrected threshold (E. Maris & R. Oostenveld, 2007). The permutation test is considered a rigorous test compared with the more commonly used manual registration method.

In study 4, a case description was made. For test data, we compared the boy's performance to norm data reported in manuals. We also applied the diagnostic index for ADHD developed in study 2. Finally, in the WinEEG program, an automatised comparison using t-tests was done relative to the HBi norm material for one of the ERP components, the Cue P3 ERP.

4 RESULTS

4.1 STUDY 1: HOW DO DIFFERENT MEASURES OF EF – ASSESSED WITH PARENT RATINGS (BRIEF), VCPT-SCORES AND ERPS AMPLITUDES – CORRELATE IN CHILDREN AND ADOLESCENTS WITH ADHD?

The BRIEF GEC data showed that both age groups scored in the "potentially clinical" range (Mean T-scores >65). There were no significant differences between the age groups in BRIEF GEC T-scores. As regards to performance on the CPT, the child group had significantly slower RT compared with the adolescent group, whereas no significant differences were seen for the number of omissions or commissions ($p > 0.12$) in the CPT test scores.

Significant and moderate correlations between BRIEF GEC scores and some CPT test scores were found in the child group, namely with number of commissions ($rho = 0.390$, $p < 0.05$) and RT ($rho = -0.409$, $p < 0.05$). This means that greater parent rated EF difficulties were associated with faster RTs and a higher number of commissions. In the adolescent group, these correlations were not found (all *p* -values > 0.12).

Moreover, significant positive correlation between the P3 no go amplitude and the parent ratings was found in the child group ($rho = 0.402$, $p < 0.05$). A negative correlation between P3 no go and reaction time ($rho = -0.573$, $p < 0.01$), and a significant positive correlation between number of commissions and P3 no go amplitude were also found ($rho = 0.497$, $p < 0.01$). The finding suggests that larger P3 no go amplitudes align with more BRIEF reported EF problems and with quick but error-filled performance on the CPT in the child group.

By contrast, in the adolescent group, the correlation directions differed from the child group in important ways: Significant correlations were found between P3 no go amplitude and the number of omissions ($rho = -0.377$, $p < 0.05$), RTvar ($rho = -0.655$, $p < 0.01$) and reaction time ($rho = -0.705$, $p < 0.01$). The direction of these correlations show that, in the adolescent group, a large P3 no go amplitude correlated with better CPT test performance. There were no

significant associations between ERP data and BRIEF parent ratings in the adolescent group.

The data from this study underscores the importance of considering age when interpreting ERPs. ERPs seem to measure different aspects of executive function compared to other EF measures, according to our study, although *some* correlations were found. Also, we found associations between some neuropsychological test scores and parent ratings of EF, but only in the child group.

4.2 STUDY 2: IS IT POSSIBLE TO DISTINGUISH BETWEEN CHILDREN WITH AND WITHOUT ADHD USING AN INDEX COMBINING TEST RESULTS AND ERP AMPLITUDES DERIVED FROM VCPT?

In the initial sample, nine variables were significantly different between children with ADHD (n = 61) and TDC (n = 69), with an effect size >0.5, i.e, omissions, commissions, rection time variability and ERP amplitudes of P2 (site O2), CueP3, CNV, P3go. N2 no go, P3 no go.

The nine variables were converted to percentiles (Ps) based on the TDC group and scored on a 1-5 scale. Ps < 80=1, Ps 80-90=2, Ps 90-95= 3, Ps 95-98=4, Ps >98=5. Each variable score was multiplied by the effect size of the variable. The sum of the variable scores was used as a diagnostic index. When applied to the sample the diagnostic index discriminated between patients and TDC with an effect size *d*=1.47), and an accuracy of 84.4%.

In the second step, the diagnostic index was applied to an independent age- and sex-matched sample of 20 individuals with ADHD and 21 controls for replication. The ES for the diagnostic index was *d*=3.03 and accuracy was 97.7%.

4.3 STUDY 3: IS VISUAL PREDICTION IMPAIRED IN ADOLESCENTS WITH AUTISM SPECTRUM DISORDER?

Grand-Averages Files (GAFs) of ERPs were compared. Components showing significant differences in WinEEG, and standard ERP components were scored manually and with a cluster-based permutation test. The results showed no significant differences in behavioural test scores, i.e. on number of omissions ("misses"), commissions (impulsive extra pressures), reaction time, or reaction time variability (which reflects that the participant slides in and out of focus). Manual registration showed that seven ERP variables were significantly different between the ASD group and the controls, and only one of these passed the "cluster-based permutation test". This component, called Visual Negativity (vN), was strongest parietally on the left side and is believed to reflect a mental preparation for receiving and interpreting visual stimulation. This finding is in accordance with theories claiming that the activation of top-down processes is impaired in ASD, meaning that the participants are less influenced by context, prior experiences and expectations during perception. This phenomenon is also called Bayesian hypo-activation.

4.4 STUDY 4: A CASE STUDY APPLYING ERP:S TOGETHER WITH STANDARD PROCEDURES

We describe the outcomes from symptomatic, cognitive, educational and electrophysiological (ERP/QEEG) multi-professional assessments in order to explore to what extent such data converge in capturing the pattern of strengths and difficulties displayed by the child, and how they informed treatment

decision-making.

By utilising such an approach, we were able to characterise a distinct profile of combined ADHD, nonverbal learning disabilities, and math and numerical difficulties, but with strong or very strong reading and verbal capacity. The diagnostic ADHD index described in study II was applied. Less than 2% of controls will score as high as this boy on the diagnostic index, supporting an ADHD diagnosis. The Cue P3 ERP component was very weak. Cue P3 is thought to reflect "identification of target". We speculate that this component may be a candidate biomarker for nonverbal learning disabilities.

5 DISCUSSION

5.1 RATIONALE AND AIMS OF THESIS

ADHD and autism (ASD) are common diagnoses in paediatric psychiatry. This thesis aimed to contribute to the body of knowledge on executive functions (EF) and Event-Related Potentials (ERPs) in ADHD and ASD compared to typically developing peers. Problems with EF are common in both ADHD and ASD (Berenguer et al., 2018; Blythe A Corbett et al., 2009; Happé et al., 2006; Semrud-Clikeman & Bledsoe, 2011), although the basis and expressions of such problems in ASD have been relatively less studied than in ADHD (Johnson, 2012; Rosenthal et al., 2013; Wallace et al., 2016). EFs are important for living an independent life, and for success in educational and vocational settings (Dijkhuis et al., 2020; Payne & Swanson, 2022; Stechnij, 2022). EFs are therefore an important target for assessment and intervention. There are several methods available to examine EF. ERPs are potential sources of information, and this is where the current thesis made some novel contributions. ERPs are direct and real time indexes of neural activity on a millisecond scale and thus have a great advantage in examining cognitive and sensory activity (Beres, 2017; Fu & Parasuraman, 2006; Lachaux et al., 2012)

The four papers that make up this thesis have different approaches, and collectively we hope they shed some new light on critical theoretical and clinical aspects of the use of EF-related ERPs in paediatric ADHD and ASD. The thesis also approaches the field of biomarkers in psychiatry. ADHD and ASD are neurodevelopmental disorders, but no brain-based measures or tests are included in the diagnostic criteria. Instead, the diagnoses are to a large extent based on subjective measures like clinical interviews, rating scales, observations and developmental history. It is assumed that biomarkers could help reduce diagnostic misclassifications, reduce the time needed to find the best treatment for the patient and to enhance the correct understanding of the individual (Kalia & e Silva, 2015; McGorry et al., 2014; Singh & Rose, 2009), although much remains to be learned before these long-term goals are realised. The ESSENCE perspective (Gillberg, 2010) underscores the overlap in symptoms between developmental disorders and problems, which might imply that finding a single biomarker that accurately discriminates clearly between for example, ADHD and ASD, will be unlikely (Thome et al., 2012). A basic assumption in this thesis is that a diagnostic index, based on several variables that discriminate between groups, could constitute a more realistic approach for biomarker validation, and that such biomarker information might supplement – rather than replace – the methods presently in use. The scores on

the variables constituting such an index may potentially also inform us about neurocognitive function of the patient in focus. The overall conclusion of the present thesis suggests that this approach seems feasible.

5.2 STUDY 1

In the first study, EFs in 59 children and adolescents with ADHD were examined by three different methods: the BRIEF parent rating scale, a continuous performance test (VCPT) and cognitive ERPs.

Our findings, in line with prior studies and existing literature (Toplak et al., 2009), showed weak or moderate correlations between ratings and VCPT scores of EF, but these were present only among children, not adolescents. In particular, we found that a high problem score on the BRIEF GEC correlated with more commissions among children. We did, however, find some correlations to the ERPs in our study. The analysis further revealed that larger P3 no go amplitudes in the young group correlated with increased impulsivity according to VCPT data on commissions and reaction time and with parental ratings. The association between high amplitudes of the P3 no go and EF problems in the child group was at first surprising since existing data on the P3no go component suggests that a strong component reflects *better* cognitive control (J. D. Kropotov, 2016). This interpretation has mainly been informed by research on adolescents and adults, however. In the adolescent group, our significant negative correlation between P3 no go and VCPT variables were in line with this body of prior research. This finding may support a view that the P3 no go component reflects different aspects of cognitive control in children and adolescents. In ERP research divergent results are often reported, mostly related to different paradigms being used. Our study also highlights that age seems to be an important factor to consider, and that differences in age composition in different studies may contribute to explain diverging findings. Indeed, it has been reported that the P3 no go component is small or not seen in younger children (Jonkman, 2006). The amplitude of P3 no go also increases when the reaction time (RT) decreases, and fast RT may reflect impulsivity (Aasen & Brunner, 2016).

The weak correlations between different methods of EF examination are well known (see, Toplak et al., 2013). Arguably, the different measures can provide different angles to the phenomena that are measured. Following Toplak et al (2013), it makes sense to suggest that results from neuropsychological tests can describe the child's level of *optimal* performance in a structured situation

whilst the EF ratings provide more information of “the use of different capacities in everyday life" (Toplak et al., 2013). ERPs, in turn, may capture unique aspects of EF. Indeed, some aspects are not measured by ratings and neuropsychological tests, for example how the brain gets into preparation mode. Interestingly, Peisch and Arnett (2021) came to a similar conclusion as regards to the prediction of ADHD symptomatology in a recent publication (Peisch et al., 2021).

There are some important limitations of this study. In terms of everyday EF-behaviours we only report data from parent ratings. In particular, we did not use self-reports or teacher ratings which could have provided further insights into the manifestation and context sensitivity of EF deficits. Taken together, our study resulted in a combination of novel findings and corroborations of prior knowledge, all in all contributing to a broader understanding of brain-behaviour relations of executive processes in paediatric ADHD.

5.3 STUDY 2

In the second study, 60 children, aged 9-12 years, diagnosed with ADHD were compared with a sex- and age-matched group of 69 typically developing controls. We computed an index for ADHD identification based on behaviour and ERP variables in the VCPT test that discriminated significantly between the groups with at least a moderate effect size. In total, 9 variables were combined into a potential biomarker index for ADHD. We found that combining ERPs with neuropsychological test scores on the VCPT increased the accuracy of the diagnostic index compared with test scores alone. In both the main study and in the replication study (20 ADHD, 21 matched TDC) we were able to successfully distinguish the groups with an accuracy of 84.4% (main study) and 97.7% (replication study). The results are promising when it comes to biomarker support for ADHD diagnosis in this age group (Faraone et al., 2021). Combining variables to increase classification accuracy is not a new approach (McLoughlin et al., 2014; Mueller et al., 2010). We are, however, not aware of other studies that have combined ERPs and scores from an attention test to compute a biomarker for children with ADHD. The results in a recent study by Peisch and Arnett align with the conclusion that the underlying liability for ADHD is complex and multifaceted, and that it likely involves multiple “hits” across neurological and cognitive-behavioural factors (Peisch & Arnett, 2022).

The application of machine learning in research has grown rapidly during the latest years. It is often used for classification purposes, for example diagnostic conclusions, cluster analysis, or prediction of treatment responses, and could have been an option in our study as well. Large amounts of data / variables are analysed by advanced algorithms, and the best predictors, often including many variables, are calculated. The predictors are then ideally tested on a new sample to check generalisability. In this thesis machine learning is not applied; however, the manual methods used in Study 2, ending up with a diagnostic index for ADHD based on nine variables, do have some similarities. The strength of our approach, we believe, is that all variables are meaningful and described in professional literature on executive functions and ERPs. By contrast, some of the variables picked out by the machine learning algorithms can sometimes make little theoretical sense. That being said, in future research, EEG and ERP data, along with neuropsychological test results, scores from rating scales, demographic information etc. can be fed into the machine learning algorithms to find the best possible predictors. It is often argued that classification accuracy > 80-85% can help clinicians during diagnostic considerations (J. D. Kropotov, 2016; Tye et al., 2014).

An important limitation of this article, however, is that we did not include a non-ADHD clinical comparison group. Thus, we do not know to what extent we actually identify "pure" ADHD or differences that are also associated with other diagnostic categories. Thus, while we believe that some important first steps were taken in the study, the importance of doing similar studies and including other diagnostic categories is stressed and will be elaborated upon further in the «future directions» section below.

5.4 STUDY 3

In this study, we compared grand-average ERPs and behavior test scores from VCPT in 63 adolescents (aged 12-17 years) diagnosed with ASD with a sex- and age-matched group of 60 typically developing controls. The exclusion criteria were, besides IQ< 70 and epilepsy, comorbid ADHD. The neuropsychological test scores were not significantly different between the groups, in accordance with some (Hwang-Gu et al., 2019; Høyland, Øgrim, et al., 2017; Karalunas et al., 2014; Kilincaslan et al., 2010; Tye et al., 2016) but not all prior studies (Adamo et al., 2014). VCPT tests are assumed to capture

important aspects of attentional control which is an important aspect of EF. Thus, any such EF impairments in this ASD group were not evident on this task. We speculate that some of the studies finding such differences may have included ASD participants with IQs < 70 and/or – diagnosed or undiagnosed – comorbid ADHD. This illustrates the importance of transparent participant characterisation in research as well rigorous and broad assessments in child psychiatry (Gillberg, 2010). The ERP components thought to reflect cognitive control, such as CNV (motor preparation of response), N2 no go (template update) and P3 no go (allocation of attention resources) also were not significantly different in the two groups. Although the current evidence base is smaller in the case of ASD compared with ADHD, this finding is broadly in line with other research studies, for example (Baruth et al., 2010; Cui et al., 2017; Høyland, Nærland, et al., 2017; Magnuson et al., 2019; Sokhadze et al., 2009).

In our study, two different methods were used: traditional manual registrations of ERPs, and a cluster-based permutation test, considered to be a strict method. Only one component, most clearly seen as a negative curve at site P3 in time interval 800-1100 ms. after stimulus presentation, passed the permutation test. This component, called Visual Negativity (vN), reflects visual preparation (Di Russo et al., 2019). Six additional components were significantly different between the groups when the computations were based on the manual registrations. The vN difference was seen in prepare condition (first picture is an animal), in ignore condition (first picture is a plant) and whether the picture required a response or not (go and no go). This indicates that the main difference of the ASD patients in this study is related to preparatory activities associated with visual processing, presumably in the left ventral-dorsal stream. We argue that the differences displayed by the ASD group, in our study, may reflect problems integrating bottom-up and top-down information. Di Russo et al. (2019) describe vN as a visual readiness activity. The Bayesian theory of autism claims that people with ASD do not modulate sensory input as much as others by integrating expectations, experience and context. Our results support this view. This line of reasoning is also consistent with the theoretical claim that ASD can be conceived as a disorder of prediction (Sinha et al, 2014). As pointed out by Sinha et al, prediction/ preparatory difficulties could potentially help explain aspects of functioning (e.g., an insistence of sameness) and mental health vulnerabilities (intolerance of uncertainty, risk of overarousal) in the

ASD population. As expressed by an adult woman with ASD in a qualitative interview refered to in Sinha's paper:

"I can't emphasize enough how critical it is to understand that staying on a script is the sole means of keeping anxiety at a minimum. Even the smallest breach becomes a crisis because all we register at that moment is unpredictability. We fear unpredictability above all else because we are out of control of our environment." (Sinha et al., 2014)

In studies 1 and 2 above, and in many other papers comparing ADHD with TDC, it turns out that ADHD patients struggle with cognitive control as reflected in neuropsychological tests and cognitive ERPs. Our present study on ASD does not find such deficits, but differences in early components and especially one, vN, as noted above. This lends support to the view that the executive problems of ADHD and ASD are different from each other, and potentially that different brain mechanisms are involved in executive behavior difficulties in everyday life.

A limitation in this study was that no rating scale of EF was used as a measure of EF in daily life, i.e. outside the clinic/lab. It has been shown in several studies that people with ASD very often display executive problems in everyday settings, for instance a lack of flexibility, which are closely associated with the diagnostic criteria. This possible discrepancy between, "optimal" performance and capacity, which can be strong in ASD, and very common daily life problems, is in itself an important topic, as described by Hadjikhani et al (Hadjikhani et al., 2023). In our study, EF rating scores could have been used to explore if the ERPs and test scores were associated with everyday functioning to increase the knowledge about neuropsychological and neural basis for deficits of EF in ASD. ASD is a condition not only associated with impairments and weaknesses, but sometimes also with strengths, not least in the domain of visual (local, detail-based) processing (Baron-Cohen, 2020; Blaser et al., 2014; Frith, 1996). Thus, if a broader neuropsychological test battery had been applied it would have been possible to explore if the vN deviances in the ASD group correlated with some aspects of EF behaviour, and both strengths and weaknesses.

5.5 STUDY 4

In study 4, the aim was to illustrate a broad multidisciplinary, and follow-up approach for neurodevelopmental assessment and intervention planning, and to test how ERP-data could be included as one, of several, methods in such work. An ESSENCE approach was central, as was the idea that a useful assessment includes identifying both strengths and difficulties dimensionally. In all case studies, generalisations should of course be done with caution (Peters & Ansari, 2019). That being said, the findings illustrate several important points. First, we illustrate how co-occurrence between different problem areas and diagnoses can present simultaneously in the same individual, and how this pattern can appear together with areas of considerable strengths. As pointed out by Wallace (2008), a unique perspective on the necessary preconditions for skill development can be gained by close-up studies of children with excellent skills in the context of a developmental disability (Wallace, 2008). Here, we found that problems in math, numerical and nonverbal cognitive skills were coexistent with ADHD, whereas verbal functions and, especially, word reading development was spared or even exceptionally strong. Second, we illustrate how VCPT data and cognitive ERP assessment can supplement other information and how such data both confirm and develop insights. Indeed, this boy also scored high (> 98th percentile) on the ADHD index described in Study 2, further underscoring its potential use in a case with complex ESSENCE presentation. The ERP component Cue P3 ("identification of target") was very small in this case. We argue, together with other research e.g. Abramov et al, that this component should be tested as a possible biomarker for nonverbal learning disabilities (Abramov et al., 2017).

6 CONCLUSION

6.1 GENERAL CONCLUSIONS, LIMITATIONS AND FUTURE DIRECTIONS

A first general conclusion is that the use of ERPs in paediatric ADHD and ASD evaluations seems worthwhile and informative. Ratings and neuropsychological test results can be considered as the end-product of several cognitive processes. The results cannot, however, tell us in detail what brain mechanisms are involved. Cognitive ERPs, elicited in the context of neuropsychological tests, have excellent time-resolution, and can provide more detail about such underlying mechanisms (Clarke et al., 2002). Although study 1 showed that much remains to be known about the functional meaning of some of the ERP components, and especially for younger children with atypical development, the results are broadly in line with the scientific literature (Johnstone et al., 2013; I. U. D. Kropotov, 2016; Luck, 2012). In studies 2 and 4, we found that the ERPs may indeed be informative for ADHD assessment and diagnostic decision making. Although the thesis does not include a direct comparison between ADHD and ASD participants, the results from studies 2 and 3 show that considerably clearer alterations and EF impairments at the behavioural and neural level seem to be evident in ADHD as compared to in patents with autism (IQs >70 and without comorbid ADHD). This is in line with several studies (Hwang-Gu et al., 2019; Karalunas et al., 2014; Tye et al., 2016). Of course, however, integrating results from Study 2 and Study 3 might be complicated since Study 2 is based on children and Study 3 on adolescents. In this thesis we argue that neuropsychological test scores and ERPs can contribute to increased understanding of the mechanisms involved in paediatric ADHD and ASD. In Study 2, a supplementary biomarker was calculated, based on nine variables that differentiated significantly between ADHD and TDC. The effect size of this biomarker was large, and potentially useful as a supplement to standard diagnostic procedures. We also argue that such supplements are needed because clinical experience and research show that information from patients, parents and teacher do not always coincide. Indeed, it is not uncommon that professionals disagree about what diagnosis best fits the available information (Russell et al., 2012).

The theme “supplementary biomarkers in neuropsychiatry” is included in this thesis. We have pointed out that diagnoses based on observed behaviour that

can also be part of other diagnostic categories cannot be captured by a single biomarker. The fact that most ESSENCE patients fulfill diagnostic criteria for more than one diagnosis also complicates the issue of diagnostic biomarkers. We have shown, however (Study 2), that an index based on several variables can differentiate ADHD and TDC with a large effect size. In Study 3, we compared adolescents with autism, without comorbid ADHD, with TDC. The deviances in the ASD group were different from what most studies find when ADHD and TDC are compared; instead, we found a potentially important role of vN, as a preparatory component. We argue that our "biomarker index approach" should be applied also to other diagnostic categories such as learning disabilities (LD) (general LD, dyslexia, dyscalculia), language disorders, Tourette syndrome, anxiety disorders, depression, conduct disorder etc. In line with published research, for example (Tye et al., 2014; Tye et al., 2016) we expect that patients with more than one diagnosis will display biomarker-scores associated with all their diagnoses. Some biomarkers (i.e. significant differences from TDC) will probably be associated with more than one diagnostic category, yet current knowledge is still at an early stage in this regard.

There are some limitations of the EEG/ERP techniques used in the current thesis that should be addressed. Regarding ERPs, what is recorded at the scalp is the sum of potentials generated in different brain areas. Although the areas closest to the site of registration will contribute more to the component than areas more remote, there are still clear limitations for localisation of sources. The Loreta technique (Pascual-Marqui et al., 2002), not used in this thesis, can contribute to more precise localisations, however. Another factor masking the association between psychological function and the peak registered at scalp surface is that the potentials from an earlier component, representing another psychological function, may interfere with the component of interest. In manual registrations this problem can to some extent be removed by registering a real peak, not the outskirts of a neighbour component. In this thesis, Independent Component Analysis (ICA) is not applied to the ERPs. This method can improve source localisations and perhaps better reveal associations between ERPs and behaviour.

Sometimes, although seldom, a person exhibits a negative peak instead of the expected positive peak. The functional meaning of such a pattern is not clear. It may be the result of small individual anatomic differences in the pattern of the folding of the cortex, i.e. the negative, and not the positive, dipole pointing

upwards (Luck, 2014) but much more research needs to be done in order to test such hypotheses.

Sometimes, it is argued that the identification of biomarkers would completely transform diagnostic practices in psychiatry from being subjective and flawed, to becoming objective and accurate (Botteron et al., 2012; Mehta et al., 2020; Müller et al., 2019). However, the findings of the current work suggest that it is more realistic to consider biomarkers as supplements to existing practices. Indeed, it is widely accepted that concurrent diagnostic biomarkers in psychiatry can "only be as good as the diagnostic behavioural criteria initially used to define group membership" (Stevenson & Kellett, 2010). In order to challenge and refine current diagnostic (DSM/ICD) nosology, other research designs, such as studies of treatment response (Ogrim et al., 2014) longitudinal studies of at-risk populations (Johnson et al., 2015) would be needed, possibly defining subgroups with regard to prognosis and treatment response. Also, in the foreseeable future it is unlikely that this (or any other "brain-based" method) could replace current diagnostic practices based on behavioural symptoms and expert clinical judgement. Real life problems should always be the basis for a diagnosis in psychiatry.

Many rigorous steps need to be taken in the scientific process of validating biomarkers for psychiatric conditions, including ADHD and autism. The level of accuracy in the discrimination of ADHD cases from non-cases in our study 2 were, however indeed promising in the main study sample and even better in the replication sample. Given the importance of reliable identification of ADHD (Pawaskar et al., 2020), these findings thus seem to hold potential clinical utility.

Finally, it is important to note that the current evaluation was carried out by comparing clinically referred cases diagnosed with ADHD with typically developing children recruited from ordinary school classes and/or recruited for the purpose of a data base development. While this is an important first step, future research is needed to evaluate the index's performance of discriminating ADHD from other clinical categories – some with ADHD-like symptoms, such as learning disabilities, sleep disorders, ASD, anxiety or depression. Thus, the issue of differential diagnostics in ordinary child psychiatry or mental health clinics needs to be further tested in keeping with criteria for biomarker validation (e.g. the World Federation of ADHD) and with follow-up approaches. Relatedly, a majority of ADHD and ASD patients, including the

ones participating in this thesis, also have other problems or diagnoses, making the issue of "comorbidity", or ESSENCE (Gillberg, 2010) important to consider.

Continued research along these lines is needed. The ESSENCE perspective highlights the importance of broad multidisciplinary examinations because these patients often have more than one diagnosis or challenge. In this thesis we argue that ERPs can contribute to improved descriptions of individual strengths and difficulties.

7 FUTURE PERSPECTIVES

While acknowledging all these caveats and challenges, we do find the results of the current studies to be promising. Further studies of multivariable, supplementary, biomarkers for ADHD and ASD should be conducted. We propose that the inclusion of ERPs and neuropsychological test results in the search for biomarkers in psychiatry will potentially contribute to progress in the field, and that such markers could prove to be clinically important for diagnosis, treatment predictions, prognosis and delineation of strengths and difficulties.

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