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Doctoral thesis
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a Case-Control Study

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Norwegian University of Science and Technology
Thesis for the Degree of
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ELEKTROFYSIOLOGISKE RESPONSER OG EKSEKUTIV FUNGERING HOS UNGDOM MED AUTISMESPEKTERFORSTYRRELSER

På tross av at autismespekterforstyrrelser (ASF) oppfattes som en nevrobiologisk utviklingsforstyrrelse, er diagnosen fortsatt basert på atferdsbeskrivelser. Årsaksforståelsen i dag er et samspill mellom genetikk og miljø. De store variasjonene i tilstandsgruppen nødvendiggjør forskjellige og individuelt tilpassete tiltak. Vår studie registrerte elektrofysiologiske responser under en databasert test. På denne måten ønsket vi å belyse hjerneaktivitet på et biologisk nivå *mellom* genetikk og klinikk.

Vi inkluderte 49 ungdommer 12 – 20 år med ASF og 49 ungdom uten lærevansker eller psykiatriske diagnoser (TD) og registrerte elektrofysiologiske responser i EEG på en test med både nøytrale og emosjonelle bilder som stimuli. Sosiale vansker og eksekutiv funksjon (egenledelse) i hverdagen ble kartlagt ved hjelp av henholdsvis Sosial responsivitetsskala (SRS) og Behavior Rating Inventory of Executive Functions (BRIEF), spørreskjemaer fylt ut av foreldrene. Høyere skårer viser økende vansker.

Resultatene viser forsinket gjenkjenning av emosjoner hos ungdom under 16 år med høy skåre på SRS. Atferdsdataene ellers er nokså like i de 2 gruppene og viser ved denne testen ikke eksekutive vansker i ASF gruppen, tvert imot var det tegn til økt utholdenhet hos de eldste deltagerne med høy SRS-skåre. De elektrofysiologiske målingene i de delene av testen hvor deltagerne skulle gjøre noe aktivt (trykke på en knapp) er også svært like i de 2 gruppene - ved begge typer stimuli. Deltagerne med ASF viste derimot forsinkete elektrofysiologiske responser relatert til bearbeiding av synsinntrykk og annerledes utslag i elektriske bølger relatert til skifte av oppmerksomhet i de passive delene av testen. Dette kan ha sammenheng med overfølsomhet for sanseinntrykk og uhensiktsmessig fokus på mindre relevante stimuli, kjente vansker ved ASF. Noen av deltagerne med ASF hadde samtidig ADHD, noe som

påvirket resultatene. Å undersøke samsykelighet ved forskning på nevropsykiatriske tilstander er derfor viktig for tolkning av resultater.

Å beskrive undergrupper innen autismespekteret med tanke på individualisering av tilbud har vist seg vanskelig. Atypiske elektrofysiologiske bølger kan være meningsfulle biologiske markører med tanke på underliggende forstyrrelser i hjerneaktivitet og på denne måten bidra til mer målrettede og effektive tiltak. Biologiske holdepunkter relatert til symptomer kan bidra til å beskrive undergrupper med tanke på både forståelse og behandling/ tilrettelegging.

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LIST OF PAPERS

Paper I: Høyland, A. L., Nærland, T., Engstrøm, M., Lydersen, S., & Andreassen, O. A. (2017). The relation between face-emotion recognition and social function in adolescents with autism spectrum disorders: A case control study. *PloS One,* 12(10), e0186124.

Paper II: Høyland, A. L., Øgrim, G., Lydersen, S., Hope, S., Engstrøm, M., Torske, T., ... & Andreassen, O. A. (2017). Event-Related Potentials in a Cued Go-Nogo Task Associated with Executive Functions in Adolescents with Autism Spectrum Disorder; A Case-Control Study. *Frontiers in Neuroscience*, 11, 393.

Paper III: Høyland, A. L., Nærland, T., Lydersen, S., Engstrøm, M., Torske, T. & Andreassen, O. A. Atypical Event Related Potentials revealed during the passive parts of a Go- Nogo task in Autism Spectrum Disorder. A case-control study. *(In review)*

ACRONYMS AND ABBREVIATIONS

ASD: Autism Spectrum Disorders

BRI: Behavior regulation Index

BRIEF: Behavior Rating Inventory of Executive Function

CNV: Contingent Negative Variation

DSM-5: The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

ECPT: Cued Go-Nogo task with pictures of emotional faces as stimuli

EEG: Electroencephalogram

EF: Executive functions

ERP: Event Related Potentials

ESSENCE: Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations

GEC: General Composite Index

Hz: Herz

ICD-10: International statistical classification of diseases and health-related – 10th edition.

ID: Intellectual Disability

IOS: Insistence of Sameness

IQ: Intelligence Quotient

kΩ: kilo ohm

MI: Metacognitive Index

ms: millisecond

NDD: Neurodevelopmental disorders

NVIQ: Nonverbal Intelligence Quotient

RRB: Restrictive and Repetitive patterns of Behavior

RSM: Repetitive Sensory Motor Action

RT: Reaction Time

RTV: Reaction Time Variability

S1/ 2: Correspondingly Stimulus 1 and stimulus 2 in the trial

SD: Standard Deviation

SRS: Social Responsiveness Scales

TD: Typically developing

VCPT: Cued No-Nogo task with pictures of plants/ animals as stimuli

VIQ: Verbal Intelligence Quotient

The ERP-components calculated: Cue P3, CNV, N2 Go/ Nogo and P3 Go/ Nogo.

SUMMARY

Autism Spectrum Disorder (ASD) is now regarded a neurobiological disorder (NDD) with perturbations of brain development. Even so, the diagnosis is still defined based on behavioral criteria, including developmental history and observations of present behavior. The wide range of ability and disability in ASD creates a need for tools that parse the phenotypic heterogeneity into meaningful subtypes with respect to both understanding disease mechanisms and managing symptoms. A steadily increasing number of genes are found to be associated with ASD, and the connections between genotype and phenotype is complex. Performance in neuropsychological tests show considerable variations within the group, and is not necessarily associated with symptom severity or core disease features.

The aim of the current study is to identify electrophysiological correlates of core features at a biological level *between* genetics and behavior and by this elucidate neuropathological mechanisms. The focus is on performance and electrophysiological parameters related to executive function (EF), the effect of emotional content in the stimuli and age related changes.

Electrophysiological data during a cognitive task performance were recorded to capture real time neurobiological activity. The participants included 49 adolescents 12 – 21 years with ASD and 49 typical developing (TD) adolescents in the same age range. Electrophysiological responses in the electroencephalogram (EEG) were registered while the participants completed a visual cued Go-Nogo task with either neutral (part one) or emotional (part two) pictures as stimuli. All data were registered in the two parts of the test separately. Social function was assessed by parent-rated Social Responsiveness Scale (SRS), EF by performance in the task and parent-rated Behavior Rating Inventory of Executive Function (BRIEF). The SRS and BRIEF scores were markedly enhanced in the ASD group (Cohens *d*

correspondingly 3.7/ 3.1). The effect of age was investigated either with age as a continuous variable or by splitting the participants at the age of 16 years. Performance data; reaction time (RT), reaction time variability (RTV), omissions and commissions, were registered. The following Event Related Potentials (ERPs) were computed: cue P3, CNV, N2 Go/ Nogo and P3 Go/ Nogo.

The first paper focuses on the performance data. In the part with emotional pictures, a positive correlation between reaction time (RT)/ reaction time variability (RTV) and social function (SRS) ($p = 0.044$/ 0.037) was found in the young age group, suggesting increasing difficulties in emotion recognition with increasing social problems. The results did not support the same in the old group or in part one of the task. In the last quartile of the test, RTV in participants over 16 years was negatively correlated with SRS ($p = 0.011$), suggesting enhanced sustained attention with increasing social problems.

In the second paper, ERPs elicited by the cued Go-Nogo task are discussed. The P3s, components related to target identification and response selection, were similar between ASD and TD. The CNV, associated with response preparation, was enhanced in the old group of ASD participants ($p = 0.015$). When excluding participants with comorbid ADHD this CNV enhancement increased ($p = 0.008$). In the ASD-group without comorbid ADHD, enhancement in the N2, a component supposed to represent conflict monitoring, was found. The ERPs related to emotional pictures were equally attenuated in all participants, suggesting a similar effect of stimulus content on neurophysiological responses in ASD and TD. Thus, performance in our task did not indicate executive dysfunction in ASD, despite markedly increased deficits in everyday EF as reported by scores on the BRIEF. On the contrary, the study supports enhanced response preparation and conflict monitoring in ASD. This may be related to the clinical core feature Insistence of Sameness (IOS).

The third paper aimed to evaluate the ERPs in the *passive* parts of the test, when no action was required. The peak amplitude and latency of the occipital N1, an early ERP related to visual perception, and the P3a amplitude, a component related to switching of attention, were calculated. The N1 peak was markedly delayed in ASD subjects, ($p < 0.001$, Cohens d = 0.75) and the P3a amplitude was increased ($p = 0.002$, Cohens $d = 0.64$). N1 latency and P3a amplitude correlated positively with the BRIEF ($r = 0.35/ 0.35$, $p = 0.003$).

This study supports delayed emotion recognition in young adolescents with ASD. No executive dysfunction in task performance was found, on the contrary, enhanced sustained attention measured as reduced RTV was found with increasing social problems. ERP components suggesting enhanced response preparation and conflict monitoring were registered in ASD. The ASD participants also showed delayed components related to perception and increased components related to attention orienting in the passive parts of the test, suggesting "hyper-awareness" and abnormal attention allocation. Our findings underscore the importance of controlling for comorbidity when interpreting results of studies on ASD.

Describing meaningful subtypes of ASD has proven difficult. ERP alterations may be useful biomarkers contributing to stratification of the disorder to better understand underlying pathology and guide effective interventions.

1 INTRODUCTION AND THEORETICAL BACKGROUND

The main topic of this thesis is Autism Spectrum Disorder (ASD). ASD is a neurodevelopmental disorder characterized by difficulties in social interaction and restricted and repetitive patterns of behavior (RRB) (DSM-5, 2013).

ASD is a multifaceted disorder with diagnostic core features and several additional atypicalities across abilities, comorbidities and development. The disorder affects daily living and quality of life (Bishop-Fitzpatrick et al., 2016; Meyer, Powell, Butera, Klinger, & Klinger, 2018). The neurobiological research in the field of ASD reflect different approaches; from identifying brain areas that exhibit aberrant functional responses (Ecker, 2017), to more emphasis on brain connections and functional neural synchronization, social brain networks, defining ASD as a general disorder of neural processing (Dinstein et al., 2012). All approaches point towards ASD as an early neurodevelopmental disorder (NDD). Understanding the underlying neurobiology could support stratification of the disorder and facilitate targeted actions; both early developmental interventions, targeted medical treatments and establishments of autism-friendly environments.

Neuropsychological assessments are used to chart cognitive functions in NDDs. Tests do not necessarily capture the severity of symptoms and core features in ASD, and the results reveal heterogeneity and contradictions. Although there is agreement that there is a neurobiological basis of the disorder, both neuropsychology and neuroimaging give diverging information, and the signs and symptoms defining an ASD-diagnosis are still behavioral.

1.1 Motivation and rationale

In this dissertation, electrophysiological data was used to investigate core features in ASD with the purpose to shed light on brain function and by that contribute to the understanding of neurobiology underlying the symptoms.

Through my 30 years of clinical work with children and adolescents with ASD, I have had the opportunity to follow both the changing ideas of the disorder *and* the increasing prevalence. A general change in the fields of psychiatry and neurology is currently also ongoing, merging these from dyadic medical disciplines to a more mutual understanding of neurodevelopment and brain function as determined by both biological premises and environmental influences. In the early period of genetics, the focus was finding *the* autism gene. Now we know several hundred genes increasing the susceptibility for ASD (https://gene.sfari.org/), and a variety of environmental factors influencing the chance of developing ASD (Mandy & Lai, 2016). The complexity in the association between genotype and phenotype is increasing.

The wide range of ability and disability in ASD creates a need for tools that parse the phenotypic heterogeneity into meaningful subtypes with respect to both understanding and managing symptoms. The growing number of patients and the heterogeneity (S. Georgiades et al., 2013; Geurts, Sinzig, Booth, & HappÉ, 2014; Lenroot & Yeung, 2013; Kevin A Pelphrey, Sarah Shultz, Caitlin M Hudac, & Brent C Vander Wyk, 2011) within the group, together with the limitations of available serviceable quantitative assessments, tickled my curiosity. May electrophysiology give insight into brain function underlying core features and by this be helpful in understanding the disorder?

1.2 A historical overview

ASD is characterized by difficulties in social interaction and RRB (DSM-5, 2013). The first patients we recognize as autism/ Asperger syndrome were reported by Kanner “Autistic

Disturbance of Affective Contact" (Kanner, 1943) and Asperger "Die "Autistischen Psychopathen" im Kindesalter" (Asperger, 1944) in the 1940ies . They separately describe children with disturbances of affective contact and restricted interests and stereotyped behavior. In his first report, Kanner hypothesized the specific cause of the disorder as " an innate inability to form the usual, biologically provided affective contact with people, just as other children come into the world with innate physical or intellectual handicap" (Kanner, 1943). Unfortunately, in the era of the psychoanalysis, Kanner later changed his assertions for the etiology of autism to the stating of cold and unemotional parents - special mothers - as the cause of autism. This idea was enforced by the psychologist Bruno Bettelheim in 1959 (Bettelheim, 1959a) who defines autism as a childhood psychosis "….the psychological origin of childhood schizophrenia in parental, particularly maternal, attitudes; …. its nature as an autonomous reaction to the nonspecific trauma of feeling subject to an extreme situation.…". Bettelheim later on also describes cure by psychoanalytic treatment in his paper "Joey" (Bettelheim, 1959b). The cases described by the child psychiatrist Hans Asperger (1944) showed disturbance of affective interaction and repetitive behavior similar to the cases described by Kanner (1943), but were generally more talented, both in regards to intellectual capacity and language. Until the 1970-ties Kanner's research mostly influenced the ideas of autism, leading to wasted and painful years of expensive psychotherapy for many affected children and their parents. From 1970, Sir Michael Rutter greatly influenced the understanding of autism by linking it to neurobiology (1971) through showing the increased prevalence of epilepsy and extensive defect in language and intellectual function in the group, brought forward by among others as Coleman and Gillberg (1985) in 1985. Today this association is inevitable. Both the concept of Theory of Mind (ToM) and mindblindness in ASD introduced by Simon Baron-Cohen and colleagues in 1985 (1985), and the Central

Coherence Theory introduced by Uta Frith (1994), have been fundamental in our understanding of the disorder.

The classical triad of impairments in social interaction, communication and imagination was described by Lorna Wing in 1981 (1981). She also introduced the term Asperger syndrome (1981a). With these changes in conceptualization, the phenotypic heterogeneity increased (Shafali S Jeste & Geschwind, 2014; K. A. Pelphrey, S. Shultz, C. M. Hudac, & B. C. Vander Wyk, 2011).

Since the first descriptions, the ASD diagnosis has undergone major changes (F. R. Volkmar & McPartland, 2013)

- from being a disease caused by emotional "cold mothers" to a neurobiological diagnosis with multifactorial genesis and prominent genetic influence
- from being a rare diagnosis with severe disabilities to one of the most prevalent NDDs with a prevalence between 1 and 2 %
- from being a diagnosis out-ruling other diagnoses to a diagnosis with frequent comorbidity with other neurodevelopmental/ psychiatric disorders

Today, ASD is accepted as a biological NDD of strongly genetic origin influenced by a variety of environmental factors.

1.3 ASD as a neurodevelopmental disorder

NDDs encompass a highly heterogeneous combination of impairments in cognition, communication, behavior and motor functioning associated with atypical brain development (Moreno-De-Luca et al., 2013).

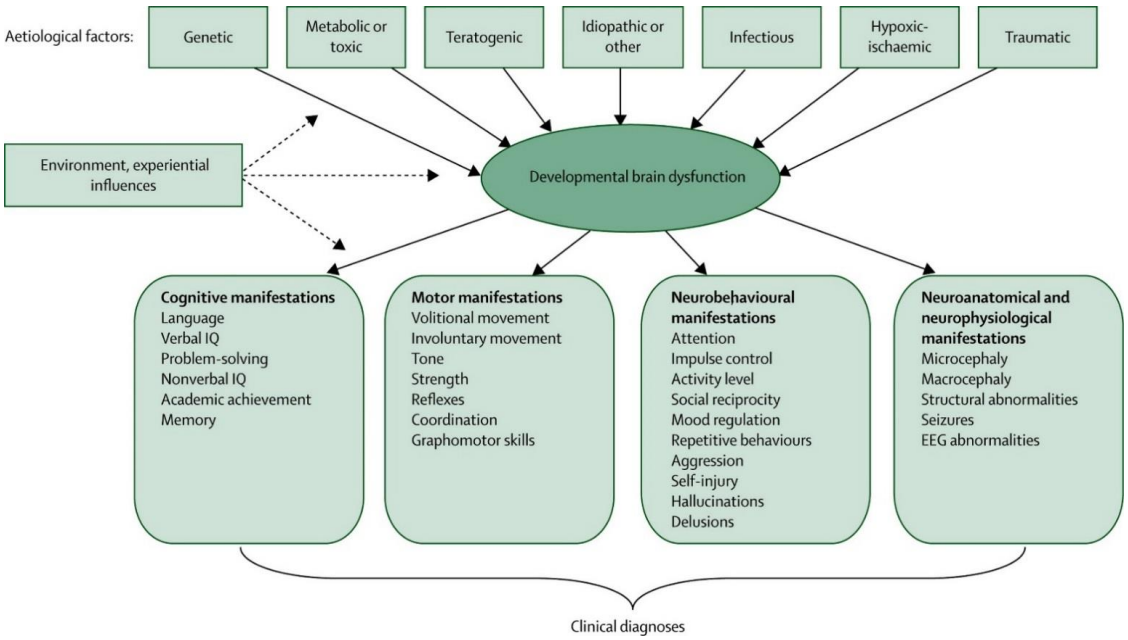

Figure 1. Model of Developmental Brain Dysfunction
Adapted from Myers (Myers, 2013)

Co-occurrence of symptoms and syndromes and diagnostic overlap among disorders that are empirically defined and categorically classified as independent disorders are common (Figure 1), and raises the question whether ASD is valid as a biological construct (Gillberg & Fernell, 2014; Hornix, Havekes, & Kas, 2018; Kas et al., 2017; L. Waterhouse & Gillberg, 2014; Lynn Waterhouse, London, & Gillberg, 2016; Zhao & Castellanos, 2016). As there have been advances in our understanding of the genetic underpinnings and environmental influences, challenges to the way boundaries have been drawn around NDDs and psychiatric disorders, and the concept of comorbidity, warrant review. Social difficulties are frequently appearing in many NDDs (Gur, Moore, Calkins, Ruparel, & Gur, 2017). Likewise, key phenotypic characteristics such as RRB are not restricted to ASD, but are also common in other syndromic and neuropsychiatric disorders as Fragile-X-syndrome, Angelman syndrome,

Tourette syndrome and Obsessive Compulsive Disorder (M. Lewis & Kim, 2009; Moss, Oliver, Arron, Burbidge, & Berg, 2009; Muehlmann & Lewis, 2012). This suggests a shared developmental brain perturbation with subsequent diverging dysfunction (M. Lewis & Kim, 2009). Through the last decades, there have been several proposals to change the outlines of the diagnoses in these groups as Gillberg's Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) (Gillberg, Fernell, & Minnis, 2014), Gilger's Atypical Brain Development (Gilger & Kaplan, 2001) and Moreno-de-Luca's Developmental Brain Dysfunction (Moreno-De-Luca et al., 2013). In the new diagnostic manual of the American Psychiatric Association, DSM-5 (DSM-5, 2013) and the proposed ICD-11 from WHO, NDD are defined as a superior category with the neuropsychiatric diagnoses e.g. ASD, attention deficit hyperactivity disorder (ADHD), and tic disorder as subtypes. This category also includes intellectual development disorder and motor disorders (DSM-5, 2013). Traditional mental disorders such as schizophrenia and bipolar disorder show developmental trajectories and have their genetic basis partly overlapping with the NDDs, and are by some researchers regarded as neurodevelopmental (Goldstein, Minshew, Allen, & Seaton, 2002; Moreno-De-Luca et al., 2013; O'shea & McInnis, 2016; Rund, 2018; Weinberger & Marenco, 2007). Growing neurobiological information showing the disease etiology and mechanisms will probably influence our diagnostic traditions (B. Albrecht et al., 2013; Hornix et al., 2018; Moreno-De-Luca et al., 2013)

1.4 Diagnosis and assessments

The changes in definitions and understanding are reflected in the diagnostic manuals. In the early diagnostic manuals (as DSM-I (1952), DSM-II (1968), ICD-8 (1968)), autism/ autistic behavior is categorized as a childhood schizophrenic reaction (Kita & Hosokawa, 2011). The next editions (DSM-III (1980) and ICP-9 (1979)) are the first to generally introduce diagnostic criteria, and describe autism as a disorder with childhood onset and distinct

subtypes. In DSM-IV (1994)/ ICD-10 (1999), Asperger syndrome appears as a defined entity. In the most recent revision of the DSM (DSM-V (2013)), there is a new change, leaving the term pervasive developmental disorder with several subtypes, and moving to one overarching diagnosis, ASD. The coming ICD-11 is expected to follow the same basic concepts.

With DSM-5 and proposed in the draft of ICD-11, the classical triad of impairments described by Lorna Wing (1979), is reduced to two symptom dimensions; social communication/ interaction and RRB (DSM-5, 2013). The deficits in social reciprocity show several different "facets", from a near absence of interest in interacting with others, to more subtle difficulties managing complex social interactions that require an understanding of other people's goals and intentions and other cues of social context (Fred R Volkmar, Cohen, Bregman, Hooks, & Stevenson, 1989; L. Wing, 1981b), and neural mechanisms underpinning poor social interaction remain unclear (Balsters et al., 2016). The other domain, RRB, is more precisely described in the latest manual revisions, and is also somewhat expanded, including sensory abnormalities (DSM-5, 2013). As important predictors of outcome, ASD-diagnosis in DSM-5 requires specification of accompanying intellectual impairment, language impairment and whether the disorder is associated with a known medical or genetic condition (DSM-5, 2013; F. R. Volkmar & McPartland, 2013).

Assessment of the behaviors that define ASD has proven difficult to do in a stringent and controlled manner (John N. Constantino & Charman, 2016). The phenotypic variation is large, both between individuals and within the life course of each individual with ASD. The core features are context-dependent, and they will typically be less apparent in situations with high degree of structure and control, compared to real life with rapidly changing multi-sensory information. The current "Gold Standard assessment" of ASD is a time-consuming process that requires suitably qualified multi-disciplinary team personnel to assess behavior

and historical information (caregiver-reported and other) (Falkmer, Anderson, Falkmer, & Horlin, 2013), including combinations of semi-structured interviews and observations (i.e. Autism Diagnostic Interview Revised (ADI-R) (Catherine Lord, Rutter, & Le Couteur, 1994) and Autism Diagnostic Observation Schedule (ADOS-2) (Catherine Lord et al., 2012)). This optimizes the diagnostic process (Falkmer et al., 2013), but the diagnostic precision is still variable as all behavioral assessments are vulnerable to the issues of subjectivity and interpretive bias.

Given the nature of developmental disorders, the expression of ASD is expected to be heterogeneous. Focused efforts to explore the neurobiological mechanisms underlying the core, homogenous components of ASD are necessary to enhance the understanding of these, and creates a need for methods to understand the phenotypic heterogeneity and define meaningful subtypes (Georgiades, Szatmari, & Boyle, 2013). The "Gold Standard" assessments are developed for diagnostic purpose (Bieleninik et al., 2017) and do not always give necessary information to identify useful endo-phenotypes that can help indexing individual differences and underlying neural processes (Bowman & Varcin, 2017).

1.5 Etiology

ASD is accepted as a NDD, with strongly genetic origin, and in interaction with environmental factors through brain development. Rutter and Sroufe (2000) introduce the concept of "developmental psychopathology" as features of psychopathology including attention to the understanding of causal processes, appreciation of the role of developmental mechanisms, and consideration of continuities and discontinuities between normality and psychopathology. This includes the idea that both typical and atypical developmental trajectories emerge from the combined effect of genes and environment, not only as additive

factors, but also in the effect of environment on genes and genetic influence on the liability to exposure of environmental factors (Rutter & Silberg, 2002).

Today we know several hundred genes (https://gene.sfari.org) implicated in ASD susceptibility. No genetic variation is pathognomonic to ASD. We also know a variety of environmental risks and protective factors influencing the chance of presenting with ASD (Kern, Geier, Sykes, & Geier, 2016; Mandy & Lai, 2016), both directly and in interplay with genes. Both the nature and the timing of these influences are crucial.

- Preconception environmental risks
    - Parental age – both paternal and maternal age is positively correlated with risk of ASD. Possible biological mechanisms include *de novo* mutations or genomic modifications associated with aging (Hultman, Sandin, Levine, Lichtenstein, & Reichenberg, 2011; Sandin et al., 2016)
- Prenatal (during pregnancy) environmental risks (H. Gardener, Spiegelman, & Buka, 2009; Mandy & Lai, 2016)
    - Maternal drug use (valproate, selective serotonin reuptake inhibitor) (J. Christensen et al., 2013)
    - Toxic chemicals (heavy metals, alcohol, chemical pesticides) (Rossignol, Genuis, & Frye, 2014)
    - Maternal severe obesity and other metabolic conditions/ hormonal regulation (Li et al., 2016)
    - Maternal immune reactions (autoimmune diseases, virus infections, other immunological mechanisms) (Brown et al., 2014; Rook, Raison, & Lowry, 2014; Zerbo et al., 2015)
- Prenatal protective factors

    - Folate supplementary to mother at start of pregnancy (Pål Surén et al., 2013)
- Perinatal risks
    - Several medical neonatal factors including perinatal asphyxia (anemia, meconium aspiration, very low birth weight) (Hannah Gardener, Spiegelman, & Buka, 2011)
- Postnatal risks
    - Severe social deprivation (not sufficient, nor necessary to *cause* ASD, but a modifier to pre-existing susceptibility to ASD) (Hoksbergen, Ter Laak, Rijk, van Dijkum, & Stoutjesdijk, 2005)
    - Neuroinflammation and encephalitis (Kern et al., 2016)

To summarize, ASD is assumed to be strongly genetic in origin, but environment may influence both emergence and subsequent developmental course of the disorder.

1.6 Epidemiology

There has been an increase in prevalence during the last 2 decades (Lyall et al., 2017). The first reports of ASD occurrence reported in 1966 (Lotter) state a prevalence of 4,5 : 10 000 children aged 8 – 10 years, while the present estimate is at least 1,5 : 100 in developed countries (Lyall et al., 2017). In the same period the share with comorbid intellectual disability (ID) falls, from approximately 85 % with intelligence quotient (IQ) < 80 in 1966 (Lotter) to 30 % with ID in 2016 (D. L. Christensen et al., 2016). The increase in prevalence cannot directly be attributed to an "epidemic" of ASD since there is evidence suggesting that changes in diagnostic criteria, diagnostic awareness, diagnostic substitution and changes in the society, both regarding special education and availability of services with a diagnosis, are considerably contributing to the rising incidence (D. V. Bishop, Whitehouse, Watt, & Line, 2008; Fombonne, Quirke, & Hagen, 2009; Lundström, Reichenberg, Anckarsäter,

Lichtenstein, & Gillberg, 2015; Lyall et al., 2017). Many, if not all, NDDs give social dysfunctions (Bora & Pantelis, 2016; Sinzig, Morsch, & Lehmkuhl, 2008), but social dysfunction is not equivalent with a diagnosis of ASD (Albin, 2017; Bunford, Evans, & Langberg, 2018) - complicating differential diagnostics. Moreover, the comorbidity seen in ASD with consequent diagnostic shading, confuses the diagnostic process (D. V. Bishop et al., 2008; Fombonne et al., 2009). The problems with accuracy in the diagnostic assessments are also revealed in incomprehensible prevalence differences as in the study of Surèn (Surén, Bakken, & Lie, 2013), showing a five-fold difference in prevalence in two neighboring Norwegian counties. Thus, the differences in prevalence are multi-causal. Despite the considerations above, a true increase of the disorder cannot be ruled out (Fombonne et al., 2009).

1.7 Developmental trajectories of core features of ASD

1.7.1 Social interaction

The earliest behavioral signs of ASD emerge in the second year of life, and the difference between children with and without ASD increases during this time with respect to social skills and language (Fombonne, 2009; Stenberg et al., 2014; Zwaigenbaum, Bryson, & Garon, 2013). The expression of the social difficulties varies, from impairments in joint attention and adverse gaze to faces in toddlers (Zwaigenbaum et al., 2013) to more subtle problems managing complex social interactions that require an understanding of other people (F. G. Happe, 1995). Behaviors related to social cognition dramatically change during adolescence, paralleled by functional changes in the social areas of the brain (Blakemore, 2008).

The ability to recognize faces is present in infants (M. H. Johnson et al., 2005) and seems to be further developed due to interactions between social stimuli and the neurobiology of "social brain circuits" (Carver & Dawson, 2002). Social reciprocity is a social norm of

responding to other people. Instant processing of others emotions is a prerequisite to this, and studies applying pictures of facial emotional expressions suggest that abnormalities in emotion recognition may underlie some of the social difficulties associated with ASD (Clark, Winkielman, & McIntosh, 2008). Lawrence et al. (2015) explored the developmental trajectory of emotion recognition in typically developing (TD) children between 6 and 16 years and found a significant age effect in the ability to recognize happiness, surprise, fear and disgust. With respect to sad and angry faces, six-year-old children demonstrated near-adult levels of accuracy. Tonks et al. (2007) assessed emotion recognition in TD children between the ages of 9 and 15 years and found that they hardly improved emotion recognition after the age of 11 (ceiling effect). Some studies show that persons with high functioning ASD have a normal ability to categorize basic facial emotions (Castelli, 2005), but show difficulties in recognition of complex emotions (Golan, Sinai-Gavrilov, & Baron-Cohen, 2015).

Improvement in emotion recognition is also seen in ASD development, but here the evidence is less clear. Peterson et al. (2015) found that children with ASD up to 12 years of age, experienced greater difficulty reading emotions from the eyes than TD. Kuusikko et al. (2009) investigated adolescents/ young adults with ASD and TD (9.8 – 21.2 years) and described reduced capabilities to recognize emotions, especially anger. Their findings support the notion that both children and adolescents with ASD have difficulties recognizing emotions and that this ability improves with age. Other findings also suggest altered ability of face recognition in ASD (Greimel et al., 2014). There was no time pressure in any of these studies and we have limited knowledge about how different age groups with ASD understand rapidly changing expressions in real-time social interaction.

Results from studies of face-emotion recognition are inconsistent in ASD and the diverging results may be due to the type of paradigm used (Lozier, Vanmeter, & Marsh, 2014; Simmons

et al., 2009). A key challenge is related to the method for presenting the facial expression. Longer reaction times were shown for individuals with ASD when identifying facial expressions was presented as a continuum of changing emotions (Teunisse & de Gelder, 2001). Clark et al. (Clark et al., 2008) argues that the duration of exposure of the pictures in the studies affects the results. Short presentation times demand a holistic strategy of facial recognition rather than focus on details (Homer & Rutherford, 2008; Teunisse & de Gelder, 2001), whereas a slower and more piecemeal mechanism for emotion recognition in ASD may contribute to the social difficulties (Deruelle, Rondan, Salle-Collemiche, Bastard-Rosset, & Da Fonséca, 2008). When pictures of faces were presented for a brief period of time, adults with ASD (mean age 26 years) were found to be significantly less accurate than TD (mean age 19,6 years) (Clark et al., 2008) . Pictures of emotional faces presented for 80 milliseconds (ms) with inter-stimulus time of 1300–1500 ms, also revealed significant differences between ASD and TD adolescents (mean age 14 years) in magnetoencephalography recordings indicating atypical neuronal activity in ASD (Leung et al., 2015).

Understanding of emotions requires interpretation of facial expressions (Rice, Wall, Fogel, & Shic, 2015) and emotional processing is closely linked to social interaction (Avery, VanDerKlok, Heckers, & Blackford, 2016). Social orienting is a prerequisite for social development, and the social motivation theory of ASD has recently gained new interest (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Clements et al., 2018). It seems likely that the ability to rapidly extract and interpret emotions (emotional processing) impacts social-emotional function and interpersonal reciprocity and thereby social motivation (Schultz, 2005). Variation in disease severity and IQ may contribute to the different findings (Lozier et al., 2014).

1.7.2 Restrictive and repetitive behavior

RRB may be subdivided in two separate categories, Repetitive Sensory Motor Action (RSM) and IOS (Cuccaro et al., 2003; Richler, Huerta, Bishop, & Lord, 2010). Richler et al. (Richler et al., 2010) investigated age trajectories of the two RRB domains in children with ASD and found divergent associations with IQ, ASD severity and age. RSM showed relationship with severity of ASD and intellectual function, and stayed stable or improved with age. Higher scores related to IOS was found with milder social/communicative deficits and with increasing age, but had no correlation to non-verbal intelligence quotient (NVIQ) at 2 years. RRB is less associated with level of language and intelligence and is thus suggested as useful in the study of neurobiology of ASD (C. Lord & Jones, 2012). The use of RRB subcategories, particularly IOS behaviors, may contribute to the creating of more behaviorally homogeneous subgroups of children with ASD (S. L. Bishop et al., 2013).

1.8 Executive function in ASD

Executive function (EF) refers to a set of higher level cognitive skills that underlie independent, goal-oriented behavior (Naomi P. Friedman & Miyake, 2017; Hughes & Ensor, 2005) necessary to complete everyday activities. Higher-order EF as reasoning, planning and problem-solving, are built on three core EFs (Diamond, 2013; Miyake et al., 2000):

- Inhibition (self-control/ behavioral inhibition and interference control (selective attention and cognitive inhibition))
- working memory
- cognitive flexibility (set shifting and mental flexibility)

EF are typically impaired in patients with acquired damage to the frontal lobes (Sbordone, 2010), but also in most NDDs. Clinicians and family members unambiguously will describe a

variety of executive dysfunctions in ASD, but this is not among the diagnostic criteria or a specific feature of the disorder. Executive dysfunction is related to quality of life in ASD (de Vries & Geurts, 2015). In subjects with ASD without intellectual disability, some studies show poor correlation between cognitive performance and symptoms of autism (Wilson et al., 2014).

1.8.1 Executive function assessments

EF pose a difficult construct to measure, partially due to the wide range of complex inter-related regulatory functions encompassed. EF is widely studied in populations of ASD – with inconsistent findings (Hill, 2004; Kenworthy, Yerys, Anthony, & Wallace, 2008). Traditionally, performance based neuropsychological testing is used for evaluation. This testing is performed in highly structured settings, where the examiner provides necessary executive control (planning, organizing, guiding and monitoring), which may limit the relevance of the results for use in real life (Isquith, Roth, & Gioia, 2013; Kenworthy et al., 2008; Wallisch, Little, Dean, & Dunn, 2018).

An alternative to testing of EF is the use of questionnaires to rate an individual's every-day real world self-regulation functioning. One widely used instrument is the Behavior Rating Inventory of EF (BRIEF) (Gerard A. Gioia, Isquith, Guy, & Kenworthy, 2000) with distinguished patterns of EF problems shown in ASD (G. A. Gioia, Isquith, Retzlaff, & Espy, 2002; Hovik et al., 2017). The metacognitive aspects of EF measured by the BRIEF are of particular importance for social abilities in children and adolescents with ASD (Torske, Nærland, Øie, Stenberg, & Andreassen, 2017). Observer-rated scales also have limitations influencing their validity (Möller, 2009).

All together there are large differences between result on performance based test results and BRIEF, and this disparity emphasizes the importance of being aware of the ecological validity

of EF assessments (Isquith et al., 2013; Kenworthy et al., 2008). Performance based and rating scale measurements provide complementary information of EF (Isquith et al., 2013).

1.8.2 Executive function and the Go-Nogo task

Performance in a Go-Nogo task requires recruitment of a variety of EF, including inhibition of prepotent responses, working memory updating/ conflict monitoring, and interference control through stimulus-driven attention/ top-down control processes (Chikazoe, 2010). Several studies show that individuals with ASD have a specific deficit in differential processing of simultaneous sources of information i.e. filtering out, or inhibiting, distracting task-irrelevant information (Adams & Jarrold, 2012; Christ, Holt, White, & Green, 2007; Christ, Kester, Bodner, & Miles, 2011; Gomot & Wicker, 2012; W. A. Johnston & Dark, 1986; Keehn, Muller, & Townsend, 2013). This is referred to as selective attention and is influenced by both bottom-up and top-down processes (Katsuki & Constantinidis, 2014; Macaluso et al., 2016). Basic sensory processing influences our cognition, and to manage a continuous input of impulses, the ability to control sensory responsiveness through gating mechanisms is considered important (Garavan, Ross, & Stein, 1999). In everyday environments, we balance bottom-up monitoring for unexpected, but potentially relevant, environmental events with top-down controlled attention to achieve goal-directed behaviors (Green, Hernandez, Bookheimer, & Dapretto, 2016; Keehn, Nair, Lincoln, Townsend, & Muller, 2016). An individual must be able to select certain sensory inputs for enhanced processing, while suppressing or filtering out others. This requires selective attention through attentional switching (Marco, Hinkley, Hill, & Nagarajan, 2011). Alerting abnormalities in ASD cannot be characterized simply by atypical levels of arousal, but may also include the impairments in regulating levels of alertness across different situations and differences in active and passive tasks (B. Keehn et al., 2013).

Some EF domains show similar results in ASD and TD (Hill, 2004), while others, as planning and mental flexibility, are affected. The review by Hill seems to suggest that school-aged and adult ASD subjects generally do not exhibit impaired inhibitory control. Response inhibition is a key deficit in ADHD (Barkley, 1997), but conflicting results are found in ASD (Adams & Jarrold, 2012; Agam, Joseph, Barton, & Manoach, 2010; K. Johnston, Madden, Bramham, & Russell, 2011).

1.8.3 Executive function and core features

ToM and EF are two separate, but central, cognitive theories linked to autistic behavior (Jones et al., 2018). ToM is assumed closely associated to impairments in imitation and social interaction (Simon Baron-Cohen et al., 1985). Evidence of significant association between poor EF and impairment in social interaction and communication exists, but null findings are more common (Jones et al., 2018).

In the review of EF in ASD, Hill associate executive dysfunction mainly with the RRB domain (Hill, 2004). The prefrontal cortex is involved in EF (Naomi P. Friedman & Miyake, 2017), and prefrontal processes seem also to be involved in RRB (Agam et al., 2010; Mosconi et al., 2009). Many studies have shown the relationship between RRB and EF (Agam et al., 2010; Boyd, McBee, Holtzclaw, Baranek, & Bodfish, 2009; Happé & Ronald, 2008; Lopez, Lincoln, Ozonoff, & Lai, 2005; Mosconi et al., 2009; Van Eylen, Boets, Steyaert, Wagemans, & Noens, 2015). Deficient response inhibition and reduced inhibitory control are specifically suggested involved in the IOS category (Agam et al., 2010; Mosconi et al., 2009; Turner, 1997). Holmboe et al. (2010) described that siblings of children with ASD showed reduced selective inhibition due to difficulties in disengaging attention, referred to as “sticky fixation”. A recent study reported reduced inhibitory control in a Go-Nogo task in adults with ASD (Uzefovsky, Allison, Smith, & Baron-Cohen, 2016) and found an association between this

and autistic traits measured by the Autism Spectrum Questionnaire. Baron-Cohen proposes a hyper-systemizing theory of autism (Simon Baron-Cohen, 2006), indicating that the "systemizing mechanism" is too high in people with ASD. As a result, they can only cope with highly lawful systems, and not with systems of high variance or change (such as the social world), resulting in resistance to change. However, this characteristic may be also facilitate superior abilities (S. Baron-Cohen, Wheelwright, Burtenshaw, & Hobson, 2007) . Also, individuals with ASD often miss "the forest", but see the trees. This may be interpreted as a weak central coherence feature (F. Happe & Frith, 2006; Van der Hallen, Evers, Brewaeys, Van den Noortgate, & Wagemans, 2015). In a review by van der Hallen (2015), they provide evidence of slow global processing; individuals with ASD are slower in grasping the gist when incongruent information is present at the local level. This suggests local-to-global interference (Van der Hallen et al., 2015).

As part of RRB are associated with talent (Simon Baron-Cohen, Ashwin, Ashwin, Tavassoli, & Chakrabarti, 2009; S. Baron-Cohen et al., 2007), it makes sense that this phenomenon is not necessarily linked to cognitive dysfunction, but other aspects of EF as rigidity and reduced flexibility.

1.9 Neurobiology

Understanding the underlying neurobiological deficits of ASD is important, and can form the basis in development of novel treatments. Functional neuroimaging studies show that several brain areas have deviant activation (Ecker, 2017; Kevin A Pelphrey et al., 2011) with some areas of particular relevance to ASD; the superior temporal sulcus, the orbital frontal cortex, the fuciform gyrus and the amygdala, and have shown good correlations between symptom severity and brain structures (Schumann, Barnes, Lord, & Courchesne, 2009). There is a considerable overlap between the neural systems underlying similar symptoms in other

psychiatric disorders and brain regions that are suggested involved in particular symptoms in ASD (Ecker, 2017). The underlying mechanisms of these deviants must be clarified to develop better disease-specific interventions. Which alterations that are primary to the symptomatology of ASD, or secondary, a downstream consequence of other basic pathological processes, are probably important, but remain mostly unknown. Studies also support abnormal electrophysiology – this is described in detail in chapter 1.10.

1.9.1 Brain development

Several studies support atypical brain development in ASD, both behavioral (Elsabbagh & Johnson, 2016; M. H. Johnson et al., 2005), electrophysiological (Belmonte et al., 2004) and neuroimaging (Ecker, 2017; Ecker, Bookheimer, & Murphy, 2015). Early neurodevelopmental perturbations are supported by enlarged brain volume (and increased head circumference) (Sacco, Gabriele, & Persico, 2015) and dynamic, age-dependent patterns of atypical structural and functional connectivity (Courchesne et al., 2007). Enlarged head circumference is significantly found in children with ASD at 2 years, but the difference declines until growth curves intersect with TD at the age of 5 – 6 years (Courchesne, 2004). This underscores the importance of critical periods for successful refinements of brain regions and connections susceptible for deviant development (LeBlanc & Fagiolini, 2011).

There are few neuroimaging studies before the age of 2 years. Studies from the first years of life have mainly reported early perturbations to the formation of white matter neurocircuitry (Ecker, 2017). Wolff et al. (2015) report increased corpus callosum area and thickness in children with ASD starting at 6 months of age, with diminishing differences by the age of 2 years. Reduced volume of corpus callosum is repeatedly found in older children and adults with ASD (Just, Cherkassky, Keller, Kana, & Minshew, 2006).

1.9.2 Brain network connectivity

During the last 10 – 15 years an increasing number of studies have investigated if ASD is a brain connectivity disorder (Belmonte et al., 2004; Dajani & Uddin, 2016; Green et al., 2016; Mark H Johnson, 2017; M. H. Johnson et al., 2005; Mark H Johnson, Jones, & Gliga, 2015; Keehn, Lincoln, Müller, & Townsend, 2010; B. Keehn et al., 2013; Padmanabhan, Lynch, Schaer, & Menon, 2017; Peters et al., 2013; Rane et al., 2015; Vertes & Bullmore, 2014; Wass, 2011; Zeng et al., 2017). The brain network is influenced by both genes and environment factors. This interaction allows formation and fine-tuning of brain circuitry, necessary to receive, organize, and respond to sensory input to behave in a meaningful and consistent manner. Just et al. (2006) suggest that the neural basis of altered cognition in ASD entails a lower degree of integration of information across certain cortical areas resulting from reduced intra-cortical connectivity. Wass (2011) gives an overview on disrupted brain connectivity in ASD and provides evidence of functional under-connectivity in mature subjects with ASD within medium- and long-range networks. ASD is by Johnson explained as an adaptive brain development pathway following diffuse aberrations in neural processing during the first year of life (Mark H Johnson, 2017; Mark H Johnson et al., 2015). Sensory atypicalities may trigger off such a deviant development (Belmonte et al., 2004). Lewis et al. (2014) suggest deficits in the optimization of both local and global aspects of network structure in regions involved in processing auditory and visual stimuli, language and nonlinguistic social stimuli in infants with ASD aged 24 months. Thus, there is an increasing support of NDD, including ASD, as a consequence of perturbed neuronal connectivity.

As described, brain development is dynamic, relying both on genetic susceptibility and interaction with environment. Neurobiological alterations affecting basic perception and

gating of inputs and attention selectivity, may disturb emphasizing and compiling of information, and thus brain development.

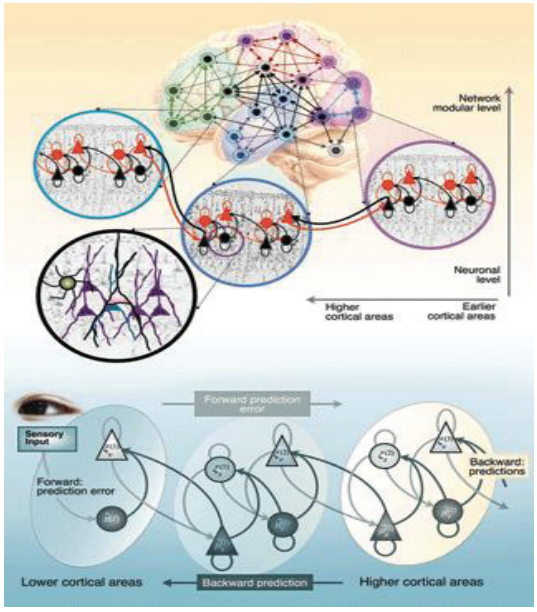

Figure 2. Schematic of the multiscale hierarchical organization of brain networks.

Brain function or cognition can be described as the global integration of local (segregated) neuronal operations that underlies hierarchical message passing among cortical areas, and which is facilitated by hierarchical modular network architectures. Park & Friston (2)

The mature brains anatomy, characterized by its connectivity, is vast, enabling action, perception, and cognition (Park & Friston, 2013). The emergence of dynamic functional connectivity, provide necessary links between structural and functional connectivity and approaches neuronal information processing that involves the dialectic between structure and function, enabling efficient hierarchical functional integration (Figure 2). Understanding these networks will require theoretical models of neuronal processing.

There is a rising amount of publications describing ASD as a consequence of atypical neurobiological networks. Attentional processes provide a critical foundation for socio-communicative abilities, and Keehn et al. (101) suggests atypical Attentional Networks as one of the primary impairments associated with ASD. Green et al. (2016) investigated The Salience Network, an intrinsic brain network thought to modulate attention to internal versus external stimuli, and found increased resting-state functional activity between salience network nodes and brain regions implicated in primary sensory processing and attention associated with sensory over-responsivity. The Default Mode Network is engaged during tasks involving social cognitive mental processes that are evaluative (Padmanabhan et al., 2017) and is implicated in several psychiatric disorders including ASD.

1.9.3 Sensory processing

Atypical sensory processing is repeatedly found in ASD since Kanners cases in 1943 (Kanner, 1943; Robertson & Baron-Cohen, 2017; Rogers & Ozonoff, 2005) and is included in RRB (DSM-5, 2013) as a core feature of ASD. Sensory abnormalities can disturb compilation of complex information (Gerrard & Rugg, 2009; Robertson & Baron-Cohen, 2017), and these sensory processing abnormalities are proposed to contribute both to the social difficulties and RRB (Brandwein et al., 2012; Gomot & Wicker, 2012). Sensory atypicalities may be divided in 3 subdomains; hyper-responsiveness, hypo-responsiveness and sensory seeking (Boyd et al., 2010). Boyd et al (2010) also report sensory abnormalities in non-autistic children with developmental delay, but found it significantly more frequent in ASD. Especially hyper-responsivity is reported in ASD, and high levels of hyper-responsiveness are found to predict high levels of RRB (Boyd et al., 2010).

Previous studies have supported atypical processing of basic visual information in ASD (Marlene Behrmann, Cibu Thomas, & Kate Humphreys, 2006) and both superior visual

research abilities (O'riordan, Plaisted, Driver, & Baron-Cohen, 2001) and inferior visual performance is described (Bertone, Mottron, Jelenic, & Faubert, 2005). Recently, Hornix et al. (2018) stated that sensory processing is affected in multiple neuropsychiatric disorders. They propose that disturbed expression levels of certain risk genes during critical neurodevelopmental periods may lead to processes within the sensory circuits with subsequent aberrant brain development.

The coexistence of atypical sensory processing and deviant change detection might contribute to intolerance of change and RRB (Cléry et al., 2013). Belmonte (Belmonte, 2017) suggests that people with ASD perceive by a process of bricolage, allowing many stimuli access to higher, more elaborated processing and that this overwhelms capacity in tasks where early filtering based on previous expectation would reduce perceptual and cognitive demands. We interpret this intolerance of change thereby linked to the clinical feature RRB in ASD, to "overcome" the load of incoming stimuli.

1.10 Electrophysiology in NDD

Electrophysiological parameters are suggested promising for advancing the diagnosis and treatment of NDD (Bowman & Varcin, 2017). The electroencephalogram (EEG) records the brain's spontaneous electrical activity over a period of time from multiple electrodes placed on the scalp. Embedded within the EEG are the neuronal responses associated with specific sensory, cognitive and motor events. It is possible to extract these responses from the overall EEG as Event Related Potentials (ERPs). ERPs are thus summated postsynaptic potentials from large synchronously activated populations of pyramidal cells in the cerebral cortex. The ERPs provide a direct and real time index of neuronal activity on a millisecond scale as series of scalp-positive and scalp-negative voltage deflections, components that are strictly time- and phase-locked to the onset of a stimulus/ an event. The ERPs are extracted in electrodes

(Figure 3) by averaging the EEG activity following multiple stimulus repetitions. Because of the excellent time-locked resolution, ERPs can reflect both low-level pathways related to perception, but also higher-level cognitive processing. ERPs are widely used to investigate neuronal activity during specific tasks in both healthy participants and subjects with neurodevelopmental and psychiatric disorders (S. S. Jeste & Nelson, 2009; Kotchoubey, 2006; Kropotov, Pronina, Polyakov, & Ponomarev, 2013; Picton & Taylor, 2007). Recent reports of relations between specific ERP-components and genes (LeBlanc et al., 2015; LeBlanc & Nelson, 2016) are also promising.

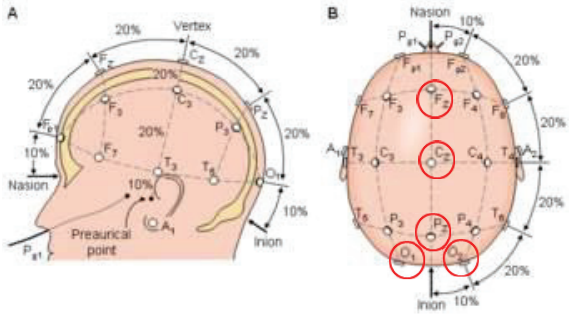

Figure 3: EEG electrodes placed according to the International 10/ 20 system
The electrodes reported in our study; Fz, Cz, Pz, O1 and O2 are marked with a red circle.

A large body of research has provided insight into how ERPs are associated with specific cognitive processes in the brain (Luck, 2014, pp. 71-117). Two main categories of ERPs are the exogenous, sensory components obligatory triggered by the presence of a stimulus, and the endogenous components reflecting task relevant cognitive processes (Luck, 2014). The deflections are named N (negative) or P (positive), and by the ordinal position of the peak in the waveform (P1, N1, P2, N2 and so on) (Figure 4). The earliest components are solely determined by the physical characteristics of the stimuli (Hopfinger & West, 2006) and the influence of endogenous attention processes increases with post-stimulus time and is altered

by attention when a discrimination is necessary. Attended stimuli generally elicit greater amplitudes. (Hopfinger & West, 2006; Vogel & Luck, 2000).

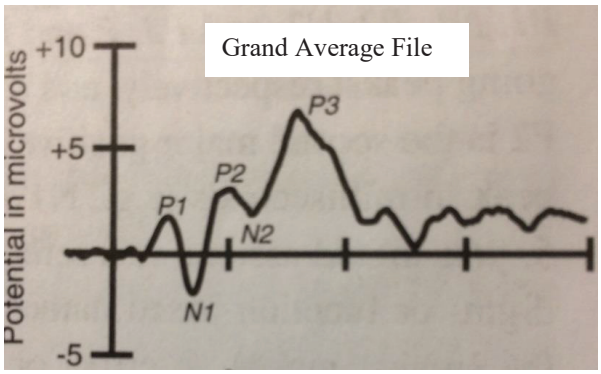

Figure 4: Overview of common Event Related Potential (ERP) components.
From Luck " An introduction to the event-related potential technique" (Luck, 2014, p. 20).

1.10.1 Electrophysiological components in the Go-Nogo task

In the cued Go-NoGo task a defined cue (S1) indicates that the subsequent stimulus (S2) may require a response. This evokes top-down response preparation processes facilitating speeded reactions (Grane et al., 2016). The contingent negative variation (CNV) is a slow negative potential elicited in the time interval between the cue and the imperative stimulus (S2), and probably indicates response preparation (Ahmadian, Cagnoni, & Ascari, 2013). The CNV is considered to be an index of both anticipatory attention for the upcoming stimulus and motor preparation needed to respond (Brunia & Van Boxtel, 2001) and is related to reaction time (RT) and reaction time variability (RTV) (Karalunas, Geurts, Konrad, Bender, & Nigg, 2014).

The N1 recorded over the visual cortex is mainly exogenous elicited by visual stimuli, but known to be modulated by top-down attention when performing discrimination tasks (Hopfinger & West, 2006). The N2 is a negative deflection approximately 200 milliseconds (ms) after S2, and is suggested to reflect conflict monitoring necessary for inhibition of a planned response (Donkers & van Boxtel, 2004). The reports of the amplitude of the frontal

N2 and also the N2-effect in the literature are conflicting (Kim, Grammer, Benrey, Morrison, & Lord, 2017; Tye et al., 2014).

The P3, a positive deflection approximately 300 ms after both stimuli (Cue P3/ P3), has been suggested to indicate the classification of the stimulus and the selection of responses (Bledowski, Prvulovic, Goebel, Zanella, & Linden, 2004) and in NoGo trials evaluate the inhibitory process after S2 (Aasen & Brunner, 2016). P3 amplitude generally is sensitive to the amount of attentional resources engaged, and will be enhanced if the subject puts more effort into the task, but attenuated if the importance of the stimuli is unclear (e.g. if the given stimulus is target or non-target) or if the task is difficult (John Polich, 1987, 2012). The characteristics of the stimuli are therefore essential for the amplitude of P3. The P3 is described with two subcomponents; an early, fronto-central component, P3a, and a later and more posterior component P3b (Y. W. Jeon & J. Polich, 2001; Nieuwenhuis, De Geus, & Aston-Jones, 2011). The P3a is thought to mirror the attention to a new object detected in the environment (Berchicci, Spinelli, & Di Russo, 2016; D. Friedman, Cycowicz, & Gaeta, 2001; J. Polich, 2007; Sokhadze et al., 2017) and to reflect activity in the prefrontal cortex and its interconnections (D. Friedman, 2008). The P3b is assumed related to target identification and response selection (Verleger, 2016).

1.10.2 Electrophysiological components associated with NDDs

Many studies have investigated EEG/ ERPs in NDDs (Ahmadlou & Adeli, 2014; Bowman & Varcin, 2017; Cui, Wang, Liu, & Zhang, 2017; Johnstone, Barry, & Clarke, 2013), but these are still mainly used in experimental task settings. However, EEG has numerous advantages that can help elucidate neurobiological pathology in NDDs. It can index neural processes independent of cognitive, linguistic and sensorimotor behavior. It tolerates motion and can be used from early infancy through adulthood. It has also low operating costs, and can be used repeatedly and potentially reveal optimal timing for intervention and treatment (Bowman &

Varcin, 2017; Luck, 2014). Some ERP studies have found increased N1 latency in ASD subjects (Baruth, Casanova, Sears, & Sokhadze, 2010; Yamasaki, Maekawa, Fujita, & Tobimatsu, 2017). Atypical visual perception together with altered connectivity of visual processing networks are suggested to contribute to the impaired social communication in ASD (Yamasaki et al., 2017). In a recent meta-analysis of ASD compared to TD, Cui et al (2016) reported some evidence for reduced P3b amplitude in ASD. Variances in paradigm and participants and also recording in the active or passive condition may contribute to this divergence (Cui et al., 2017; Keehn, Müller, & Townsend, 2013). At the same time, there are limitations to ERPs (Luck, 2014, pp. 29-31). An ERP waveform is the sum of many underlying components and it is difficult to decompose the mixture. Similarly, it is difficult to determine the neural generator locations of these individual contributors to the ERP. Further, not all mental or neural processes have an ERP "signature", as certain biophysical conditions must be met to obtain a recordable ERP. ERPs are small voltages relative to noise level and many measures are usually required to demonstrate a given ERP effect. Non-neural factors also easily create artifacts. ERPs are also not suitable for measuring large, slow voltage drifts as these are more vulnerable for noise.

1.11 Specific rationale for the current study

Core features of ASD are often easily recognizable in unstructured clinical and real life situations, but more difficult to capture in laboratory settings, and the results from laboratory tests do not necessarily reflect symptom severity (Kenworthy et al., 2008). Describing meaningful subtypes of ASD has proven difficult. Impairment may only be visible and evident later in development, although the disorders likely have roots in aberrant neural structure and function that can be traced back to the first months and years of life.

Electrophysiology has the potential to map neural functioning in many aspects; from specific components related to sensory information processing, through deviant oscillatory patterns and connectivity, to more complex, higher-level social information processing. Electrophysiological alterations may shed light on brain function at a stage *between* genetics and behavior and thus bridge different levels of analysis (low- to high-level neural processing, genes to brain, and brain to behavior) (Bowman & Varcin, 2017). ERPs may thus be useful biomarkers contributing to stratification of the disorder to better understand underlying pathology and guide effective treatment and interventions.

2 AIMS

The overall aim of this thesis is to identify electrophysiological characteristics of core clinical features in ASD with the purpose to elucidate neuropathological mechanisms. The focus is on executive aspects, the effect of emotional stimuli and relation to age.

Paper 1

- to investigate emotion processing in ASD focusing on rapid and fluent recognition using a Go-Nogo task with emotional pictures as stimuli, and compare with TD.
- to investigate the relation between task-performance and social functioning measured by the SRS
- to explore age-related aspects of emotion recognition

Paper 2

- to identify neurophysiological parameters (ERPs) related to response preparation, conflict monitoring and response inhibition in ASD in the *active* parts of the Go-Nogo task compared to TD
- to investigate the influence of the emotional content of the stimuli on these ERPs

- to explore age-related changes in these ERPs

Paper 3

- to identify neurophysiological parameters (ERPs) related to visual perception and attention orienting in ASD in the *passive* part of the Go-Nogo task compared to TD
- to investigate the relation of these ERPs with EF assessed by the BRIEF
- to explore age-related changes in these ERPs

3 METHOD

3.1 Design

A case-control study was conducted in autism spectrum disorder (ASD) and age and gender-matched typically developing (TD) adolescents. Electrophysiological components, Event Related Potentials (ERPs), were used to index neuronal activity with the purpose to elucidate neuropathological mechanisms. EFs were observed using a computerized cognitive (Go-Nogo) task with neutral and emotional pictures as stimuli. Performance data and ERPs in the different parts of the task and through the ages 12-20 years were investigated.

3.2 Participants

Fifty adolescents with a confirmed diagnosis of ASD without intellectual disability from outpatients attending St. Olavs hospital, Trondheim, Norway, were included in the study during 2013 - 2016. The sample consisted of 13 girls and 37 boys, aged 12 - 21 years, average 15.6 years. Forty-nine TD, matched for age and gender, were recruited from adjacent schools through invitations/bulletins to all students/ parents. The parents of TD participants confirmed in writing that their child did not suffer from any chronic disease or psychiatric problems presently or previously. Eighteen girls and 31 boys 12 - 20 years were included.

Intelligence Quotients (IQs) were obtained for those in the ASD group, we assumed the TD to have IQ in the normal range because they had no learning problems.

The parents of all participants completed the lifetime version of the Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003) and the Social Responsiveness Scales (SRS) (John N Constantino & Gruber, 2012) (the instruments are described in paragraph 3.5). The ASD-group had markedly increased scores on the SCQ ($p < 0.001$, Cohens $d = 3.4$) and the SRS ($p < 0.001$, Cohens $d = 3.7$) compared to the TD. The parents also filled in the Behavior Rating Inventory of Executive Function (BRIEF) (Gerard A. Gioia et al., 2000) with significant differences between ASD and TD ($p < 0.001$, Cohens $d = 3.1$).

The functioning of networks involved in cognitive control are thought to reach adult level about the age of 15 years (Solomon et al., 2014). To test if our results were associated with age, we divided the participants into two groups, above and below 16 years of age. The young group included 27 TD and 26 ASD, and the older group included 22 TD and 23 ASD individuals. This dichotomy approach was used in the first papers. Because of big latency-changes in N1-peak throughout our age span, we used age as a covariate in the third paper.

One of the participants in the ASD group scored >70% on the inattention subscale of the performance test and was excluded. The others, 49 ASD individuals and 49 TD, were all included in the study.

3.3 Diagnosis

The ASD participants were diagnosed according to the ICD-10 F.84 criteria for pervasive developmental disorder based on developmental information and clinical assessments. ADOS (C. Lord et al., 2000) was used in 43 of the 50 cases. All diagnoses were confirmed by experienced clinicians in the field of ASD. The diagnosis was underpinned by parents fulfilling the Social Communication Questionnaire (SCQ) as part of the study.

3.4 Cognitive test paradigm

Our paradigm was a visual cued Go-Nogo task which measures response preparation, conflict monitoring and response inhibition, all variables of executive function (EF) (Mueller, Candrian, Kropotov, Ponomarev, & Baschera, 2010). The categories of visual stimuli included 15 pictures of each category; animals, plants and humans in part one (VCPT), and facial emotions (angry, happy and neutral from Ekmans Pictures of facial affect (Ekman & Friesen, 1975)) in part two (ECPT). By supplementing the VCPT with an equivalent test using pictures of emotional faces, the influence of picture content both on performance and ERPs was explored. All participants completed 300 trials VCPT followed by 300 trials ECPT. Each trial consisted of a pair of stimuli (S1-S2). When S1 was a cue (animal/ angry face), the S2 was either animal/ angry face (Go trials), or plant/ happy face (Nogo trials). The When S1 was plant/ happy face (non-cue S1) they should never give response to S2. S1 and S2 are presented for 100 milliseconds (ms) with an 1100 ms inter-stimulus interval and an inter-trial interval of 3000 ms. The participants were told to response by pressing a button with their index finger as quickly as possible without making mistakes in all Go trials and otherwise refrain from responding. The time interval from the presentation of the second stimulus, S2, to the response (reaction time (RT)) and RT variability (RTV) was registered by VCPT/ ECPT software. The software also registered omissions and commissions.

3.5 Electrophysiological recordings

Electroencephalogram (EEG) was recorded using a Mitsar (http://www.mitsar-medical.com) EEG system with a 19-channel tin electrode cap (Electro-cap International, Eaton, OH, USA). The electrodes were placed according to the international 10-20-system. The input signals were referenced to earlobe electrodes and filtered between 0.5 Hz and 50 Hz and digitized at a sampling rate of 500 Hz. Impedance was kept below 5 kΩ for all electrodes. Quantitative data were obtained from the WinEEG software (www.mitsar-medical.com) in common average

montage prior to data processing. Eye blink artefacts were corrected by zeroing the activation curves of individual independent components corresponding to eye blinks. In addition, epochs of the filtered EEG with excessive amplitude (> 100 μV) and/ or slow (> 50 μV in the 0–1 Hz-band) and excessive fast (> 35 μV in the 20 – 35 Hz-band) frequency activity were automatically excluded from further analysis.

All participants had a six-minute resting EEG registration and a specialist in clinical neurophysiology examined the registrations and found no epileptic activity.

The ERPs for each individual were based on averaging the trials of the respective task condition with correct response after artefact correction. The number of artifact-free trials averaged were 269 (± 22.4, range 191-300) for TD, 261(± 37.9, range 109-295) for ASD. This makes a non-significant difference in averaged trials. The ERPs were measured by convention as mean or peak amplitudes in the stated electrode and time window as showed by the grand average file. Although mean amplitudes generally has several advantages over peak latency and amplitude (Luck, 2014), mean amplitude can lead to spurious results if there are big variations in the latency of the components. Both previous research and characteristics of the focused components have influenced which method is selected in our studies. The topography of the components is described or illustrated in Figures x, y z.

The following ERPs: Cue P3, CNV, N1, N2, P3a and P3b were computed. The N2-effect, defined as the difference between N2 Go and N2 Nogo, was also calculated.

3.6 Assessments

3.6.1 Social Communication Questionnaire (SCQ)

The SCQ (C Lord & Rutter, 2003) is a brief questionnaire that helps evaluate communication and social functioning in children who may have ASD. It is completed by a care-giver. The

content parallels that of the ADI-R, but is meant as a screener prior to a diagnostic evaluation. We used the Lifetime form that obtains information both on developmental aspects and current function.

Several studies have evaluated the SCQ (Chandler et al., 2007; Schwenck & Freitag, 2014) and confirms is utility as a screening instrument for ASD.

3.6.2 Social responsiveness Scale (SRS)

The SRS (John N Constantino & Gruber, 2012) is a 65-item questionnaire which measures various dimensions of interpersonal behavior, communication, and repetitive/stereotypic behavior characteristic of ASD. The scores are obtained for 5 treatment subscales; Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behavior. The test is validated and found acceptable for measuring social function in ASD (Bolte, Westerwald, Holtmann, Freitag, & Poustka, 2011; Bölte, Poustka, & Constantino, 2008; Murray, Mayes, & Smith, 2011).

3.6.3 Brief Rating Inventory of Executive Function (BRIEF)

The BRIEF (Gerard A Gioia, 2000) is a questionnaire designed to investigate EF problems in everyday settings. It is divided into a Behavioral Regulation Index (BRI), and a Metacognition Index (MI), which together form a Global Executive Composite (GEC). The BRI comprises the child's ability to modulate both behavior and emotional control, and the ability to move flexible from one activity to another. The MI is related to the child's ability for active problem solving, and to initiate, organize and monitor their own actions. BRIEF has shown to give an ecologically valid measurement of EF in ASD in everyday life (Hovik et al., 2017; Isquith et al., 2013; Kenworthy et al., 2008).

3.7 Statistics

Descriptive data as percentage, central tendency (Mean) and variation (SD) are reported for all measures.

Groups were compared using the Pearson chi squared test for categorical variables (Within ASD group: Subtypes of ASD, ADHD yes/no) and the Student's t-test for continuous variables (Case-control differences in: performance data; ERPs; questionnaires of ASD symptoms and BRIEF). The number of failures in ECPT (omissions and commissions) had to be log transformed to obtain approximate normality. Number of failures and differences in omissions between VCPT and ECPT were compared using Student's t-test of the log transformed variable.

Effect size was calculated as Cohens *d.*

All variables used in case-control comparisons were used as continues scales. All measures had normal distribution. Correlations are therefore calculated with Pearson's *r.* Where relevant, we also calculated partial correlations between RT ECPT and diagnosis/ SRS scores adjusting for the age and gender.

We carried out regression analyses with performance data as dependent variables and measures of ASD symptoms and diagnose as independent variables. These analyses were done for the complete sample adjusted for age group, separately for each age group, and for the complete sample including age group and its interaction with diagnosis, SRS total scale or subscales. ERP amplitudes were analyzed as dependent variables in mixed model analyses with subject as random effect, and ECPT versus VCPT, gender, and diagnosis (ASD versus TD) as independent variables. We did the analyses first for the whole sample, then separately for the two age groups. Finally, we also included the interaction between diagnosis and age group as independent variable. When relevant, we repeated the analyses for TD and ASD

without comorbid ADHD. All analyses were adjusted for gender. The assumptions of linearity, independence of errors, homoscedasticity, unusual points and normality of residuals were met.

Two-sided p-values < 0.05 were considered statistically significant, and 95% confidence intervals were reported where relevant. Due to multiple comparisons, p-values between 0.01 and 0.05 are encouraged to be interpreted with caution.

All statistical analyses were carried out in IBM SPSS Statistics v 23-25.

4 RESULTS

4.1 Paper 1

Høyland, A. L., Nærland, T., Engstrøm, M., Lydersen, S., & Andreassen, O. A. (2017). The relation between face-emotion recognition and social function in adolescents with autism spectrum disorders: A case control study. PloS one, 12(10), e0186124.

The aim of the first paper was to investigate emotion processing in ASD, focusing on rapid and fluent recognition of facial emotions in different age groups of adolescents and compared to TD. We also aimed to determine the relation between performance and social functioning measured by the SRS. A cued Go-Nogo task with pictures of facial expressions was used, ECPT, and RT (RT ECPT), RTV (RTV ECPT) and omissions/commissions were recorded. The SRS was used as a measure of social function. Analyses were conducted for the whole group and for young (< 16 years) and old (≥ 16 years) age groups.

No significant differences in any task measures between the whole group of ASD and TD and no significant correlations with the SRS was found. However, there was a non-significant tendency for longer reaction time in the young group with ASD ($p = 0.09$). In the young group, the SRS correlated positively with RT ECPT ($r = 0.30$, $p = 0.032$) and RTV ECPT ($r =$

0.28, $p = 0.037$), and, in contrast, negatively in the old group ($r = -0.23$, $p = 0.13$; $r = -0.38$, $p = 0.01$, respectively). This gives significant age group interactions for both RT ECPT ($p = 0.008$) and RTV ECPT ($p = 0.001$). When plotting the results in a scatter plot including a Loess curve separately for ASD and TD, the possible maturation/ development of emotion recognition between the groups was visualized (see Figure 4).

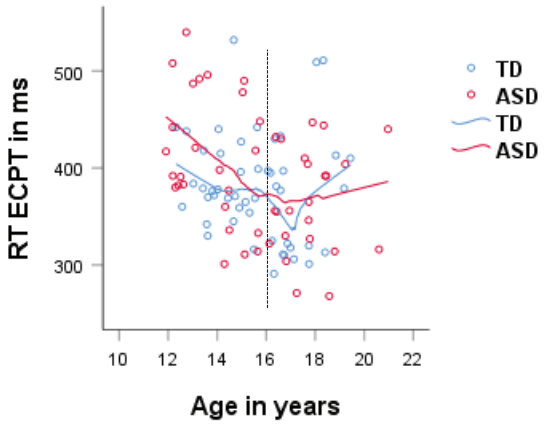

Figure 4. Loess curve Reaction Time (RT) ECPT
Age related changes in RT in Autism Spectrum Disorders and typically developing (ASD/TD).

This suggests a "ceiling-effect" of emotion recognition in ASD around 16 years, i.e. increased time for emotion recognition in the ASD participants < 16 years, but similar to TD in the old group. The TD seem to have adult emotion recognition abilities in this task before 12 years of age.

The findings suggest an age-dependent association between emotion recognition and severity of social problems indicating altered development of emotional understanding in ASD.

The RTV ECPT was also positively correlated with degree of social problems in the young participants, negatively in the older group in the in the present study, giving a significant age group * RVT interaction. In the young ASD-group increased RVT in the ECPT may be

associated with experienced task difficulty and increased cognitive effort. In the old group reduced RTV may suggest increased attentional control.

The participants also performed a similar task with neutral pictures (VCPT). In this task equal mainly similar performance between the groups of participants (TD and ASD) was found, indicating equivalent EF in the groups. RTV in both parts of the test was diminished in the old ASD group. This measure is reported to be a marker for the efficiency of top-down attentional control, and reduced RTV points towards increased top-down attentional control.

4.2 **Paper 2**

Høyland, A. L., Øgrim, G., Lydersen, S., Hope, S., Engstrøm, M., Torske, T., ... & Andreassen, O. A. (2017). Event-Related Potentials in a Cued Go-NoGo Task Associated with Executive Functions in Adolescents with Autism Spectrum Disorder; A Case-Control Study. Frontiers in neuroscience, 11, 393.

In paper 2**,** the aim was to identify differences between ASD and TD adolescents in ERPs associated with response preparation, conflict monitoring and response inhibition using the cued Go-Nogo paradigm. The effect of emotional content of the paradigm related to these ERPs, and the age-related associations was also investigated. The ASD diagnosis was underpinned by SCQ and EF problems through BRIEF, both parent rated. The ASD group showed markedly higher scores than TD in both SCQ and BRIEF. Behavioral performance and ERPs were recorded during the VCPT and the ECPT and the amplitudes of ERPs associated with response preparation, conflict monitoring and response inhibition were analyzed.

As reported in Paper 1, the performance data showed no case-control differences in either the VCPT or ECPT in the whole sample. The ERPs from in the whole groups of ASD and TD

were also mainly similar. Using emotional pictures as stimuli, elicited correspondingly attenuated ERPs in both ASD and TD. This does not support deviant processing of emotional stimuli in ASD.

N2 is thought to reflect conflict-monitoring. No difference was found between the total ASD and TD groups in the amplitude of N2 Nogo or the N2-effect. Excluding participants with comorbid ADHD, revealed a significantly increased N2 Nogo (p=0.016) and N2-effect (p=0.023) in the ASD group. The enhanced N2 Nogo and N2-effect in ASD without ADHD suggest increased conflict monitoring and detection of changes, a phenomenon that might be part of the core feature RRB as IOS and resistance to change. This pinpoints the need of a precise description of comorbid disorders when investigating ASD, as comorbidity is quite common (Gjevik, Sandstad, Andreassen, Myhre, & Sponheim, 2015) and considerably influences the results of the studies.

There were no case-control differences in the P3-components elicited in the active parts of the task, indicating normal electrophysiological correlates to EF. In this paper, local peak measures of P3b was used. The P3b-component was identical between the groups when repeating the measurement using mean amplitude ((mean (SD): TD 4.14 (2.26), ASD 4.14. (2.83)).

Splitting on age, the CNV was found significantly enhanced (p =0.015) in the old ASD. Excluding participants with comorbid ADHD increased the enhancement (p = 0.008). This suggests increased response preparation in adolescents with ASD older than 16 years, and corresponds to the reduced RTV reported in Paper 1. The CNV also showed altered age-related changes in ASD and TD, see Figure 5.

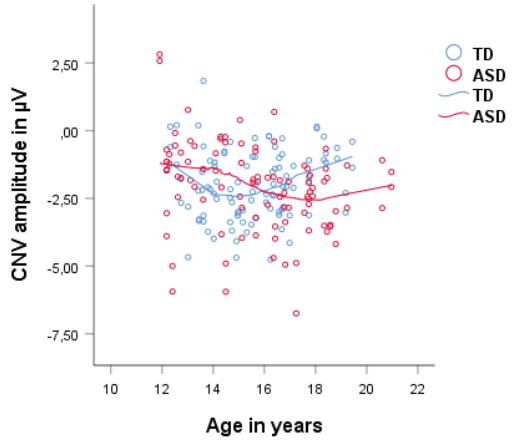

Figure 5. Contingent Negative variation (CNV) related to age
CNV from Visual Go-Nogo test with neutral pictures (VCPT) and emotional pictures (ECPT)

4.3 Paper 3

Høyland, A. L., Nærland, T., Lydersen, S., Engstrøm, M., Torske, T., Andreassen, O. A. (in review). Atypical Event Related Potentials revealed during the passive parts of a Go- Nogo task in Autism Spectrum Disorder. A case-control study.

Core features of autism spectrum disorder (ASD) are easily recognizable in clinical and real life situations. The features may be more difficult to capture in laboratory settings, and the results from laboratory-tests do not necessarily reflect symptom severity. Despite altered emotion recognition ability in young participants with ASD as found in Paper 1, the ERPs during performance were quite similar between the ASD and TD in paper 2. Given the discrepancy between the BRIEF-scores (markedly elevated) and the measured EF (mainly similar), the study aimed to map also the neurophysiological processing related to the *passive* parts of the cued Go-Nogo task.

The same sample of participants and the same tasks and questionnaires were used as in the previous studies. In this part of the study the ERPs in the passive parts of the test, that means after S1 and *non*-cue S2, when no action was required, were computed. The occipital N1 and the P3a were calculated and investigated.

During passive conditions, the ASD-group had statistical significantly longer N1 latency ($p < 0.001$, $d = 0.75$) and enhanced amplitude of P3a ($p = 0.002$, $d = 0.64$) compared to the TD, despite no differences in the same ERPs in the active condition. Both components correlated significantly to the Behavior Regulating Index of the BRIEF (partial correlation $r = 0.35$, $p = 0.003$).

The N1 was dependent of age, with negative correlations in both TD and ASD (TD: $r = -0.41$, $p = 0.004$; ASD: $r = 0.52$, $p < 0.001$), P3a showed no correlation with age (TD: $r = 0.06$, $p = 0.66$; ASD: $r = 0.03$, $p = 0.86$).

The delayed N1 response indicates altered visual perception and the enhanced P3a response indicates increased neural activation related to attention allocation, suggesting atypical control of alertness and "hyper-awareness". These ERP findings may be related to altered sensory processing and aberrant attention allocation, which are suggested as core features in ASD and are correlated to real-life EF measured by the BRIEF. These assessments during *passive* settings seem to reveal core neuropathological substrates of ASD and also suggest new approaches to laboratory testing in ASD.

5 DISCUSSION

5.1 Main findings

A visual cued Go-Nogo task with emotional pictures as stimuli was used to investigate emotion recognition. The SRS correlated positively with RT ECPT ($r = 0.30$, $p = 0.032$) and

RTV ECPT ($r = 0.28$, $p = 0.037$) in the young age group supporting *altered emotion recognition.* *No* indications of *altered emotion recognition* associated with the SRS in adolescents *16 years and older* was demonstrated.

Using non-emotional stimuli in the same task, mainly similar performance (RT, RTV, omissions and commissions) was found in ASD adolescents compared to TD. This supports *intact* EF in the ASD group regarding *response preparation, conflict monitoring and response inhibition* in this setting.

The *ERPs associated with* the *performance* parts of the test were also mainly *similar*. In the part of the task using emotional pictures, correspondingly attenuated ERPs were elicited in both TD and ASD. This does *not* support *deviant processing of emotional stimuli* in this context in ASD.

In the old age groups, the study showed reduced RTV correlated to SRS (VCPT/ ECPT $r = -0.23$, $p = 0.13$/$r = -0.38$, $p = 0.01$ respectively). Increased CNV ($p = 0.015$) was also computed in this group. These results were interpreted as *increased response preparation* and *enhanced sustained attention*, regarded as potentially superior cognitive abilities.

When analyzing ERPs *in the passive parts* of the Go-Nogo task, divergent components was found in ASD. Occipital ERP components, elicited in the early stage of visual perception, were significantly delayed ($p = 0.001$, $d = 0.75$). The study also showed an enhanced ERP component, P3a, in the central midline associated with the attention orienting ($p = 0.002$, $d = 0.64$). These findings were interpreted as associated with *altered sensory processing* and *aberrant attention allocation*, both frequent clinical features reported in ASD. There was a significant correlation between real-life EF measured by the BRIEF and these ERP components.

When excluding ASD participants with comorbid ADHD, enhanced N2 Nogo and N2-effect was found, supporting *increased conflict monitoring*. This may be related to IOS and resistance to change. The results underscore the *importance of* influence of *comorbidity* in ASD research.

The ERPs *CNV and N1* showed *age-related alterations* in ASD. The developmental trajectory of CNV seems delayed and the latency of N1 in the age group investigated is increased.

5.2 Altered emotion recognition in ASD

Social reciprocity, a core feature of ASD, requires understanding of the intentions, motivations and emotional reactions of other people. In the younger group in our study, we found similar accuracy, but a positive correlation between RT ECPT and SRS (Hoyland, Naerland, Engstrom, Lydersen, & Andreassen, 2017). We interpret the extended RT ECPT to be related to difficulty with emotion recognition. In a similar study, Akechi et al. (2009) recorded performance after presenting from the same stimuli set to children with ASD and TD aged 9 to 14 years. They found no differences in accuracy or RT regarding the recognition of emotions. However, their inter-stimulus interval was adjusted to the time the individual needed to respond or at maximum five seconds. This differs significantly from the 1800 ms used in our study, which may explain the divergent results. In older adolescents (≥ 16 years), we found no difference between the ASD group and the TD, suggesting equal ability of emotion recognition with our paradigm.

The RT in a visual selection task reflects target evaluation and is affected by age/ maturation, but also by difficulty of the task (Rojas-Benjumea, Sauque-Poggio, Barriga-Paulino, Rodriguez-Martinez, & Gomez, 2015). We did not find any significant correlation with SRS using pictures of animals/ plants in the VCPT.

Although some studies show that ASD subjects recognize still-picture basic emotional expressions as well as TD (Tanaka et al., 2012), micro-expressions with presentation time < 200 ms are suggested to be more difficult – also for TD individuals (Clark et al., 2008; Shen, Wu, & Fu, 2012). In everyday life, we meet constantly changing facial expressions. In our study, the presentation time was 100 ms, which we expected would be a challenge for the ASD group. However, the difference between rate of omissions/ commissions in the two parts of the task was not different in the ASD and TD groups (p = 0.15, Cohens d = 0.29). The lack of significant difference may be attributable to low power, as there were trend level differences.

Previous studies have shown that more complicated and subtle emotional expressions are more difficult to recognize for individuals with ASD than the basic emotions as we used in the present study (M. Behrmann, C. Thomas, & K. Humphreys, 2006). This may also have reduced the opportunity to find differences in our study.

We assessed emotion recognition ability indirectly, by measuring RT with angry face as Go-stimulus. In several studies ASD subjects show enhanced visual discrimination ability (Bertone et al., 2005; F. Happe & Frith, 2006; Shah & Frith, 1993), and could by this detect two similar pictures more easily. However, also the two happy faces were identical and had to be ruled out.

The studies included in the meta-analysis of Lozier et al. (2014) yielded inconsistent findings. Their results indicate that ASD is associated with face-emotion recognition deficits across multiple expressions and that the magnitude of these deficits increases with age. In the present study, we found the largest difference in RT ECPT in the younger group. This suggests altered face emotion recognition in ASD below the age of 16 years; after the age of 16, we found no significant differences between ASD and TD. Thus our results do not support the

conclusion of Lozier et al. (2014). As discussed in their paper, the differences may be due to differences in participants and paradigm. TD showed equal RT ECPT in the two age groups, indicating that the ability to recognize emotions in TD is established at age 12 years.

We repeated our analyses using the SRS subscale for social motivation instead of SRS total score. This subscale also correlated positively with RT ECTP among the younger (12–16 years) adolescents in the present study. This finding is consistent with the social motivation theory of autism, which proposes that ASD is an extreme case of diminished social motivation (Chevallier et al., 2012; Clements et al., 2018).

The RTV was also positively correlated to social problems in the young adolescents. RTV is related to attention deficits (Gonen-Yaacovi et al., 2016), but enhanced RTV is also found with increased cognitive demands (Vaurio, Simmonds, & Mostofsky, 2009). The increased RTV ECPT may therefore support that young ASD participants experienced difficulties with the task.

The current study supports altered emotion recognition related to increasing social problems measured by SRS in adolescents before the age of 16 years. This may be due to alterations of both biological maturation and cognitive training (Lozier et al., 2014).

5.3 Cognitive performance

We used a cued Go-Nogo task as a laboratory test of the EFs: inhibition of prepotent responses, conflict monitoring, and interference control. All participants completed the VCPT first, then the ECPT. The performance in the second part of the test including emotional pictures is described in the previous section, interpreted as related to emotion recognition in the young group, not as executive dysfunction. The performance in the part using neutral pictures as stimuli, the VCPT, was mainly similar in the ASD and TD participants. A

significant negative correlation between RTV ECPT and SRS and a non-significant correlation in the same direction in RTV VCPT was found in the old group.

The performance data do not indicate executive dysfunction in the Go-Nogo task. RTV is reported to be a marker for the efficiency of top-down attentional control (K. A. Johnson et al., 2007; Kaiser et al., 2008; Tamm et al., 2012). In a CPT-study by Lundervold et al. (2016), ASD-subjects generally performed better than TD. Other studies have shown special talents associated with an excellent attention to details and hyper-systemizing in ASD subjects (Simon Baron-Cohen et al., 2009; S. Baron-Cohen et al., 2007). Following routines may be understood as a part of RRB (DSM-5, 2013), and completing tasks is a behavior consistent with this feature. In the present study, non-systematic observation of the participant's general behavior was performed. During the test procedure, the TD participants, especially in the old group, complained about the task being boring, and yawning and groaning were observed towards the end of the test. This was not observed in the ASD group, who seemed to enjoy the task all the way through. The ECPT performance was more vulnerable to exhaustion, as this was the last part of the task, always presented after VCPT. Thus, it was an unsystematic impression of the test administrator that the motivation and attention of the TD participants decreased faster than the ASD participants.

The performance in the non-emotional Go-Nogo task was not associated with social problems measured as SRS or executive problems in daily life as expressed by the parent-rated BRIEF. The reduced RTV with increasing SRS in participants 16 years and older may reflect a talent through better sustained attention.

5.4 Event Related Potentials associated with Executive Function

In the present study ERPs associated with performance in the Go-Nogo task were mainly similar between the ASD and TD groups.

Discrimination tasks influences N1 (Hopfinger & West, 2006). Classification of the stimulus is obligatory to obtain acceptable performance in the Go-Nogo task, and the need of discrimination initiates top-down attentional influence (Hopfinger & West, 2006). In the active part of the task, when a response may be required (S2 = Go or Nogo), the occipital N1, both amplitude and latency, was similar between the ASD cases and TD.

The N2 component, supposed to represent conflict monitoring (Donkers & van Boxtel, 2004), may subsequently be related to experienced conflict (Hammerer, Li, Muller, & Lindenberger, 2010). There was no difference between the total ASD group and TD in the amplitude of N2 Nogo or the N2-effect. Tye et al. (2014) reported attenuated N2-effect in children with ASD aged 8-13 years. Faja et al. (2016) found overall enhanced N2-components in ASD in children aged 7-11 years, but similar N2-effect. Both these studies included children younger than our participants.

Reduced N2 and N2-effect is reported in ADHD (Bjoern Albrecht et al., 2008; Johnstone et al., 2013). In the present study, 17 ASD participants (35%) with comorbid ADHD were included. When excluding participants with comorbid ADHD, we found a significantly increased N2 Nogo (p=0.016) and N2-effect (p=0.023) for the whole age group. The enhanced N2 Nogo and N2-effect in the ASD participants without ADHD in this study support increased conflict monitoring and detection of changes linked to ASD. Alterations in conflict monitoring suggest increased change detection, a phenomenon that might be part of the core ASD features RRB including IOS and resistance to change. These findings of N2 deviance may implicate pathological neuronal excitability associated with arousal and flexible attention allocation.

Similar amplitudes in the ASD and TD groups were calculated in the P3 components related to the active parts of the test. There are few studies investigating the Cue P3 in ASD. Cue P3

is described attenuated in ADHD and this seems related to poorer performance (Johnstone et al., 2013). Tye et al. (2014) studied children with ASD and ADHD and combined ASD/ ADHD, and found attenuated Cue P3 related specifically to ADHD, regardless of the comorbidity with ASD. The results of the present study support similar Cue P3 in ASD and TD. However, when calculating the Cue P3 amplitude, this study did not replicate Tyes results of attenuation with comorbid ADHD (Tye et al., 2014).

The present study finds similar P3b amplitude and latency in TD and ASD. In their meta-analysis of P3 in ASD, Cui et al. (Cui et al., 2017) found mixed results. Most studies included showed reduced amplitude attributed to cognitive, attentional, and working memory processing deficiency. This reduced amplitude was only found in studies using an oddball-paradigm (Cui et al., 2017). Again, different paradigms may explain the differences in ERPs. In the present study we presented all stimuli with the same frequency, and the divergence may be explained by difference in paradigm. Cui reports similar P3b latency (Cui et al., 2017).

The CNV is an index of cortical arousal related to anticipatory attention (Tecce, 1971). Increased CNV suggests *better* attentional control (Karalunas et al., 2014). The present study found significantly increased CNV in adolescents 16 years and older with ASD compared to TD ($p = 0.015$). The amplitude of CNV was significantly negatively correlated to both RT and RTV for all participants in line with previous reports (Karalunas et al., 2014). This correlation may reflect the neuronal resources involved in the preparatory process affecting performance. Attenuated CNV is reported to be associated with attentional problems in ADHD (Doehnert, Brandeis, Imhof, Drechsler, & Steinhausen, 2010) and excluding ASD participants with comorbid ADHD increases the CNV-difference between ASD and TD also in this study ($p = 0.008$).

A detail-focused style is part of the altered perception in ASD (Mottron, Dawson, & Soulieres, 2009) and the present findings of enhanced CNV in ASD may represent a superior detail-focused cognitive style (F. Happe & Frith, 2006), the opposite of attention deficits. This is in accordance with decreased RTV. However, enhanced arousal may also be linked to the "sticky fixation" phenomenon explained as less flexible attention allocation (Holmboe et al., 2010). The increased level of attention may lead to reduced flexibility and thus problems with set-shifting; features related to IOS (Yerys et al., 2009). IOS is described to be non-related to IQ and symptom severity (Richler et al., 2010) and the enhanced CNV supports an association between CNV and IOS.

We did not replicate earlier findings of enhanced CNV in younger children with ASD (Tye et al., 2014). This may be due to differences in participants and paradigm, including inter-trial interval and the time interval for assessing the CNV.

An interesting aspect of the current study is the relations between the ERPs in VCPT and ECPT, i.e. the effect of the emotional content of the stimuli. The differences in ERPs from VCPT to ECPT were basically equivalent between ASD and TD adolescents. Generally, the ERPs were attenuated in the ECPT. Also, the age-related change in CNV in the ASD group appeared both in VCPT and ECPT. The differences may represent influence of emotional stimuli on attention and information-processing (Conroy & Polich, 2007; Delplanque, Silvert, Hot, Rigoulot, & Sequeira, 2006). As the changes were similar in ASD and TD, the study did not confirm a hypothesis of deviant brain processing of emotional pictures in ASD.

In summary, the current study demonstrates mostly similar ERPs related to cognitive performance in ASD and TD. In the old group, the CNV supports enhanced response preparation in ASD. When excluding participants with comorbid ADHD, the study suggests

increased components associated with conflict monitoring which may be related to resistance to change and IOS.

5.5 Altered sensory processing and aberrant attention allocation

The performance in the present test and the ERPs related to this, do not support executive dysfunction in ASD and do neither reflect executive problems in daily life as expressed by the parent-rated BRIEF. In the last part of the study, the focus was on the *passive* parts of the Go-Nogo test, the situations when no execution from the participants was needed. In these conditions, significantly delayed occipital N1-components and an increased fronto-central P3a-amplitude in ASD was found**.**

Visual stimuli evoke neural activity in the visual cortex that will be captured by occipital electrodes. Top-down modulation of attention increases alertness, and thus processing of new information (Hopfinger & West, 2006; Brandon Keehn et al., 2013). Attention to stimuli, and not passive watching, enhances N1 amplitude (Luck & Kappenman, 2012) and is expected to affect N1 in the present study. The N1 attention effect on the amplitude is shown to be the same for both target and non-target stimuli, consistent with a simple modulation of feedforward sensory activity (Luck & Kappenman, 2012). No group differences in N1 amplitude was found, suggesting similar attentional effect on N1 in TD and ASD.

Significantly delayed N1 is found in ASD in all passive conditions. Increased N1 latency may be associated with greater complexity (Johannes, Munte, Heinze, & Mangun, 1995; Ritter, Simson, & Vaughan, 1983), demonstrating an association between latency and processing effort. Atypical representations in primary sensory areas with altered sensory perception are described as central in ASD (Robertson & Baron-Cohen, 2017). The delay may reflect increased neuronal involvement of both important and unimportant stimuli, and as such be a neurophysiological correlate of hyper-awareness, impaired ability to suppress irrelevant or

interfering stimuli as described by Garavan (Garavan et al., 1999). The findings are in line with the assertion that abnormal processing of stimuli is a key feature of ASD cognitive style (Belmonte, 2017) and suggests that ASD individuals have difficulties with the ability to gate sensory information. Reduced sensory gating might contribute to sensory overload and experienced hypersensitivity (Pellicano & Burr, 2012). Integration of multiple local sensory stimuli into a global concept, requires temporal processing and perceptual compiling of auditory and visual signals are fundamental to language perception integrating vocal and facial cues. Aberrant dynamic integration of sensory information is suggested to perturb building of social information into meaningful representations (Robertson & Baron-Cohen, 2017). The enhanced N1 latency may represent both aberrant sensory processing and altered attentional effect. In real-life this can reflect difficulties in ignoring distracting information.

In the passive conditions, a more fronto-centrally located deflection, interpreted as P3a, was identified. This component was slightly earlier than the parietal target P3b (274 ms in contrast to 324 ms). The fronto-central P3a-component is described to reflect attention orientation to information about an impending change in the task (Barcelo, Escera, Corral, & Periáñez, 2006; Y.-W. Jeon & J. Polich, 2001). This component deflects approximately 100 ms later post-stimulus than N1, and thus, the deviances in N1 and P3a may represent different processing aspects. Our task requires discrimination, and a P3a was expected. The P3a showed a correspondingly enhanced amplitude in ASD in all passive conditions. An increased P3a amplitude mirror more effort involved in allocation or orientation to novelty and change (Cui et al., 2017).

Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment are part of RRB in DSM-5 (DSM-5, 2013). We have no clinical measurements of sensory processing in our study. Friedman and Miyake sought to examine the association

between inhibition related functions, and found that resistance to distractor interference, the ability to gate sensory information, was closely related with other components of everyday EF such as task switching ability (Naomi P Friedman & Miyake, 2004).

We found a positive correlation of both N1 and P3a with BRIEF, most markedly to the BRI index. BRI comprises the ability to modulate both behavior and emotional control, which can be affected by the "hyper-awareness". Cognitive aspects captured by the MI are less correlated to these ERPs.

The results indicate atypical visual processing supporting hyper-awareness and altered attention allocation in the passive part of the test, suggesting abnormal response to novelty. The coexistence of atypical sensory processing and deviant attentional salience detection and responses to change, will cultivate need of predictability and resistance to change, aspects of RRB (Gomot, Belmonte, Bullmore, Bernard, & Baron-Cohen, 2008; Gomot et al., 2006).

5.6 The influence of comorbidity

As described in the introduction, NDD is a heterogeneous group of disorders with overriding symptoms and frequent comorbidities. In our current diagnostic manual, ICD-10, pervasive developmental disorder (F84) is still a formal exclusion criterion for the diagnosis of Disturbance of activity and attention (F90). This may influence the diagnostic process. Mounting evidence show that comorbidity is common in ASD, with comorbid attention deficit disorder in about 30 % of subjects (Gjevik et al., 2015). In our study, comorbid ADHD is reported in about 35 % of subjects. The subgroups with comorbidity will greatly impact the findings of many studies of ASD, but are only occasionally reported.

The boundaries between the NDDs are blurred, and the rate of comorbidity is high. The influence of comorbid disorders on the ERPs illuminates the importance of detailed survey and descriptions of the participants.

5.7 Adolescence and age-related changes

Both performance and electrophysiological measurements are influenced by neurodevelopment. The ability to recognize face emotions is developed through childhood, and emotion recognition time is reduced with age until it reaches adult levels of accuracy.

TD recognize face emotions appropriately before 12 years, i.e. before the age span of this study. Face emotion recognition is found altered in ASD below the age of 16 years, as there was a positive correlation between SRS-scores and RT ECPT/ RTV ECPT in the young group. McGovern and Sigman (2005) reported a significant improvement in social function in ASD between mid-school and adolescence measured by the ADI-R. They reported different results for the younger and older age groups, consistent with the findings in the current study.

Both RT and RTV is reported generally correlated to age, decreasing in childhood and adolescence and increasing in adults (Dykiert, Der, Starr, & Deary, 2012). As discussed in the previous paragraph, changes in RT ECPT and RTV ECPT in the young group are interpreted related to emotion recognition. RT VCPT was not correlated with age in the present study (r = -0.06, p = 0.58). RTV VCPT in the whole group of participants decreases with age (r = - 2.9, p = 0.004), consistent with more stable attention in older adolescents.

Earlier studies have found increasing CNV amplitude in TD until 15 years and thereafter gradual attenuation (Cohen, 1973; Tecce, 1971). The findings in the current study are in line with this observation. In the ASD group, however, the CNV amplitude increased until approximately 17.5 years before attenuating. As the CNV is associated with attentional preparation, this alteration may reflect benefit in reaction time (Thillay et al., 2015). At the age of 20 years, the upper age limit in this study, the CNV amplitude remained enhanced in the ASD group, suggesting that these abnormalities may persist into adulthood (Thillay et al.,

2016). The reported age-related alterations of CNV in ASD may indicate a pathophysiological mechanism of executive dysfunction in ASD which could be overlapping with RRB.

N1 is recordable in infants, with decreasing latencies during infancy, childhood and adolescence (R. Johnson, 1989; Taylor & McCulloch, 1992). The present study shows a negative association between N1 latency and age. By calculating Pearson correlation, the age-related changes in ASD (r = - 0.52) and TD (r = - 0.41) are similar, indicating similar, but time-lagged, maturation processes. Enhanced N1-latency may reveal both aberrant sensory processing and altered attentional effect. To estimate the origin of these processes in early life is uncertain, and should be investigated in smaller children.

The other ERPs investigated did not show significant changes in amplitude nor latency through the studied age span.

In conclusion, age related alterations were found in both performance data (RT/ RTV ECPT and ERPs (CNV, N1) among adolescents with ASD. Longitudinal studies are needed to determine the life span patterns of these alterations.

5.8 Interpretation/ clinical implications

The most striking finding of this study is the finding of aberrant ERPs related to visual stimuli in the passive part of the cognitive task. We interpret this as altered sensory processing and aberrant attention allocation.

Atypicalities of all sensory modalities are common in ASD. The compiling of perceptual information is essential in neurodevelopment. If the temporal synthesis of sensory signals is perturbed, this may impact early brain development.

Aberrant attention allocation may suggest an inclination to process task irrelevant stimuli in the ASD group. Individuals with ASD are slower in grasping the gist when incongruent

information is present at the local level. Such processing style is likely to impact everyday performance.

If these findings in the passive parts of laboratory testing are substantiated in future studies, this may impact assessments of ASD-difficulties. Over and above, these findings highlights the importance of taking account of sensory issues in ASD interventions.

6 METHODOLOGICAL CONSIDERATIONS – STRENGTHS AND LIMITATIONS

6.1 Internal validity of the study

Internal validity refers to the degree to which the differences in our dependent variables are direct effects of our independent variables; that means if these associations most probably are real and not attributed to some other factors.

6.1.1 Bias – potential systematic errors?

6.1.1.1 Measurement bias

ERPs are eligible to cognitive factors as level of alertness and technical factors as synchronizing of the equipment. To obtain valid and reliable electrophysiological recordings, the participants must attend to the task. Acceptable reaction times and intra-individual variability and low frequency of omissions/ commissions support sufficient sustained attention. Drowsiness and hunger may affect the ERPs. To achieve a high rate of attendance, the participants could choose time for the investigation, and most EEGs were obtained after school. All participants were offered juice to drink, and breaks every 100 pair of pictures. They were tested by the same technician in the same lab to reduce variations caused by testing conditions. The task-instructions were standardized. By these adaptions we reduced the measurement biases.

6.1.1.2 Selection bias

Subjects with ASD were recruited from St. Olavs hospital. Patients attending the out-patient-unit in the current timeframe were asked to participate. To obtain a sufficient number of participants, we also invited earlier patients by an invitation letter. The major part of the patients who were invited, consented and were enrolled in the study.

A control group of TD adolescents was recruited from nearby schools. Invitations were distributed to the parents and students through the headmaster of the schools. As enrollment of ASD-subjects was fulfilled first, the inclusion of TD adolescents was controlled to the ASD-sample by frequency matching age and gender to reduce bias due to age.

6.1.1.3 Confounding factors

Since maturational processes in the brain may be deviant in the studied groups, this may contribute to confounding effect despite the matching on age and gender. Emotion recognition measured as RT/ RTV in the ECPT was age related in ASD with a ceiling effect around 16 years, with no correlation to age in TD. In study 1 and 2, we therefore split our participants in a young, under 16 years of age, and an old, 16 years and above, group. We calculated the statistics in these papers both for the whole group adjusting for age group, then for each age group separately. We also investigated the effect of group by including age group in an interaction analysis. The ERPs in paper 3 were also age-related, but with no distinct ceiling effect, and we adjusted for age as a continuous variable.

Individuals with ASD typically have discrepant profiles within cognitive tests. Studies show different discrepancies among ASD subjects – some with significantly higher verbal IQ (VIQ), others the opposite – significantly higher NVIQ (Chiang, Tsai, Cheung, Brown, & Li, 2013). This is also the case with the participants in our study. Due to the recruitment

procedure with healthy children attending mandatory public schools, we expected the TD to have IQ in the normal range and we did not obtain IQs in the control group. Lack of IQ in the TD made it impossible to adjust for IQ. However, matching ASD individuals and TD on IQ is challenging (Jarrold & Brock, 2004; Laurent Mottron, 2004) and finding matching controls with similar discrepancy without learning difficulties would be difficult. We therefore accepted participants in the broad category "IQ in the normal range". The uncertainty regarding possible group differences in IQ-profiles makes it necessary to be cautious in attributing group differences to ASD.

Can our results be the effect of comorbidity – e.g. ADHD in the ASD-group – and not to ASD? As the heterogeneity in ASD is common, we included ASD with comorbidity in our study. To adjust for this potential confounder, we repeated some analyses in ASD with and without ADHD. As reported, the differences were sometimes more salient in the ASD-group without ADHD. This comorbidity seems to weaken rather than strengthen the results.

6.1.1.4 May our results be due to chance?

ERP experiments generate large datasets containing many values for each participant, even after averaging. The richness of these datasets can lead to effects that are statistically significant due to chance, but do not reflect true differences among groups, i.e. false positive findings (Steven J Luck & Gaspelin, 2017). By focusing on ERPs described relevant in our paradigm (Brunner et al., 2015; Grane et al., 2016), we reduced this risk of Type 1 errors. We also report effect size using Cohens *d* in addition to significance in some of our calculations. The significance of probability was also considered reduced due to multiple comparisons in paper 2.

Sample size is a major determinant of how chance affects the results (Altman, 1990). Some of our results show trend significance which may be attributed to small sample size, e.g. RTV

VCPT and the difference in omissions/ commissions between the two categories of stimuli. In ASD, with so great heterogeneity, analyses of ERPs in more subgroups would be interesting. The ASD subgroups in this study contains 13 – 18 participants. Although our moderate sample size was large comparable to other studies within this field (Cui et al., 2017; Monteiro, Simões, Andrade, & Branco, 2017), the relatively small sample size limits subgroup analyses, as well as increases the risk of Type 2 errors.

6.1.2 Reliability and validity of the assessments

6.1.2.1 Behavior assessments

The questionnaires used in this study (SRS and BRIEF totals scores and subscales) are considered to have acceptable reliability and validity to assess social function and everyday EF (Bruni, 2014; Gerard A. Gioia, Isquith, Guy, & Kenworthy, 2000). However, there are also a risk of systematic distortions in observer-rated scales (Möller, 2009). The assessor's expectations influence the result of the assessment and there may be a tendency to systematically over- or under-rate the degree of disturbance. The results of assessment of one characteristic are influenced by the overall impression of the subject. The result of the assessment is influenced by the assessor's theoretical and logical preconceptions.

6.1.2.2 Outcome measures

The ERPs are averaged EEG deflections in a given location, time locked to an event. The method of calculating the ERPs will affect the results (Steven J Luck, 2014). The peak and latency in our study are manually recorded by inspecting individual ERPs. The time window for each component is defined by the average of ERPs for the whole group analyzed, the grand average file. Some ERP curves are influenced by baseline noise even after averaging and the peak may be difficult to define. In addition, deflections occur simultaneously, and will

affect each other. In our study we mostly use “local peak” measures, defined by Luck (S. J. Luck, Fan, & Hillyard, 1993) as the largest peak surrounded on both sides by lower voltages. Despite this, some peaks were difficult to identify, and a few (< 1 %) were not calculated. When there are big standard variations in the peak latencies (as in N1 in Paper 3, mean (SD) = 174.9 (18.5)), and the peaks are “narrow”, it seems inconvenient to measure mean amplitudes. Mean amplitudes within a time window are calculated by the EEG software. This method is used for estimating P3a in Paper 3. This may also be a better method for the P3s used in paper 2. However, when we checked our results using mean amplitudes, we obtained similar results.

6.2 External validity

External validity refers to the extent to which the results of a study can be generalized to other settings. Our reported ERPs are thought to mirror perceptual and cognitive brain processes. One should keep in mind, that these represent minor electrical currency measured outside the scull, and as such may be revealed as imprecise regarding underlying neural processes. The deflections found in our ERPs are though comparable with ERPs described by other research groups. Our findings pinpoint differences – or lack of differences – between the ASD group and the TD on well described ERP-components.

The heterogeneity in the ASD population limits the generalization of studies to similar subgroups within the specter. Including the potential influence of the frequent comorbidities is also necessary to interpret the results. This always should be incorporated in the discussion of results.

7 CONCLUSION

Our study supports altered emotion recognition with increasing scores on the SRS in the total sample of young adolescents. We find mainly similar performance and performance-related

ERPs in ASD compared to TD in the active part of a cognitive task, the Go-Nogo test. Emotional pictures as stimuli generally attenuate the ERPs, but similarly in ASD and TD. ERPs related to response preparation are increased in ASD 16 years and older. However, parent-rated BRIEF reveals substantial executive dysfunction in everyday life. We find aberrant ERP signals in ASD during the passive part of the Go-Nogo test, suggesting "hyper-awareness", abnormal attention allocation and atypical control of alertness. There was a significant relation between real-life EF measured by BRIEF and these components. This suggests that assessments during the passive parts of testing may reveal important information of core neuropathophysiology in ASD. We also find atypical age-related changes in some ERPs.

Investigating a developmental disorder in adolescence challenges our understanding on how the present pathology could have emerged from abnormal developmental processes and sensory alterations several years prior to the present symptoms. Perturbed brain development is suggested as an adaptive and compensatory process in ASD following mild, but widespread disturbances in early years. These disturbances may be due to genetics and environment or most often, the combination of these factors. We are still at a promising start in describing the developmental formation of complex brain networks in humans, and the ways in which brain networks can develop atypically in patients with NDDs. Electrophysiology has the potential to map neural functioning in many aspects and bridge different levels of analysis. This knowledge will hopefully in the future inform both treatment strategies and other interventions.

As the overall aim of this thesis was the use of electrophysiological data to illuminate core features in ASD, we consider the results to contribute to understanding of the neurobiology

underlying the symptoms. Longitudinal studies including young children would give further information on brain development in NDD.

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Paper I

PLOS ONE

RESEARCH ARTICLE

The relation between face-emotion recognition and social function in adolescents with autism spectrum disorders: A case control study

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Abstract

An altered processing of emotions may contribute to a reduced ability for social interaction and communication in autism spectrum disorder, ASD. We investigated how face-emotion recognition in ASD is different from typically developing across adolescent age groups. Fifty adolescents diagnosed with ASD and 49 typically developing (age 12–21 years) were included. The ASD diagnosis was underpinned by parent-rated Social Communication Questionnaire. We used a cued GO/ NOGO task with pictures of facial expressions and recorded reaction time, intra-individual variability of reaction time and omissions/commissions. The Social Responsiveness Scale was used as a measure of social function. Analyses were conducted for the whole group and for young (< 16 years) and old (≥ 16 years) age groups. We found no significant differences in any task measures between the whole group of typically developing and ASD and no significant correlations with the Social Responsiveness Scale. However, there was a non-significant tendency for longer reaction time in the young group with ASD ($p = 0.099$). The Social Responsiveness Scale correlated positively with reaction time ($r = 0.30$, $p = 0.032$) and intra-individual variability in reaction time ($r = 0.29$, $p = 0.037$) in the young group and in contrast, negatively in the old group ($r = -0.23$, $p = 0.13$; $r = -0.38$, $p = 0.011$, respectively) giving significant age group interactions for both reaction time ($p = 0.008$) and intra-individual variability in reaction time ($p = 0.001$). Our findings suggest an age-dependent association between emotion recognition and severity of social problems indicating a delayed development of emotional understanding in ASD. It also points towards alterations in top-down attention control in the ASD group. This suggests novel disease-related features that should be investigated in more details in experimental settings.

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by a reduced ability to participate in social interactions and a tendency to engage in repetitive and stereotypic behaviors [1]. Recent research on the neurobiology of ASD has provided insight into the genetic basis [2], the brain abnormalities [3, 4] and the cognitive aspects of the impairments [5]. Deficits in emotional understanding are identified as one of the diagnostic criteria for ASD in both the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association 2013) and the International Statistical Classification of Diseases and Related Health Problems, (ICD-10, World Health Organization 2004). Face-emotion recognition precedes emotional understanding and studies applying pictures of facial emotional expressions suggest that abnormalities in emotion recognition may underlie some of the social difficulties associated with ASD [6]. Furthermore, it seems like age is of importance in emotional understanding [7]. An interesting hypothesis is that deviant development trajectories underlie the face processing impairments in individuals with ASD [8].

The development of emotional understanding has been extensively studied. The ability to recognize faces is present in infants [9] and seems to be further developed through childhood and adolescence due to interactions between social stimuli and the neurobiology of "social brain circuits" [10]. Lawrence et al. [7] explored the developmental trajectory of emotion recognition in typically developing (TD) children between the ages of 6 and 16 years. They found a significant age effect in the ability to recognize happiness, surprise, fear and disgust. With respect to sad and angry faces, six-year-old children demonstrated near-adult levels of accuracy. Tonks et al. [11] assessed emotion recognition in TD children between the ages of 9 and 15 years and found that they hardly improved emotion recognition after the age of 11 (ceiling effect). Behaviors related to social cognition dramatically change during adolescence, and this is paralleled by functional changes in the social areas of the brain [12]. Deviant emotional processing seems also to play a role in ASD development, but here the evidence is less clear. Peterson et al. [13] found that children with ASD up to 12 years of age experienced greater difficulty reading emotions from the eyes than TD. Kuusikko et al. [14] described reduced capabilities to recognize emotions, especially anger. Their findings support the notion that both children and adolescents with ASD have difficulties recognizing emotions and that this ability improves with age. Other findings also suggest delayed ability of face recognition in ASD [8]. There was no time pressure in any of these studies and we have limited knowledge about how different age groups with ASD understand rapidly changing, steady upcoming facial expressions.

Understanding of emotions requires interpretation of facial expressions [15]. Results of studies of face-emotion recognition are inconsistent in ASD and the diverging results may be due to the type of paradigm used [16]. A key challenge is related to the method for presenting the facial expression. Clark et al. (2008) argues that the duration of exposure of the pictures in the studies affects the results. Short presentation times demand a holistic strategy of facial recognition rather than focus on details [17], whereas an altered mechanism for emotion recognition in ASD may contribute to the social difficulties [18]. When pictures of faces were presented for a brief period of time, adults with ASD (mean age 26 years) were found to be significantly less accurate than TD (mean age 19,6 years) [6]. Pictures of emotional faces presented for 80 milliseconds (ms) with inter-stimulus time of 1300–1500 ms also revealed significant differences between ASD and TD adolescents (mean age 14 years) in magnetoencephalography recordings indicating atypical neuronal activity in ASD [19].

Emotional processing is closely linked to social interaction [20]. Social orienting is a prerequisite for social development, and the social motivation theory of ASD has recently gained new interest [21]. It seems likely that the ability to rapidly extract and interpret emotions

(emotional processing) impacts social-emotional function and interpersonal reciprocity and thereby social motivation [22]. Some studies show that persons with high functioning ASD have normal ability to categorize basic facial emotions [23]. ASD show difficulties in recognition of complex emotions [24]. Longer reaction times were shown for individuals with ASD when identifying facial expressions presented in a continuum of changing emotions [25]. However, the relationship is still not well understood. There may be other factors explaining the differences in the literature. Variation in disease severity and IQ may contribute to the different findings [16].

In addition to reaction time on a face-emotion recognition task, recent evidence suggests that intra-individual variability (IIV) may distinguish ASD from other developmental disorders and TD [26]. Lundervold et al. [26] found less variability in the ASD group compared to ADHD, combined ASD and ADHD and TD using Conners' Continuous Performance Test (CPT-II) [27]. Vaurio et al.[28] reported increased IIV with increased cognitive load. However, no study has investigated how variability changes with age in ASD. The visual CPT (VCPT) has been used in studies with neuropsychiatric disorders such as ADHD [29], but not yet in ASD and there have been few attempts to compare the differences when using neutral or emotional stimuli in a cued GO/ NOGO paradigm. Since emotional processing seems affected in ASD, it would be of interest to investigate differences between a standard VCPT paradigm and VCPT with emotional pictures, ECPT [30].

The aim of the current study was to investigate aspects of emotion processing in ASD focusing on rapid and fluent recognition of facial emotions in different age groups of adolescents with ASD compared to TD. We also aimed to determine the relation between ECPT performance and social functioning measured by the SRS. We applied a novel paradigm presenting the stimuli as a continuous load of brief pictures in a cued GO/ NOGO paradigm using pictures of emotional faces, ECPT. This design requires both emotion recognition, attention orienting and inhibition control. We hypothesized that the time to extract emotions, reaction time (RT ECPT), is increased in the adolescents with ASD compared to the TD group. We expected these abnormalities to be associated with core ASD symptoms in social functioning and consistent through our age span. Because the evaluation time for each stimulus was limited, we expected the ASD group to fail more often in the recognition of emotions. As understanding of emotions and motivation for social interaction are both crucial for social function, we also investigated the relations between RT ECPT and the subscales Social Cognition and Social Motivation in the SRS. Reduced IIV is reported in ASD [26], and we also investigated the IIV in relation to diagnosis, severity of social symptoms and age group.

Methods

Participants

Fifty adolescents with a prior diagnosis of ASD without intellectual disability from outpatients attending St. Olavs Hospital, Trondheim, Norway, were included in the study (Table 1).

The participants were between 12 and 21 years with 13 girls and 37 boys. The ASD individuals were diagnosed according to the ICD-10 F.84 criteria for pervasive developmental disorder based on developmental information and clinical assessments. They were also subgrouped into infantile autism, Asperger's syndrome and pervasive developmental disorder, unspecified, PPD-NOS. The ADOS (Autism Diagnostic Observation Schedule [31]) was used in 43 of 50 cases. IQs were obtained in the ASD group. Full-scale IQs (FIQs) ranged between 67 and 133. When the difference between verbal and performance IQs was $\geq$ 30, we did not calculate FIQs. To be included in the study, verbal or performance IQ had to be within the normal variation ($\geq$ 70). Eighteen (37%) individuals in the ASD group had neuropsychiatric

Table 1. Demographics.

	ASD		TD	
	n	%	*n*	%
	49	**100**	**49**	**100**
Gender				
Male	36	73.5	31	63.3
Female	13	26.5	18	36.7
ASD subgroup				
Infantile autism	13	26.5		
Asperger disorder	18	36.7		
PDD NOS	18	36.7		
Age–years				
Mean (*SD*); range	15.6 (±2.4); 11.9–20.9		15.6 (±1.8); 12.3–19.4	
< 16 years	26	53.1	27	55.1
Mean (*SD*); range	13.7 (±1.3); 11.9–15.7		14.2 (±1.0); 12.3–15.7	
≥ 16 years	23	46.9	22	44.9
Mean (*SD*); range	17.8 (±1.3); 16.1–21.0		17.3 (±1.1); 16.1–19.4	
IQ Mean (*SD*); range				
Full scale IQ (*n* = 36)	91.9 (±17.7); 67–133			
Verbal IQ (*n* = 47)	87.6 (±19.0); 52–130			
Nonverbal IQ (*n* = 48)	98.1 (±19.3); 58–139			
Comorbidity				
No comorbidity	31	63.3		
More than one comorbidity	7[1]	14.3		
Comorbid AD/HD	17[1]	34.7		
SCQ Mean (*SD*); range	18.7 (±6.7); 5–34		1.9 (±2.3); 0–8	
SRS Mean (*SD*); range	80.1 (±14.4); 47–109		40.6 (±4.2); 34–51	

[1] All but one participant with comorbidity had comorbid AD/HD. These are hence reported twice in the table, both in "More than one comorbidity" and "Comorbid AD/HD".

Separate information for each diagnostic group (S1 Table) and for each age group (S2 Table) is available in Supporting Information.

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comorbidity, all but one with attention problems (Attention Deficit Disorder with or without hyperactivity (AD/HD)). The differences in comorbidity with AD/HD in the younger versus older is not significant (Pearson's chi squared, $p = 0.234$). Eight (16%) had more than one comorbid diagnosis. Six (12%) had an epilepsy diagnosis, all but one with co-occurring AD/HD. All participants had a six-minute resting EEG registration. A specialist in clinical neurophysiology examined the registrations and found no epileptic activity. Twelve (25%) of the ASD individuals received medication. Four were on stimulants, two used atomoxetine and the six with epilepsy were on antiepileptic medication.

We recruited 49 TD adolescents, matched for age and gender as a control group. These individuals were recruited from adjacent schools through invitations/bulletins to all students/parents. Also, the parents were involved, and in writing confirmed that their child did not suffer from any chronic disease or psychiatric problems now or previously.

To investigate developmental differences, we divided the participants into two age groups. We split at the age of 16 years to obtain equal group sizes. The < 16-years group (young group) included 27 ASD individuals and 27 TD, and the ≥ 16-years group (old group) included 23 ASD individuals and 22 TD.

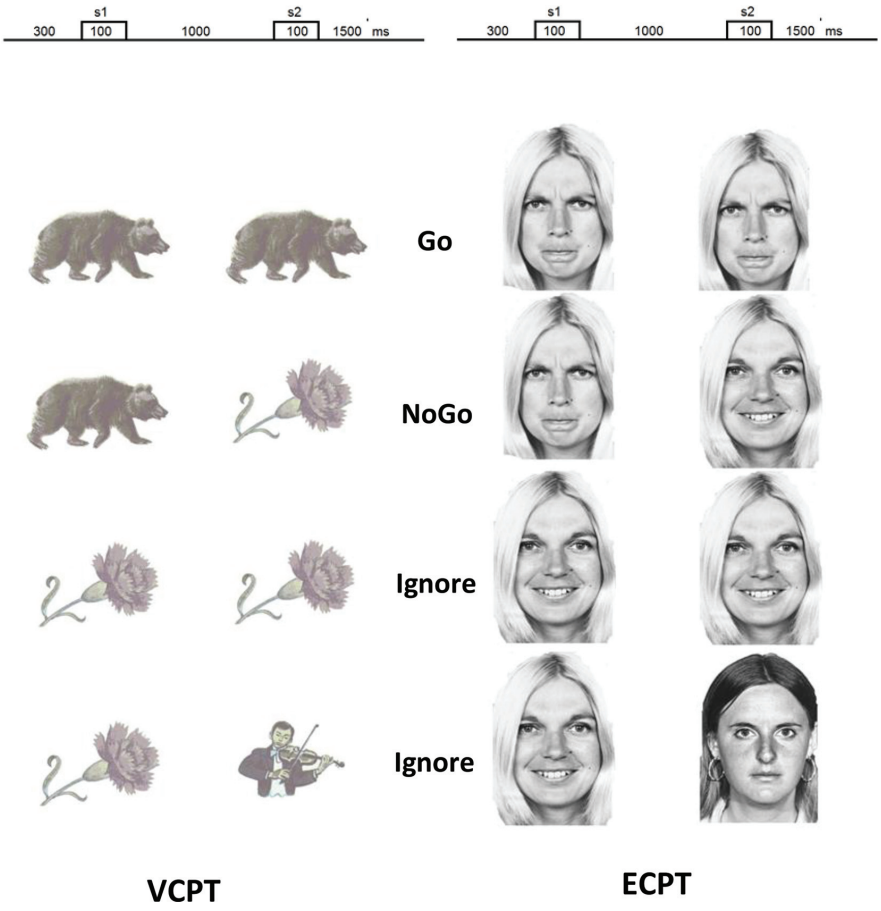

Fig 1. Task stimuli, VCPT and ECPT.

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One of the participants in the ASD young group scored > 70% inattention on the continuous performance test and was excluded. The others, 49 ASD individuals and 49 TD, were included in the study.

Measures

Cued GO/NOGO task. The Visual Continuous Performance Test (VCPT) measures variables of attention and reaction time using a cued GO/ NOGO task [29]. The three categories of visual stimuli include 15 pictures of animals, 15 pictures of plants and 15 pictures of humans (Fig 1). The Emotional Continuous Performance Test (ECPT) is a similar test as the VCPT but uses pictures of faces with emotional affect [32] from Ekman and Friesen [33]. The categories of the pictures on the ECPT include 15 pictures of angry faces, 15 pictures of happy faces and 15 pictures of neutral faces (Fig 1). The trials present pairs of pictures: animal–animal on

the VCPT or angry–angry on the ECPT (GO trials), animal–plant/ angry–happy (NOGO trials), plant–plant/ happy–happy and plant–human/ happy–neutral (IGNORE trials). The participants were asked to respond by pressing a button with right index finger as quickly as possible without making mistakes in all GO trials and otherwise refrain from responding. Each trial consists of two pictures presented for 100 ms with an 1100 ms inter-stimulus interval and an inter-trial interval of 3000 ms. The trials for each task (VCPT and ECPT) are grouped into three blocks separated by a short break. In each block, a unique set of five pictures from each picture category is selected. Each block consists of a pseudo-random presentation of 100 stimuli pairs with equal probability for each trial category.

All participants were first presented the VCPT, which was immediately followed by the ECPT. The participants sat in a comfortable chair 1.2 m from the computer screen during the task. The pictures were presented on an 18-inch monitor using the Psytask (http://bio-medical.com/products/psytask.html) software (from Bio-medical, Clinton Township, Michigan USA). The time interval from the presentation of the second stimulus to response was registered by VCPT/ECPT software as the reaction time (RT VCPT/ RT ECPT). The reported reaction time is the average time for correct responses. The intra-individual variability, IIV, measured as Standard Error, $\frac{SD}{\sqrt{n}}$, and the number of omissions and commissions (response in NOGO-trials) were also registered.

All participants were tested by the same technician in the same lab to reduce variations caused by testing conditions.

Social Communication Questionnaire (SCQ) and Social Responsiveness Scale (SRS). The ASD diagnosis was supported by the Social Communication Questionnaire (SCQ) [34]. The SCQ is a 40-item parent report questionnaire based on the Autism Diagnostic Interview–Revised (ADI–R; Lord et al. 1994) and is validated for the diagnosis of autism (Berument et al. 1999). The autistic symptom severity was measured by the Social Responsiveness Scale (SRS) [35]. SRS is a 65-item questionnaire for caregivers where they quantify the level of autistic traits or autistic severity [36]. The reliability and validity of SRS seems satisfactory [37, 38], and SRS scores are associated with Autism Diagnostic Interview–Revised (ADI–R) scores [39]. It generates scale scores for specific symptom domains as well as a singular total score, which indicates the severity of social impairment [40]. We registered the total score and two subscale scores, Social Cognition and Social Motivation, in both the ASD and the TD.

The ASD group had significantly higher mean symptom scores on both instruments compared to the TD group. (SCQ $p<0.001$ and SRS $p<0.001$). There were no differences in these scores between the different age groups.

Study design and outcomes

The primary outcome for this study was facial emotion recognition time, i.e. RT ECPT, related to diagnosis and social function measured by SRS total score. This reaction time is influenced by the participants' ability to rapidly and correctly recognize the emotions, but also the individual's general reaction time. We therefore adjusted our analyses for RT VCPT as an estimate of general reaction time. Subsequently we investigated the relation between RT ECPT and the sub-scales Social Cognition and Social Motivation of the SRS, and the results from the sub-scales are reported as sub-analyses.

Secondary outcomes were failures of omissions, failures of commissions and intra-individual variability, IIV, measured as the standard error.

Measure scores were analyzed for the whole group of participants and separately within each of the two age groups.

Statistical analysis

Groups were compared using the Pearson chi squared test for categorical variables and the Student's *t*-test for continuous variables.

We compared the difference between RT ECPT and RT VCPT using independent *t*-tests and we computed the association between RT ECPT and RT VCPT for all participants using Pearson's correlation coefficient. We carried out regression analyses with Reaction Time, RT ECPT, as dependent variable, and diagnosis (ASD versus TD), SRS total scale or subscales one at a time as independent variables. These analyses were done for the complete sample adjusted for age group, separately for each age group, and for the complete sample including age group and its interaction with diagnosis, SRS total scale or subscales. All these analyses were adjusted for RT VCPT. Where relevant, we also calculated partial correlations between RT ECPT and diagnosis/ SRS scores adjusting for the same variables. We compared RT ECPT separately for ASD and for TD between the young and old age groups using Student's *t*-test. We also computed correlations between SRS and subscales and IQ.

The number of failures in ECPT (omissions and commissions) plus one were log transformed to obtain approximate normality. Number of failures and differences in omissions between VCPT and ECPT were compared using Student's *t*-test.

We then used IIV ECPT and IIV VCPT as dependent variables in linear regression analyses with diagnosis and SRS with subscales, respectively, as independent variables. These analyses were done for the complete sample adjusted for age group, separately for each age group, and for the complete sample including age group and its interaction with diagnosis and SRS. We also computed the partial correlations between these variables adjusting for age group.

We analyzed the correlations between RT ECPT/ VCPT and IIV ECPT/ VCPT and IQ in the ASD group.

Normality of residuals was checked using visual inspection of Q-Q plots. Two-sided *p*-values < 0.05 were considered statistically significant, and 95% confidence intervals were reported where relevant. Due to multiple comparisons, *p*-values between 0.01 and 0.05 should be interpreted with caution. Statistical analyses were carried out in SPSS 24.

Results

Reaction time (RT)

TD and ASD group comparisons. RT ECPT and RT VCPT, IIV ECPT and IIV VCPT are presented in Table 2.

The RT ECTP was significantly longer than RT VCPT both in the TD ($p<0.001$) and in participants with ASD ($p<0.001$). RT VCPT correlated significantly with RT ECPT in TD ($r = 0.79$, $p<0.001$) and ASD ($r = 0.79$, $p<0.001$). There was no significant difference between ASD and TD in RT ECPT adjusted for RT VCPT, see Table 3. We repeated these analyses separately for the two age groups. There were no significant differences in RT ECPT in the two age groups.

We computed the age-related differences in RT ECPT separately within the ASD and the TD and found a significant reduction of RT ECPT only in ASD ($p = 0.008$, TD; $p = 0.26$).

Relation to degree of social problems. No significant association was found between the SRS total score and RT ECPT for the whole group of participants (Table 3, part a). For the young group, the RT ECPT correlated significantly with the SRS total score ($r = 0.30$, $p = 0.032$), see Fig 2. The RT ECPT correlated also significantly with the social motivation subscale ($r = 0.38$, $p = 0.006$) and was borderline significant with SRS social cognition ($r = 0.26$, $p = 0.065$). We did not find significant correlations with SRS total scale or subscales in the old

Table 2. Reaction time, RT, for ECPT and VCPT and intra-individual variability, IIV, for ECPT and VCPT; mean ± SD; range. All in milliseconds.

		ASD, *n* = 49	TD, *n* = 49
RT ECPT	All	393.9 ± 70.2 (268 to 583)	380.4 ± 54.8 (291 to 532)
	< 16 years	418.4 ±74.2 (301 to 583)	388.4 ±45.1 (316 to 532)
	≥ 16 years	366.3 ± 54.7 (268 to 447)	370.4 ±64.6 (291 to 511)
	All	338.3 ± 65.0 (251 to 542)	330.5 ±62.0 (254 to 559)
RT VCPT	< 16 years	346.2 ± 71.5 (251 to 542)	328.9 ±46.4 (271 to 480)
	≥ 16 years	329.4 ± 57.1 (260 to 490)	332.6 ±78.2 (254 to 559)
	All	14.8 ± 5.9 (5.4 to 33.8)	14.5 ± 4.7 (5.4 to 29.8)
IIV ECPT	< 16 years	17.4 ± 5.7 (8.9 to 33.8)	15.2 ± 4.4 (8.8 to 29.8)
	≥ 16 years	11.8 ± 4.5 (5.4 to 21.4)	13.6 ± 4.9 (5.4 to 22.8)
	All	9.9 ± 3.6 (3.8 to 20.3)	10.0 ± 3.7 (3.8 to 21.6)
IIV VCPT	< 16 years	11.4 ± 3.7 (4.9 to 20.3)	10.7 ± 3.9 (4.1 to 21.6)
	≥ 16 years	8.2 ± 3.3 (3.8 to 17.9)	9.2 ± 3.4 (3.8 to 17.9)

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group (SRS total score: r = -0.23, see Fig 2, p = 0.13; social cognition: r = -0.24, p = 0.12; social motivation: r = -0.26, p = 0.091), but note that all correlations in this age group were negative; i.e. in the opposite direction of the young.

When including the interaction between SRS scores and age group in the linear regression, we found significant interactions with SRS total score (p = 0.008), social cognition (p = 0.014)

Table 3. Linear regression with Reaction Time ECPT (RT ECPT) as dependent variable, and diagnosis, SRS total score (primary outcome) and the subscales (sub-analyses) one at a time as independent variables. Complete sample (a), Separate analyses for each age group (b and c), and complete sample including age group and its interaction with diagnosis, SRS total score or subscales (d). All analyses are adjusted for RT VCPT.

Independent variables	Regression coefficient β, (*confidence interval*), *p*
(a) ASD vs. TD	7.98(-6.53 to 22.48), p = 0.28
SRS total score	0.08(-0.25 to 0.41), p = 0.65
SRS–Social cognition	0.03(-0.30 to 0.36), p = 0.87
SRS–Social motivation	0.14(-0.25 to 0.53), p = 0.48
(b) < 16 years	
ASD vs. TD	14.91(-2.91 to 32.73), p = 0.099
SRS total score	0.43(0.04 to 0.82), p = 0.032*
SRS–Social cognition	0.39(-0.03 to 0.80), p = 0.065
SRS–Social motivation	0.66(0.20 to 1.12), p = 0.006**
(c) ≥ 16 years	
ASD vs. TD	-2.53(-26.20 to 21.13), p = 0.83
SRS total score	-0.41(-0.94 to 0.13), p = 0.13
SRS–Social cognition	-0.40(-0.92 to 0.11), p = 0.12
SRS–Social motivation	-0.52(-1.13 to 0.09), p = 0.091
(d) Interaction with age group	
ASD vs. TD * age group	p = 0.20
SRS total score * age group	p = 0.008**
SRS–Social cognition * age group	p = 0.014*
SRS–Social motivation * age group	p = 0.002**

* Significant at 0.05-level

** Significant at 0.01-level

https://doi.org/10.1371/journal.pone.0186124.t003

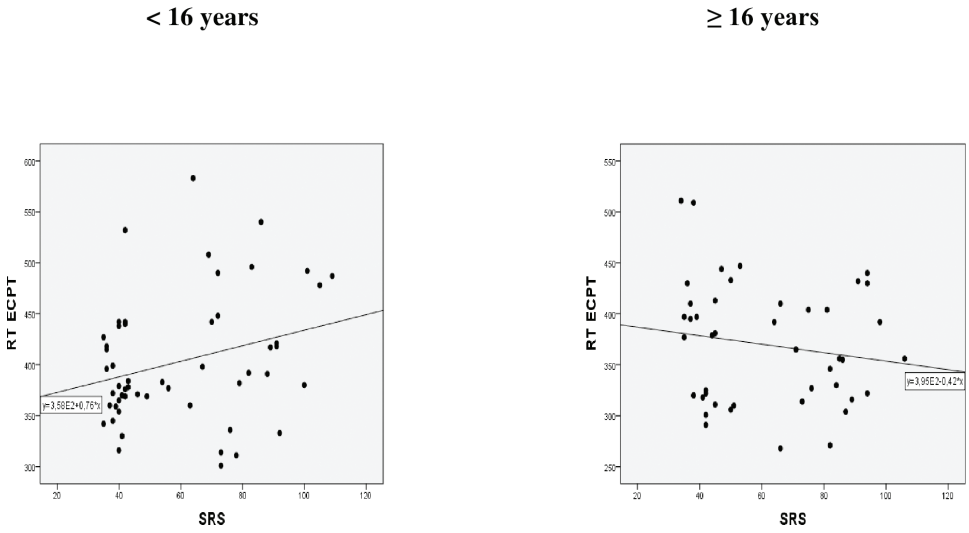

Fig 2. Scatter plots of RT ECPT related to SRS in the two age groups.

https://doi.org/10.1371/journal.pone.0186124.g002

and social motivation ($p = 0.002$), see Table 3 part (d). We computed correlations between SRS with subscales and IQ without finding significant relations.

Omissions / Commissions

Number of omissions (mean ± SD) was not significantly different (t (96) = -0.4, $p = 0.73$) between the the ASD (7.8 ± 9.7)and the TD groups (5.9 ± 4.9), and errors of commissions were also not different (t (96) = 0.8, $p = 0.42$) between ASD (2.5 ± 2.7), and TD (3.2 ± 3.7). The difference in omissions between VCPT and ECPT in the two groups was also non-significant (t(96) = 1.5, $p = 0.15$). Separate analysis for each of the two age groups yielded similar results. There were no significant correlations between omissions / commissions and the SRS with subscales.

Intra-individual variability (IIV)

No significant association was found between IIV ECPT and diagnosis or SRS total score for the whole group of participants (Table 4). However, IIV ECPT and diagnosis correlated in different directions in the age groups (young group $r = 0.21$, $p = 0.12$ and old group $r = -0.19$, $p = 0.21$) giving a significant age group * IIV ECPT interaction ($p = 0.049$). IIV ECPT also correlated significantly with SRS in opposite directions in the two age groups (young group $r = 0.29$, $p = 0.037$ and old group $r = -0.38$, $p = 0.011$)), with a significant interaction between SRS scores and age group ($p = 0.001$). The IIV VCPT correlated non-significantly, but in the same directions as IIV ECPT for the two age groups (young group $r = 0.11$, $p = 0.43$ and old group $r = -0.21$, $p = 0.18$), giving a non-significant interaction, $p = 0.14$. Secondary analyses for adolescents within the different subgroups and with and without comorbidity gave substantially the same main results. Further, for the ASD, we computed correlation analyses for IQ and RT VCPT, RT ECPT, IIV VCPT and IIV ECPT without significant relations.

Table 4. Linear regression with Intra-individual variability in reaction time, IIV, as dependent variable, and diagnosis and SRS total score (primary outcome) and the subscales (sub-analyses) one at a time as independent variables. Complete sample (a), Separate analyses for each age group (b and c), and complete sample including age group and its interaction with diagnosis or SRS total scale (d).

Independent variables	IIV ECPT Regression coefficient β, (*confidence interval*), *p*	IIV VCPT Regression coefficient β, (*confidence interval*), *p*
(a) ASD vs. TD	0.30(-1.83 to 2.43), $p = 0.78$	-0.13(-1.61 to 1.35), $p = 0.86$
SRS total score	0.00(-0.05 to 0.05), $p = 0.92$	0.00(-0.04 to 0.03), $p = 0.79$
SRS–Social cognition	-0.01(-0.06 to 0.04), $p = 0.72$	-0.01(-0.04 to 0.03), $p = 0.61$
SRS–Social motivation	0.00(-0.06 to 0.06), $p = 0.94$	0.00(-0.04 to 0.04), $p = 0.95$
(b) < 16 years		
ASD vs. TD	2.20(-0.62 to 5.02), $p = 0.12$	0.74(-1.36 to 2.84), $p = 0.48$
SRS total score	0.07(0.00 to 0.13), $p = 0.037$*	0.02(-0.03 to 0.07), $p = 0.43$
SRS–Social cognition	0.01(-0.06 to 0.04), $p = 0.06$	0.02(-0.03 to 0.07), $p = 0.42$
SRS–Social motivation	0.09(0.01 to 0.16), $p = 0.021$*	0.04(-0.02 to 0.09), $p = 0.17$
(c) ≥ 16 years		
ASD vs. TD	-1.78(-4.60 to 1.04), $p = 0.21$	-1.05(-2.91 to 0.81), $p = 0.26$
SRS total score	-0.08(-0.14 to -0.02), $p = 0.011$*	-0.03(-0.07 to 0.01), $p = 0.18$
SRS–Social cognition	-0.07(-0.13 to -0.01), $p = 0.018$*	-0.03(-0.07 to 0.01), $p = 0.12$
SRS–Social motivation	-0.09(-0.16 to -0.016), $p = 0.017$*	-0.04(-0.09 to 0.01), $p = 0.088$
(d) Interaction with age group		
ASD vs. TD * age group	$p = 0.049$*	$p = 0.21$
SRS total score * age group	$p = 0.001$**	$p = 0.14$
SRS–Social cognition	$p = 0.003$**	$p = 0.12$
SRS–Social motivation	$p = 0.001$**	$p = 0.034$*

* Significant at 0.05-level

** Significant at 0.01-level

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Discussion

The main findings of the current study were that the younger ASD group (12–16 years) demonstrated a tendency to require more time recognizing facial emotions than the TD. Furthermore, in this age group, enhanced IIV ECPT correlated positively with social problems measured by SRS. In older adolescents (≥16 years), there was no difference between the ASD group and the TD, while the reaction time and IIV correlated negatively with social problems. This resulted in a significant age-dependent interaction between RT and IIV ECPT with social problems. Given the high heterogeneity within ASD generally as also reflected in the participants of this study, the findings should be replicated in an independent sample to be sure it is generalizable to ASD in general.

Others have also studied reaction times in recognition of emotion paradigms. The present mean RT ECTP was significantly longer than RT VCPT which is consistent with the findings of Markovska-Simoska and Pop-Jordanova[30]. They suggested that increased RT in ECTP could be due to the influence of emotional stimuli on attention and information-processing. Akechi et al. [41] recorded reaction times after presenting from the same stimuli set as used in our study to children with ASD and TD aged 9 to 14 years. They found no differences in accuracy or reaction time regarding the recognition of emotions. However, their inter-stimulus interval was adjusted to the time the individual needed to respond or at maximum five seconds. This differs significantly from the 1800 ms used in our study, which may explain the divergent results.

The SRS subscale for social motivation correlated positively with RT ECTP among the younger (12–16 years) adolescents in the present study. This finding is consistent with the social motivation theory of autism, which proposes that ASD is an extreme case of diminished social motivation [21]. Social motivation may drive the development of basic skills necessary for appropriate social interaction as interpretation of faces [21]. Lozier et al. [16] found a large and generalized defect in facial emotion recognition in individuals with ASD and that the magnitude of this defect increased with age. In our study, we found the largest difference from TD in the younger group (12–16 years).

After the age of 16, we found no significant differences between TD and ASD in RT ECPT. This suggests that the ASD group was able to obtain normal emotion recognition, but at a later age than the TD. The delayed emotion recognition development in ASD may be due to both biological maturation and cognitive training. Further, TD showed equal RT ECPT in our age groups, supporting that the ability to recognize emotions is established at age 12 years. McGovern and Sigman [42] reported a significant improvement in social function in ASD between mid-school and adolescence measured by the ADI-R. Their different results for the younger and older age groups are consistent with the findings of the current study.

We found differences in the intra-individual reaction time variability (IIV) in the present study. This measure is reported to be a marker for the efficiency of top-down attentional control [43–45]. Vaurio et al. [28] found increased variability with increased cognitive demands. The increased IIV ECPT in young ASD may reflect the difficulty of the task. Karalunas et al. [46] reported conflicting findings in IIV in ASD. During our test procedure, it was observed that participants motivated to complete the test properly had better endurance. It was the impression of the test administrator that the motivation of the TD group decreased faster than in ASD, especially in the old group. Decreased IIV with age in TD is consistent with more stable attention and is in line with earlier findings [47].

In the present study, IIV ECPT was positively correlated with social problems for younger ASD participants (12–16 years), and negatively correlated for the older group ($\geq$ 16 years) resulting in a significant interaction between SRS and age group. The specific underlying mechanisms contributing to these age-dependent results are not known and the current findings should be followed up with more investigations. However, it is possible that an increase in cognitive demands due to difficulties in emotion recognition may underlie the increased IIV ECPT in the younger ASD group. Reduced IIV associated with higher SRS scores in the older ASD group ($\geq$ 16 years) may reflect the observation that TD group seemed less engaged in the task than the ASD individuals.

The emotion recognition task applied in the current study included micro expressions with presentation times below 200 ms. Shen et al. [48] found that micro expressions challenge the ability of emotion recognition in TD individuals. In our study, the presentation time was 100 ms, which we expected would be a challenge for the ASD group. However, the rate of omissions/commissions was not different in the TD and ASD groups. This lack of significant differences may be attributable to low power, as there were trend level differences. Another aspect of the paradigm is related to the use of basic emotions. The participants were only asked to recognize a single basic emotion, anger. They implicitly had to exclude happy to define the "GO-condition". Previous studies have shown that more complicated and subtle emotional expressions are more difficult for individuals with ASD to recognize than the basic emotions [49]. Thus, this may have reduced the opportunity to find differences in our study.

Social-emotional functions are one of the hallmarks of ASD. Biological abnormalities in the social motivation network may influence the basic premise for social interactions, given that social orienting and attachment are necessary for the continued development of social functioning through childhood and adolescence [21]. Moreover, social interaction requires the

rapid processing of emotions to ascertain the intentions, motivations and emotional reactions of other people. Thus, a less immediate understanding of emotions in children with ASD may impact social training [10]. The significant correlation between the SRS subscale social motivation and RT ECPT for the young groups (< 16 years) in the present study supports a relationship between coping and motivation. Targeted training in understanding emotions could improve ASD symptoms. and should be included in treatment programs. Furthermore, interacting socially with peers also provide useful experience. Enhanced emotional understanding in early childhood may increase social interaction and influence the development of abnormal social reciprocity in individuals with ASD.

Strengths and limitations of the study

Though we included patients previously diagnosed with ASD, we did not repeat the diagnostic assessment. The frequencies of diagnostic subcategories are not balanced between the two age groups. As autistic symptoms also occur to some extent in the population of TD, we addressed this by completing SCQ and SRS in both ASD individuals and TD without revealing significant differences between the diagnostic groups. Therefore, we carried out analyses based on the dichotomous diagnostic groups, as well as based on the autistic symptoms measured through SRS. This enabled the inclusion of all participants in our analyses.

We did not obtain the IQs for the TD, and were thus unable to match the IQs in the healthy control group and individuals with ASD. Cognitive level would be expected to influence both RT and IIV and could bias the results. However, individuals with autism typically have divergent verbal IQs compared to performance IQs which makes it challenging to match a control group. In the invitation letter and recruitment posts we specifically invited healthy adolescents. Thus, adolescents with learning difficulties such as dyslexia were not motivated to participate. Also, the parents were involved, and in writing confirmed that their child did not suffer from any chronic disease or psychiatric problems presently or previously. Due to the recruitment procedure, we expected most of the participants to have IQ in the normal range.

Another limitation may be the lack of randomization of VCPT vs ECPT order. The VCPT and ECPT are reported to have different performance measures, with RT and IIV increased in ECPT compared to VCPT. This is attributed to the emotional content of the ECPT-pictures. Our main objective was to compare the differences in performance between ASD and TD and we therefore presented the two parts in the same order. Fatigue may influence the performance data. However, this will affect all participants, both TD and ASD, and we have therefore not adjusted for this in the analyses. Different motivation for the test in the oldest ASD and TD groups could have some influence on the results.

Conclusion

ASD adolescents between 12 and 16 years showed a tendency to need more time recognizing emotions than TD. In this age group, reaction time and IIV correlated positively with social problems measured by SRS. In adolescents over 16 years, there was no difference between ASD and TD in reaction time, while the IIV correlated negatively with social problems. This resulted in a significant age-dependent interaction between reaction time and reaction time variability and social problems.

The present study suggests a specific cognitive abnormality in ASD that may contribute to the social difficulties and therefore should be investigated in more detail in experimental settings.

Declarations

Ethics approval and consent to participate

The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics South East (2013/1236/REK South-East). Written informed consent was obtained from participants and/or parents when necessary due to age.

Supporting information

S1 Table. Demographics for each diagnostic group. Significance of difference between ASD and TD in right column (*p*-value).
(DOCX)

S2 Table. Demographics for each age group. Significance of difference between age groups in right column (*p*-value).
(DOCX)

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SUPPORTING INFORMATION - 1

The relation between face-emotion recognition and social function in adolescents with autism spectrum disorders: A case control study

S1 Table. Demographics for each diagnostic group. Significance of difference between ASD and TD in right column (*p*-value).

	ASD		TD		*p*-value
	n	%	n	%	
	49	100	49	100	
Gender					
Male	36	73.5%	31	63.3%	*p*=0.28
< 16 years	20		19		*p*=0.59
≥ 16 years	16		12		*p*=0.30
Female	13	26.5%	18	36.7%	
< 16 years	6		8		
≥ 16 years	7		10		
Age – years	49	100%			
Mean (SD); range	15.6 (±2.4); 11.9-20.9		15.6 (±1.8); 12.3-19.4		*p*=0.95
< 16 years	26	53.1%	27	55.1%	
Mean (SD); range	13.7 (±1.3); 11.9-15.7		14.2 (±1.0); 12.3-15.7		*p*=0.09
≥ 16 years	23	46.9%	22	44.9%	
Mean (SD); range	17.8 (±1.3); 16.1-21.0		17.3 (±1.1); 16.1-19.4		*p*=0.12
SCQ	49	100%	47	96%	
Mean (SD); range	18.7 (±6.7); 5-34		1.9 (±2.3); 0-8		*p*<0.001**
< 16 years	18.3 (±5.9); 6-31		1.5 (±2.2); 0-7		*p*<0.001**
≥ 16 years	19.1 (±7.6); 5-34		2.5 (±2.4); 0-8		*p*<0.001**
SRS	49	100%	48	98%	
Mean (SD); range	80.1 (±14.4); 47-109		40.6 (±4.2); 34-51		*p*<0.001**
< 16 years	80.1 (±14.6); 54-109		40.0 (±3.3); 35-49		*p*<0.001**
≥ 16 years	80.2 (±14.4); 47-106		41.3 (±5.1); 34-51		*p*<0.001**

[1] All but one participant with comorbidity had comorbid AD/HD. These are hence reported twice in the table, both in “More than one comorbidity” and “Comorbid AD/HD”.

S2 Table. Demographics for each age group. Significance of difference between age groups in right column (*p*-value).

	< 16 years		**≥ 16 years**		***p*-value**
	n	%	n	%	
	53	100	45	100	
Gender					
Male	39	58%	28	42%	
ASD	20		16		*p*=0.56
TD	19		12		*p*=0.23
Female	14	45%	17	55%	
ASD	6		7		
TD	8		10		
ASD subgroup					
Infantile autism	5		8		*p*=0.22
Asperger disorder	7		11		*p*=0.13
PDD-NOS	14		4		*p*=0.008**
IQ Mean (SD); range					
Full scale IQ (n=36)	94.5 (±13.2); 73-127		88.9 (±21.7); 67-133		*p*=0.37
Verbal IQ (n=47)	89.1 (±16.0); 58-117		86.0 (±22.2); 52-130		*p*=0.58
Nonverbal IQ (n=48)	104.7 (±15.1); 73-139		90.4 (±21.1); 58-129		*p*=0.009**
Comorbidity					
No comorbidity	15		16		*p*=0.51
Comorbidity	11		7		
More than one comorbidity	5		2		*p*=0.34
ADHD/ ADD	11		6		*p*=0.23
SCQ Mean (SD); range					
ASD	18.3 (±5.9); 6-31		19.1 (±7.6); 5-34		*p*=0.67
TD	1.5 (±2.2); 0-7		2.5 (±2.4); 0-8		*p*=0.16
SRS Mean (SD); range					
ASD	80.1 (±14.6); 54-109		80.2 (±14.4); 47-106		*p*=0.99
TD	40.0 (±3.3); 35-49		41.3 (±5.1); 34-51		*p*=0.29

Paper II

frontiers in Neuroscience

ORIGINAL RESEARCH
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Event-Related Potentials in a Cued Go-NoGo Task Associated with Executive Functions in Adolescents with Autism Spectrum Disorder; A Case-Control Study

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Executive functions are often affected in autism spectrum disorders (ASD). The underlying biology is however not well known. In the DSM-5, ASD is characterized by difficulties in two domains: Social Interaction and Repetitive and Restricted Behavior, RRB. Insistence of Sameness is part of RRB and has been reported related to executive functions. We aimed to identify differences between ASD and typically developing (TD) adolescents in Event Related Potentials (ERPs) associated with response preparation, conflict monitoring and response inhibition using a cued Go-NoGo paradigm. We also studied the effect of age and emotional content of paradigm related to these ERPs. We investigated 49 individuals with ASD and 49 TD aged 12–21 years, split into two groups below (young) and above (old) 16 years of age. ASD characteristics were quantified by the Social Communication Questionnaire (SCQ) and executive functions were assessed with the Behavior Rating Inventory of Executive Function (BRIEF), both parent-rated. Behavioral performance and ERPs were recorded during a cued visual Go-NoGo task which included neutral pictures (VCPT) and pictures of emotional faces (ECPT). The amplitudes of ERPs associated with response preparation, conflict monitoring, and response inhibition were analyzed. The ASD group showed markedly higher scores than TD in both SCQ and BRIEF. Behavioral data showed no case-control differences in either the VCPT or ECPT in the whole group. While there were no significant case-control differences in ERPs from the combined VCPT and ECPT in the whole sample, the Contingent Negative Variation (CNV) was significantly enhanced in the old ASD group ($p = 0.017$). When excluding ASD with comorbid ADHD we found a significantly increased N2 NoGo ($p = 0.016$) and N2-effect ($p = 0.023$) for the whole group. We found

no case-control differences in the P3-components. Our findings suggest increased response preparation in adolescents with ASD older than 16 years and enhanced conflict monitoring in ASD without comorbid ADHD during a Go-NoGo task. The current findings may be related to Insistence of Sameness in ASD. The pathophysiological underpinnings of executive dysfunction should be further investigated to learn more about how this phenomenon is related to core characteristics of ASD.

Keywords: ASD, executive functions, Go-NoGo task, ERP, CNV, N2, P3, insistence of sameness

INTRODUCTION

Autism spectrum disorder (ASD) is a developmental disorder with impaired reciprocal interaction and a restricted pattern of behavior (ICD-10, 1992)/(DSM-5, 2013). Insistence of sameness was described as part of autism already by Kanner in 1943 who stated "anxiously obsessive desire for the maintenance of sameness" as part of the behaviors of the disorder (Kanner, 1943). Insistence of sameness and resistance to change are core features of the Restrictive and Repetitive Behavior, RRB, in DSM-5 and the two categories of ASD symptoms in DSM-5 may represent independent cognitive components and neural patterns (Happe and Frith, 2006; Mandy and Skuse, 2008; Brunsdon and Happé, 2014).

A potential cognitive process that may be related to RRB is executive functions, which are high-level cognitive processes that control goal-directed behavior and include abilities such as response inhibition, interference control, working memory, and set shifting (Friedman and Miyake, 2017). Executive functions are often affected in neurodevelopmental disorders such as ASD (Hill, 2004; Pugliese et al., 2014) and have been shown to have broad and significant implications for everyday life (Miyake and Friedman, 2012; Downes et al., 2017). The prefrontal cortex is regarded as the main brain region involved in executive functions (Friedman and Miyake, 2017), and prefrontal processes seem also to be involved in RRB (Mosconi et al., 2009; Agam et al., 2010). RRB may be subdivided in two separate categories, Repetitive Sensory Motor Action and Insistence on Sameness. The use of RRB subcategories, particularly Insistence of Sameness behaviors, can create more behaviorally homogeneous subgroups of children with ASD (Bishop et al., 2013).

Many studies have explored the relationship between RRB and executive functions (Lopez et al., 2005; Happé and Ronald, 2008; Boyd et al., 2009; Mosconi et al., 2009; Agam et al., 2010; Van Eylen et al., 2015). Deficient response inhibition and reduced inhibitory control are specifically suggested involved in the Insistence of Sameness category (Turner, 1997; Mosconi et al., 2009; Agam et al., 2010). Holmboe et al. (2010) described that siblings of children with ASD showed reduced selective inhibition due to difficulties in disengaging attention, referred to as "sticky fixation." This concept may be related to Insistence of Sameness. A recent study reported reduced inhibitory control in a Go-NoGo task in adults with ASD (Uzefovsky et al., 2016) and found an association between this and autistic traits measured by the Autism Spectrum Questionnaire. Investigating the neurobiology of these deficits, may contribute to a better understanding of the RRB in ASD.

The conventional measurement of executive functions has been cognitive performance-based tests (Toplak et al., 2013). This involves structured tasks in quiet, calm, distraction-free environments which may not represent the real-life situation with multiple demands and unclear goals in an environment of disturbing stimuli. Thus, the ecological validity of such measures is debated (Anderson et al., 2002; Mahone et al., 2002; Kenworthy et al., 2008; Isquith et al., 2013; Toplak et al., 2013). A supplement to laboratory testing is rating scales of executive functions in everyday life. The Behavior Rating Inventory of Executive Function, BRIEF (Gioia et al., 2000), is a questionnaire developed to identify everyday executive function abilities. These tests are thought to capture different levels of executive functions and provide a more complete picture of executive functions in everyday life (Isquith et al., 2013; Toplak et al., 2013). The parent rating scales (BRIEF) are capturing other aspects of executive functions than conventional performance-based tests, shown by the low-to-moderate correlations between them (Silver, 2014).

Little is known about the underlying pathobiology of executive dysfunction in ASD. One fruitful approach to investigating the pathobiology related to executive functions is through electrophysiology. Event Related Potentials (ERPs) are cerebral generated electrical voltages recorded on the scalp in response to specific stimuli or responses (Luck, 2014). A Go-NoGo task elicits ERPs associated with response preparation, conflict monitoring, and response inhibition; processes important to establish efficient and goal directed behavior and thus executive functions (Jonkman, 2006). Several lines of evidence suggest ERP correlates to executive dysfunction in psychiatric and neurodevelopmental disorders (Johnstone et al., 2013; Ogrim et al., 2014; Bridwell et al., 2015; Araki et al., 2016; Grane et al., 2016; Zielińska et al., 2016).

In the cued Go-NoGo task a defined cue (S1) indicates that the subsequent stimulus (S2) may require a response. This evokes top-down response preparation processes facilitating speeded reactions (Grane et al., 2016). The CNV is a slow negative potential elicited in the time interval between the cue and the imperative stimulus (S2), and probably indicates response preparation (Ahmadian et al., 2013). The main neural generators of the CNV are thought to be in the frontal cortex (Battaglini et al., 2017) which plays a central role by exerting top-down response preparation (Stuss, 2007). The CNV is considered to be an index of both anticipatory attention for the upcoming stimulus and motor preparation needed to respond (Brunia and

Van Boxtel, 2001) and is related to reaction time (RT) and reaction time variability (RTV) (Karalunas et al., 2014). The ERP amplitude generally reflects current neuronal activity (Luck, 2014), and the amplitude of the CNV may therefore represent the neuronal resources involved in the preparatory process. Preparation for fast responding also leads to an augmented need for abortion of the prepared response when the S2-stimulus is a NoGo stimulus. The reactive control processes after S2 therefore include conflict monitoring *and* execution *or* inhibition of the planned response. The N2 is a negative deflection ∼200 ms after S2, and is suggested to reflect the cognitive control necessary for interference suppression and successful inhibition (Donkers and Van Boxtel, 2004; Downes et al., 2017) and thereby conflict monitoring or the degree of experienced conflict (Hammerer et al., 2010). The P3, a positive deflection ∼300 ms after both stimuli (S1 and S2), has been suggested to indicate the classification of the stimulus and the selection of responses, and in NoGo trials evaluate the inhibitory process after S2 (Aasen and Brunner, 2016). P3 amplitude generally is sensitive to the amount of attentional resources engaged, and will be enhanced if the subject puts more effort into the task, but attenuated if the importance of the stimuli is unclear (e.g., if the given stimulus is target or non-target) or if the task is difficult (Polich, 1987, 2012). The characteristics of the stimuli are therefore essential for the amplitude of P3.

Generally, the literature supports that executive function skills improve in subjects with ASD through childhood and adolescence (Rosenthal et al., 2013), but the maturation is slower and may remain impaired into adulthood. Further, the role of comorbid Attention-Deficit/ Hyperactivity Disorder (ADHD) related to executive dysfunction is also not fully clarified. A recent review of executive functions in ASD, ADHD and comorbid ASD *and* ADHD found inconsistent results across studies attributed to differences in sample characteristics and assessment methods (Craig et al., 2016). They reported response inhibition impaired only in the groups with comorbid ADHD compared to "clean" ASD and typically developing (TD) children. They were not able to identify differences between the diagnostic groups regarding response preparation and monitoring.

Some studies have investigated ERPs associated with attention and inhibition in ASD (Tye et al., 2014; Cui et al., 2016; Faja et al., 2016; Thillay et al., 2016; Kim et al., 2017). Enhanced CNV was reported in children 8–13 years with ASD compared to TD (Tye et al., 2014). Thillay et al. (2016) found enhanced CNV in both ASD and TD before predictable targets, but only in ASD when targets were random. This altered CNV suggests an altered top-down response preparation in ASD. Tye et al. (2014) also reported reduced N2 amplitude enhancement from Go to NoGo trials (the N2-effect) in ASD, but no significant differences in neither N2 Go nor N2 NoGo. Generally larger N2 amplitudes were reported in children 7–11 years with ASD in a flanker test, suggesting that they recruit more neuronal resources when monitoring conflicting information. Kim et al. (2017) found no amplitude differences in N2 Go, N2 NoGo nor N2-effect in kindergartens with ASD. Thus, there are conflicting findings according to N2. A recent meta-analysis of P3 amplitude and latency in ASD (Cui et al., 2016) reported great variability and attribute this to differences in tasks and participants. However, they summarized that ASD showed attenuated P3b amplitudes and attributed this to abnormal information processing in the selection of responses. Deviant Cue P3, N2, and P3 NoGo are frequently found in other neurodevelopmental disorders (Johnstone et al., 2013; Downes et al., 2017).

Age-related changes of ERP components related to response preparation, conflict monitoring, and response inhibition are previously investigated in TD (Tecce, 1971; Cohen, 1973; Jonkman, 2006; Lamm et al., 2006; Lewis et al., 2006; Downes et al., 2017). Jonkman (2006) found CNV amplitude significantly larger in adults than children indicating a linear increase with age. Other studies found a linear increasing CNV in pre-adolescence with maximum amplitude at 15 years (Tecce, 1971; Cohen, 1973). The Cue P3 is also shown to be stronger in children compared to adults. Both the enhanced CNV and Cue P3 are suggesting a higher response preparation (Jonkman, 2006). The amplitude of N2 is typically described as decreasing with age (Jonkman, 2006; Downes et al., 2017), but also dependent on task performance; better performance is associated with reduced amplitude (Lamm et al., 2006). Hammerer et al. (2010) described decreasing N2 from childhood to young adulthood, steeper decreasing in NoGo than Go condition. They suggested this was related to improved executive functions and thus reduced experienced conflict with age. The P3 NoGo is often absent in small children and increase in amplitude until adolescence (Jonkman, 2006). However, to the best of our knowledge, there are few studies of these ERP-components in *adolescents* with ASD.

We have previously reported similar performance between TD and ASD in a visual cued Go-NoGo task (Høyland et al., in review). The task stimuli were split, the first part containing neutral pictures of animals/plants (VCPT) and the second, pictures with emotional faces (ECPT). Degree of social difficulties was determined on all participants by the Social Responsiveness Scales. We found enhanced reaction time in young adolescents correlated with social difficulties, but not the same enhancement in older adolescents. This suggests altered development of emotional understanding in adolescents with ASD. We also found that RTV and social function correlated significantly, but in opposite directions in the two age groups giving a significant interaction between score of social function and age group. In the older adolescents, more social difficulties correlated negatively with RTV. This could indicate better sustained attention in the ASD over 16 years.

The aim of the present study was to identify differences between ASD and TD on ERP- components associated with response preparation, conflict monitoring, and response inhibition during a cued Go-NoGo task. These executive function components may represent cognitive processes relevant for Insistence of Sameness and thereby for the diagnostic category of RRB in ASD. We hypothesized that ERP components associated with response preparation (CNV) were increased in ASD in both Go-NoGo paradigms (VCPT and ECPT). Due to delayed development of executive functions and the clinical feature Insistence of Sameness in ASD, we also expected the conflict monitoring N2-effect to be increased. The components associated with classification of the stimulus and selection of responses (Cue P3 and P3 Go/NoGo) were expected to

be unaffected by neutral stimuli (VCPT), but attenuated by emotional stimuli (ECPT) in ASD, due to emotion processing difficulties. Age-related changes in these components between 12 and 21 years were investigated, and we expected more enhanced differences in the young group due to the maturational delay in executive functions in ASD. Lastly, we investigated if RT and RTV was related to the ERP component of response preparation, CNV, and we expected shorter RT and less RTV with increasing CNV amplitude.

MATERIALS AND METHODS

Participants

Fifty adolescents with a confirmed diagnosis of ASD without intellectual disability from outpatients attending St. Olavs Hospital, Trondheim, Norway, were included in the study during 2013–2016 (**Table 1**). The sample consisted of 13 girls and 37 boys, aged 12–21 years, average 15.6 years. The ASD patients were diagnosed according to the ICD-10 F.84 criteria for pervasive developmental disorder based on developmental information and clinical assessments. The Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) was used in 43 of 50 cases.

Forty-nine typically developing adolescents, matched for age and gender, were recruited from adjacent schools through invitations/bulletins to all students/parents. In the invitation letter and recruitment posts we invited healthy adolescents. The parents confirmed in writing that their child did not suffer from any chronic disease or psychiatric problems presently or in previously. Eighteen girls and 31 boys between 12 and 20 years were included.

The functioning of networks involved in cognitive control are thought to reach adult level about the age of 15 (Solomon et al., 2014). To test if our results were associated with age we divided the participants into two groups, above and below 16 years of age. The young group included 27 TD and 26 ASD, and the older group included 22 TD and 23 ASD individuals.

Intelligence Quotients, IQs, were obtained for those in the ASD group. Most of the IQs were done previous of this study, including one participant who was assessed using the Leiter test because of specific language problems. The others were tested using the Wechsler tests. Some subjects were tested after recruitment into the current study applying the Wechsler Abbreviated Scales of Intelligence. When the difference between verbal and performance IQs was ≥30, we did not calculate full scale IQ (FIQ). To be included in the study, verbal (VIQ) or performance IQ (PIQ) had to be within the normal variation (≥70). Eighteen (37%) individuals in the ASD group had neuropsychiatric comorbidity, all but one with attention problems [Attention Deficit Disorder (ADD) with or without hyperactivity (ADHD)]. Eight (16%) had more than one comorbid diagnosis. Six (12%) had a diagnosis of epilepsy, all but one with co-occurring ADHD/ADD. Twelve (25%) of the ASD individuals used medication regularly. Four were on stimulants, two used atomoxetine and the six with epilepsy were on antiepileptic medication.

TABLE 1 | Demographics; number (*n*) and mean ± *SD*.

	TD		ASD	
	***n* = 49**		***n* = 49**	
GENDER				
Male	31		36	
Female	18		13	
ASD SUBGROUP				
Infantile autism			13	
Asperger disorder			18	
PDD NOS			18	
AGE–YEARS				
All	49	15.6 ± 1.8	49	15.6 ± 2.4
<16 years	27	14.3 ± 1.0	26	13.7 ± 1.3
≥16 years	22	17.3 ± 1.1	23	17.8 ± 1.3
IQ			49	
Full scale IQ			36	91.9 ± 17.7
Verbal IQ			47	87.6 ± 19.0
Nonverbal IQ			48	98.1 ± 19.3
SCQ	47	1.9 ± 2.3	49	18.7 ± 6.7
Infantile autism			13	19.7 ± 6.0
Asperger disorder			18	17.7 ± 6.9
PDD NOS			18	19.0 ± 7.1
BRIEF				
GEC All	36	42.0 ± 6.0	37	67.6 ± 10.2
<16 years	23	41.9 ± 6.4	22	64.8 ± 8.9
≥16 years	13	42.2 ± 5.4	15	71.6 ± 10.8

SCQ, Social Communication Questionnaire; BRIEF, Brief Rating Inventory of Executive Function; GEC, Global Executive Composite score; PDD NOS, Pervasive Developmental Disorder Not Otherwise Specified.

To identify characteristics associated with ASD the parents of all participants completed the lifetime version of the Social Communication Questionnaire (SCQ) (Rutter et al., 2003). The questionnaire is based on the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994) and is found valid for the ASD diagnosis (Berument et al., 1999; Corsello et al., 2007). It has shown good ability to discriminate between ASD and non-ASD (Chandler et al., 2007). The ASD-group had markedly increased scores on SCQ compared with TD ($p < 0.001$, **Table 1**).

The parents also filled in the Behavior Rating Inventory for Executive Functioning (BRIEF) (Gioia et al., 2000) as a description of everyday executive function abilities in the participants. BRIEF showed significant differences ($p < 0.001$, **Table 1**) between ASD and TD.

One of the participants in the ASD group scored >70% on the inattention subscale of the performance test and was excluded. The others, 49 ASD individuals and 49 TD, were included in the study. The behavioral results of the current sample were reported earlier (Høyland et al., in review).

Experimental Task, Electrophysiological Recording, and Analysis

Experimental Task

We used a cued Go-NoGo task which measures variables of attention and reaction time (Mueller et al., 2010). The categories of visual stimuli (see Figure S1, http://bio-medical.

com/products/psytask.html) include 15 pictures of each category; animals, plants and humans in part one (VCPT), and facial emotions (angry, happy, and neutral from Ekmans Pictures of facial affect; Ekman and Friesen, 1976) in part two (ECPT). All participants completed 300 trials VCPT followed by 300 trials ECPT. Each trial consisted of a pair of stimuli (S1–S2). When S1 was a cue (animal/angry face), the S2 was either animal/angry face (Go trials), or plant/happy face (NoGo trials). When S1 was plant/happy face they should never give response to S2 (ignore trials). S1 and S2 are presented for 100 ms with an 1,100 ms inter-stimulus interval and an inter-trial interval of 3,000 ms. The trials are grouped into blocks separated by a short break. In each block, a unique set of five pictures from each picture category are selected. Each block consists of a pseudo-random presentation of 100 stimulus pairs with equal probability for each trial category. The participants were told to response by pressing a button with their index finger as quickly as possible without making mistakes in all Go trials and otherwise refrain from responding. For more details, see also Høyland et al. (in review).

During the task, subjects were seated in a comfortable chair that was 1.2 m from the computer screen. The pictures (size $\sim$20 $\times$ 15 cm) were presented in the middle of an 18-inch monitor using the Psytask (http://bio-medical.com/products/psytask.html) software (from Bio-medical, Clinton Township, Michigan USA). The time interval from the presentation of the second stimulus to the response (RT) and RTV was registered by VCPT/ECPT software. The ERPs are averaged through trials with correct responses. The software also registered omissions and commissions.

Electrophysiological Recordings

Electroencephalogram (EEG) was recorded using a Mitsar (http://www.mitsar-medical.com) EEG system with a 19-channel tin electrode cap (Electro-cap International, Eaton, OH, USA). The electrodes were placed according to the international 10-20-system. The input signals were referenced to earlobe electrodes and filtered between 0.5 and 50 Hz and digitized at a sampling rate of 500 Hz. Impedance was kept below 5 kΩ for all electrodes. Quantitative data were obtained from the WinEEG software (www.mitsar-medical.com) in common average montage prior to data processing. Eye blink artifacts were corrected by zeroing the activation curves of individual independent components corresponding to eye blinks. In addition, epochs of the filtered EEG with excessive amplitude (>100 μV) and/or slow (>50 μV in the 0–1 Hz-band) and excessive fast (>35 μV in the 20–35 Hz-band) frequency activity were automatically excluded from further analysis.

All participants had a 6-min resting EEG registration and a specialist in clinical neurophysiology examined the registrations and found no epileptic activity.

The ERPs for each individual were based on averaging the trials of the respective task condition with correct response after artifact correction. The number of artifact-free trials averaged were 269 (±22.4, range 191–300) for TD, 261(±37.9, range 109–295) for ASD. This makes a non-significant difference in averaged trials. The ERPs were measured by convention as mean or peak amplitudes in the stated electrode and time window as showed by the grand average file, see **Table 2**. The topography of the P3 components is illustrated in **Figure 1**.

TABLE 2 | Electrophysiological measures, ERPs.

Cue P3	Maximum positive peak in Pz 260–360 ms after S1
CNV	Averaged amplitude in Cz 1,000–1,100 ms after S1(immediately before S2)
N2 Go/ NoGo	Maximum negative amplitude in Fz 90–290 ms after stimuli 2
P3 Go	Maximum positive peak in Pz 260–360 ms after S2
P3 NoGo	Maximum positive peak in Cz 270–420 ms after S2

Study Design and Outcomes

The primary outcome for the current study was to compare differences between TD and ASD in the amplitude of the following ERPs elicited during a cued Go-NoGo task: Cue P3, CNV, N2 Go and NoGo, P3 Go and P3 NoGo. The N2-effect was also calculated as N2 Go minus N2 NoGo. Outcomes were analyzed for the whole group of participants, and separately within each of the two age groups.

Statistical Analysis

The descriptives for all ERPs are reported. Subsequently, ERP amplitudes were analyzed as dependent variables in mixed model analyses with subject as random effect, and ECPT vs. VCPT, gender, age group, and diagnosis (ASD vs. TD) as independent variables. We did the analyses first for the whole sample, then separately for the two age groups. Finally, we also included the interaction between diagnosis and age group as independent variable. We repeated the analyses for ASD without comorbid ADHD vs. TD. We also made a scatter-plot (Loess curve) with CNV in both ECPT and VCPT as function of age. Partial correlation with gender as covariate was used to explore the relationship between the performance measures RT/RTV and CNV. All analyses were adjusted for gender.

Normality of residuals was checked by visual inspection of Q-Q plots. Statistical analyses were carried out in IBM SPSS Statistics 23.0. Two-sided $p < 0.05$ were considered statistically significant, however, due to multiple comparisons p-values between 0.01 and 0.05 should be interpreted with caution.

Ethics

The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics South East (2013/1236/REK South-East). Written informed consent was obtained from participants and/or parents when necessary due to age.

RESULTS

Total Sample

ERPs in the three midline electrodes (Fz, Cz, Pz) are presented in supplement (Figures S2, S3), and examples are provided in **Figure 2**. Descriptives of ERP amplitudes in the different groups are shown in **Table 3**. None of the ERPs associated with response preparation (Cue P3 and CNV) and conflict monitoring and

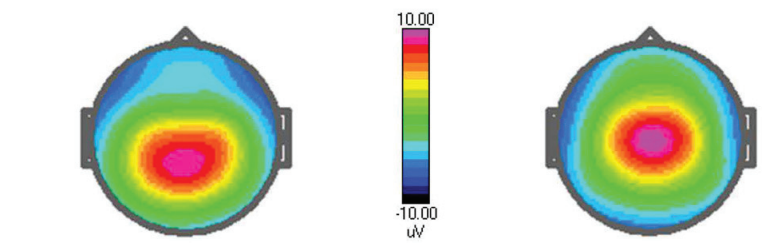

FIGURE 1 | Amplitude voltage map [in μvolts (μV)] at peak latency in Go and NoGo trials. The cued Go NoGo task elicits a maximum Go P3-component after 308 ms when stimulus 2 is target (Go condition) and a NoGo P3-component after 338 ms when stimulus 2 is non-target. Observe the topography of the P3, with a maximum at more parietal site in Go condition and centrally in NoGo condition.

response inhibition (N2 Go/ NoGo, N2-effect, P3 Go/NoGo) were significantly different between the ASD and TD groups in the combined VCPT and ECPT (**Table 4**).

Seventeen of the adolescents in the ASD group had comorbid ADHD. When excluding the ASD with comorbid ADHD, the N2 NoGo was significantly increased in the ASD group ($p = 0.016$, **Table 4**). The N2-effect was correspondingly enhanced ($p = 0.023$, **Table 4**).

We found significant correlations between RT and CNV (VCPT $r = 0.29$, $p = 0.004$; and ECPT $r = 0.47$, $p < 0.001$) for all participants. We also found significant correlations between RTV and CNV (VCPT $r = 0.29$, $p = 0.004$; and ECPT $r = 0.34$, $p = 0.001$).

Age Related Differences

There were no significant differences in the CNV amplitudes in the combined VCPT and ECPT data between cases and controls in the young age group, see **Table 4**. In the older age group, CNV was significantly ($p = 0.015$) enhanced in ASD compared to TD (**Table 4**). We also found a corresponding age × diagnosis interaction for CNV (**Table 4**, **Figure 3**). When plotting CNV vs. age as a continuous scale we found maximum amplitude at ∼15 years in TD, 17 years in ASD (**Figure 4**). The other ERPs recorded were not significantly different between ASD and TD in either age group (**Table 4**).

Repeating the analyses after excluding the participants with comorbid ADHD generally increased the differences between ASD and TD (**Table 4**).

DISCUSSION

We show ERPs related to response preparation, conflict monitoring and response inhibition in adolescents with ASD, all related to the clinical phenomenon Insistence of Sameness. The main findings of the present study were age related alterations in CNV and differences in N2 in the visual cued Go-NoGo task in ASD, while the behavioral performance was similar to the TD group. The age-related development of CNV in adolescents with ASD is not described previously. Our results contribute to the neurophysiology associated with executive dysfunction in ASD, and suggest biological underpinnings associated to a core RRB characteristic in ASD.

An enhanced CNV is thought to reflect increased response preparation (Brunia and Van Boxtel, 2001). This may lead to reduced flexibility and thus problems with set-shifting; features related to Insistence of Sameness (Yerys et al., 2009). Further it may be linked to the "sticky fixation" phenomenon associated to reduced selective inhibition described by Holmboe et al. (2010). Mosconi et al. (2009) also relate reduced inhibitory control to the Insistence of Sameness category of RRB. *Attenuated* CNV is reported to be associated with attentional problems in ADHD (Doehnert et al., 2010). The present findings of increased CNV in ASD above 16 years of age may represent a superior detail-focused cognitive style (Happe and Frith, 2006), the opposite of attention deficits. The detail-focused style is part of the altered perception in autism (Mottron et al., 2009), which may be associated with Insistence of Sameness. The CNV was significantly correlated to both RT and RTV for all participants (increased CNV associated with reduced reaction time and less RTV) in line with previous reports (Karalunas et al., 2014). This relation may reflect the neuronal resources involved in the preparatory process and thus performance. We did not replicate earlier findings of enhanced CNV in younger children with ASD (Tye et al. (2014). This may be due to differences in age of participants, paradigms, inter-trial interval and also time interval for assessing the CNV. In a longitudinal study, Doehnert et al. (2010) found reduced CNV in ADHD compared to TD from childhood to adolescence. After excluding participants with comorbid ADHD, we found an increased CNV in the group over 16 years, showing the same effect of ADHD. Thus, the reported enhanced CNV seem to be specific for ASD and may indicate a pathophysiological mechanism of executive dysfunction in ASD which could be overlapping with RRB.

The current findings of an ASD specific age-related development of CNV in adolescence are in line with abnormal brain development in ASD (Solomon et al., 2014). Earlier studies have found increasing CNV amplitude in TD until 15 years and thereafter gradual attenuation (Tecce, 1971; Cohen,

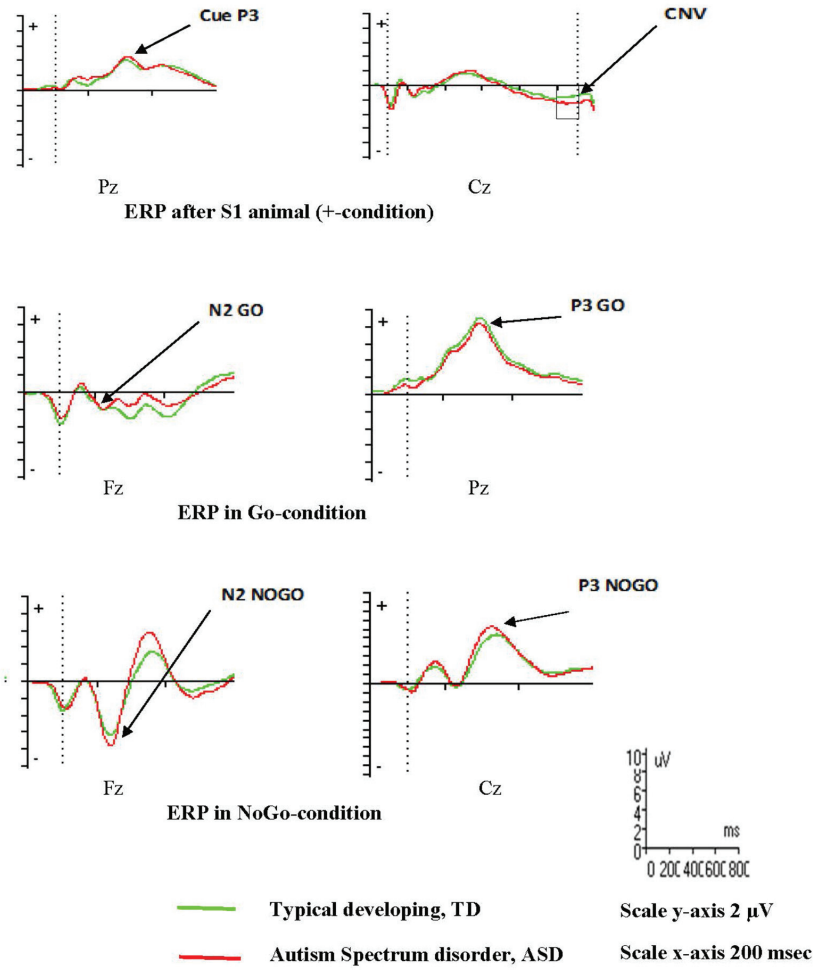

FIGURE 2 | Event Related Potentials, ERPs, VCPT adolescents 16 years and older.

1973). Our findings are in line with this observation. In the ASD group, however, the CNV amplitude increased until 17 years before attenuating. This suggests an altered development of neurophysiological processes underlying CNV in ASD. At the age of 20 years, the upper age-limit in our study, the CNV amplitude remained enhanced in the ASD group, suggesting that these abnormalities may persist into adulthood (Thillay et al., 2016). However, longitudinal studies are needed to determine the life span patterns of neurophysiological parameters in ASD.

We found no difference between the total ASD group and TD in the amplitude of N2 NoGo or N2-effect. Tye et al. (2014) reported attenuated N2-effect in children with ASD aged 8–13 years. Faja et al. (2016) found overall enhanced N2-components in ASD in children aged 7–11 years, but similar N2-effect. Both these studies included children younger than our participants. Several studies found decreasing N2 NoGo from childhood to adulthood in TD (Lamm et al., 2006; Hammerer et al., 2010). A reduced N2-effect is reported in ADHD (Albrecht et al., 2008). The ASD group in the study by Faja et al. (2016) included 8 children (29%) with ADHD which may affect their results. In our study, we included 17 ASD participants with comorbid ADHD. When they were excluded, we found both N2 NoGo and N2-effect significantly enhanced. These results are in line with our hypothesis, but must be interpreted with caution considering the multiple statistical testing. Thus, both the age and the inclusion/exclusion of participants with comorbid ADHD may influence

TABLE 3 | Event Related Potentials, ERPs, in VCPT and ECPT, for TD, ASD, and ASD without comorbid ADHD (ASD–ADHD).

		VCPT			ECPT		
		***n* = 49** **TD**	***n* = 49** **ASD**	***n* = 32** **ASD–ADHD**	***n* = 49** **TD**	***n* = 49** **ASD**	***n* = 32** **ASD–ADHD**
CNV	All	−1.86 ± 1.2	−1.96 ± 1.5	−2.05 ± 1.6	−2.12 ± 1.4	−2.20 ± 1.8	−2.33 ± 1.73
	<16 years	−2.08 ± 1.3	−1.53 ± 1.6	−1.33 ± 1.6	−2.24 ± 1.4	−1.74 ± 1.9	−1.56 ± 2.0
	≥16 years	−1.59 ± 1.0	−2.43 ± 1.2	−2.59 ± 1.2	−1.97 ± 1.3	−2.72 ± 1.5	−2.90 ± 1.3
N2 Go	All	−4.97 ± 2.7	−4.07 ± 2.9	−4.42 ± 2.8	−2.96 ± 2.3	−2.79 ± 3.2	−3.61 ± 3.1
	<16 years	−5.90 ± 2.0	−4.63 ± 3.1	−5.55 ± 2.6	−3.57 ± 2.0	−3.45 ± 3.3	−5.11 ± 2.5
	≥16 years	−3.83 ± 3.0	−3.43 ± 2.6	−3.43 ± 2.4	−2.21 ± 2.5	−2.05 ± 2.9	−2.29 ± 3.1
N2 NoGo	All	−9.13 ± 3.3	−8.74 ± 3.9	−9.86 ± 3.3	−4.98 ± 2.6	−5.21 ± 4.0	−6.52 ± 4.1
	<16 years	−10.57 ± 2.7	−8.85 ± 4.7	−10.98 ± 3.9	−5.15 ± 2.6	−5.24 ± 4.9	−7.63 ± 4.8
	≥16 years	−7.35 ± 3.3	−8.60 ± 2.9	−8.88 ± 2.3	−4.77 ± 2.6	−5.17 ± 2.9	−5.54 ± 3.1
N2-effect [a]	All	4.15 ± 2.6	4.67 ± 3.2	5.44 ± 2.8	2.02 ± 2.2	2.42 ± 3.1	2.90 ± 3.5
	<16 years	4.67 ± 2.9	4.23 ± 3.0	5.43 ± 2.6	1.58 ± 1.9	1.80 ± 3.3	2.51 ± 4.0
	≥16 years	3.52 ± 2.1	5.17 ± 3.3	5.44 ± 3.1	2.56 ± 2.4	3.13 ± 2.7	3.24 ± 3.1
Cue P3	All	5.46 ± 2.7	5.66 ± 3.0	5.27 ± 2.4	4.56 ± 2.2	5.26 ± 2.9	5.05 ± 2.08
	<16 years	6.09 ± 2.4	5.92 ± 3.1	5.55 ± 2.8	5.05 ± 2.2	5.87 ± 3.1	6.03 ± 3.1
	≥16 years	4.69 ± 2.8	5.37 ± 2.9	5.03 ± 2.0	3.97 ± 2.1	4.56 ± 2.5	4.19 ± 2.3
P3 Go	All	9.24 ± 4.1	9.36 ± 3.0	9.60 ± 2.9	8.24 ± 2.9	8.80 ± 4.3	9.47 ± 4.6
	<16 years	9.21 ± 5.0	9.64 ± 3.1	9.75 ± 3.6	8.57 ± 3.1	8.96 ± 4.4	9.44 ± 5.2
	≥16 years	9.27 ± 2.8	9.06 ± 2.9	9.46 ± 2.3	7.83 ± 2.5	8.59 ± 4.3	9.50 ± 4.3
P3 NoGo	All	11.66 ± 4.2	11.94 ± 6.0	13.13 ± 6.7	10.57 ± 4.5	10.08 ± 6.7	11.10 ± 7.41
	<16 years	11.24 ± 3.5	10.76 ± 6.4	11.88 ± 8.1	9.60 ± 3.0	8.48 ± 6.9	9.07 ± 8.7
	≥16 years	12.17 ± 4.9	13.27 ± 5.3	14.23 ± 5.3	11.77 ± 5.7	11.88 ± 6.1	12.89 ± 5.8

[a] *N2–effect, N2 Go vs. N2 NoGo. All amplitudes reported in μV, mean ± SD.*

the results. N2 is supposed to represent conflict monitoring (Donkers and Van Boxtel, 2004) which subsequently may be related to experienced conflict (Hammerer et al., 2010). Thus, these findings of N2-deviance may also be related to the clinical feature of Insistence of Sameness. Taken together, the current findings of both CNV and N2-deviance in ASD seem to implicate pathological neuronal excitability as a link between executive function and Insistence of Sameness.

We found similar amplitudes in the ASD and TD groups in the P3 components. In a recent meta-analysis of ASD compared to TD, Cui et al. (2016) found diverging P3 results which they attributed to high heterogeneity among the studies. They reported some evidence for reduced P3b amplitude in ASD. We did not find significant attenuation of P3 in ASD. This discrepancy could be due to differences in participants and paradigms (Cui et al., 2016). The performance-results in our study were mainly similar between TD and ASD supporting normal abilities in classification of the stimulus and selection of responses after S2.

An interesting aspect of the current findings is the relations between VCPT and ECPT. The ASD had basically equivalent ERPs to TD despite the emotional content of the stimuli. Thus, we did not confirm our hypothesis of a deviant effect of emotional pictures in ASD, and our results are in line with previous findings; participants with ASD are able to recognize basic emotions (Tanaka et al., 2012). Generally, the ERPs related to target classification (Cue P3/P3) of the emotional stimuli in the ECPT were corresponding to the ERPs in VCPT, but attenuated. Also, the age-related changes in CNV in the ASD group appeared both in VCPT and ECPT. In N2 Go and N2 NoGo the attenuation from VCPT to ECPT is significant in both TD and ASD. This may represent influence of emotional stimuli on attention and information-processing (Delplanque et al., 2006; Conroy and Polich, 2007). Since the VCPT was always presented before the ECPT, the lack of difference may also reflect exhaustion of the participants.

Strengths and Limitations of the Study

We included patients previously diagnosed with ASD, but did not repeat the diagnostic assessment. The distribution between the diagnostic subgroups shows an overrepresentation of PPD-NOS in the participants under the age of 16 years. However, there were no significant differences in the ASD symptoms as assessed by SCQ. We did not perform tests to estimate IQs for

TABLE 4 | Mixed model analysis with the reported Event Related Potentials, ERPs, as dependent variables.

		ASD vs. TD	(ASD–ADHD) vs. TD
		β (confidence−interval), *p*	**β (confidence−interval), *p***
CNV	All	−0.08 (−0.63 to 0.48), $p = 0.79$	−0.15 (−0.78 to 0.48), $p = 0.63$
	<16 years	0.56 (−0.25 to 1.36), $p = 0.17$	0.75 (−0.23 to 1.74), $p = 0.13$
	≥16 years	−0.86 (−1.55 to −0.18), $p = 0.015$*	−1.01 (−1.74 to −0.28), $p = 0.008$**
	Interaction with age group	$p = 0.017$*	$p = 0.006$**
N2 Go	All	0.53 (−0.44 to 1.50), $p = 0.28$	−0.29 (−1.30 to 0.72), $p = 0.57$
	<16 years	0.73 (−0.56 to 2.03), $p = 0.26$	−0.57 (−1.83 to 0.70), $p = 0.37$
	≥16 years	0.26 (−1.27 to 1.80), $p = 0.73$	0.04 (−1.61 to 1.69), $p = 0.96$
	Interaction with age group	$p = 0.68$	$p = 0.44$
N2 NoGo	All	0.07 (−1.18 to 1.32), $p = 0.91$	−1.25 (−2.71 to −0.28), $p = 0.016$*
	<16 years	0.89 (−0.99 to 2.76), $p = 0.35$	−1.45 (−3.34 to 0.44), $p = 0.13$
	≥16 years	−0.98 (−2.57 to 0.60), $p = 0.22$	−1.43 (−3.01 to 0.15), $p = 0.075$
	Interaction with age group	$p = 0.20$	$p = 0.76$
N2−effect[a]	All	0.46 (−0.47 to 1.39), $p = 0.33$	1.21 (0.17 to 2.24), $p = 0.023$*
	<16 years	−0.15 (−0.39 to 1.08), $p = 0.80$	0.88 (−0.58 to 2.34), $p = 0.23$
	≥16 years	1.24 (−0.18 to 2.67), $p = 0.085$	1.47 (0.07 to 3.01), $p = 0.060$
	Interaction with age group	$p = 0.19$	$p = 0.69$
Cue P3	All	0.43 (−0.56 to 1.42), $p = 0.39$	0.23 (−0.80 to 1.26), $p = 0.66$
	<16 years	0.22 (−1.15 to 1.59), $p = 0.75$	−0.11 (−1.69 to 1.47), $p = 0.89$
	≥16 years	0.78 (−0.63 to 2.19), $p = 0.27$	0.42 (−0.92 to 1.76), $p = 0.53$
	Interaction with age group	$p = 0.78$	$p = 0.95$
P3 Go	All	0.34 (−0.98 to 1.67), $p = 0.61$	0.92 (−0.62 to 2.46), $p = 0.24$
	<16 years	0.32 (−1.63 to 2.28), $p = 0.74$	0.43 (−2.15 to 3.02), $p = 0.74$
	≥16 years	0.45 (−1.30 to 2.22), $p = 0.60$	1.21 (−0.51 to 2.93), $p = 0.16$
	Interaction with age group	$p = 0.92$	$p = 0.90$
P3 NoGo	All	−0.08 (−2.16 to 1.99), $p = 0.99$	1.11 (−1.35 to 3.57), $p = 0.37$
	<16 years	−0.95 (−3.68 to 1.77), $p = 0.49$	−0.27 (−3.95 to 3.41), $p = 0.88$
	≥16 years	1.16 (−1.92 to 4.25), $p = 0.45$	2.16 (−1.15 to 5.47), $p = 0.20$
	Interaction with age group	$p = 0.49$	$p = 0.56$

[a] *N2-effect, N2 Go vs. N2 NoGo.*

**Significant at the 0.05 level (2-tailed). **Significant at the 0.01 level (2-tailed). The fixed effects were diagnostic group [typically developing (TD) vs. autism spectrum disorder (ASD)], task (VCPT vs. ECPT) and gender. We first analyzed using the whole sample, then separately for each age group. We then included the interaction between age group and diagnostic group. The analyses were finally recomputed for the groups TD vs. ASD without comorbid ADHD (ASD–ADHD).*

TD, but the parents of our control group reported no learning problems or psychiatric problems, and they were recruited from school children with normal school performance. Individuals with classical autism typically have significantly lower verbal IQs compared to performance IQs, although this varies within the ASD group. This situation also makes it challenging to match a control group (Harms et al., 2010).

We used the BRIEF, a parent-report measure, as a description of the presence of executive dysfunction in the participants. Research indicates that disagreement exists between performance-based tests and parent-report measures of executive functions (Silver, 2014). Performance-based measurements of executive functions could have contributed to a broader evaluation of executive dysfunction in the participants. We also used parent-report BRIEF for all participants even though some of them were over 18 years old. This because we had information that all participants still lived with their parents and we wanted to use the same BRIEF method across age groups.

The participants were in the ECPT asked to recognize a single basic emotion, anger. They also implicitly had to exclude happy as an emotion to define the "Go condition." Previous studies have shown that more complicated and subtle emotional expressions are more challenging to recognize for individuals with ASD than the basic emotions (Behrmann et al., 2006). Thus, the present paradigm may have reduced

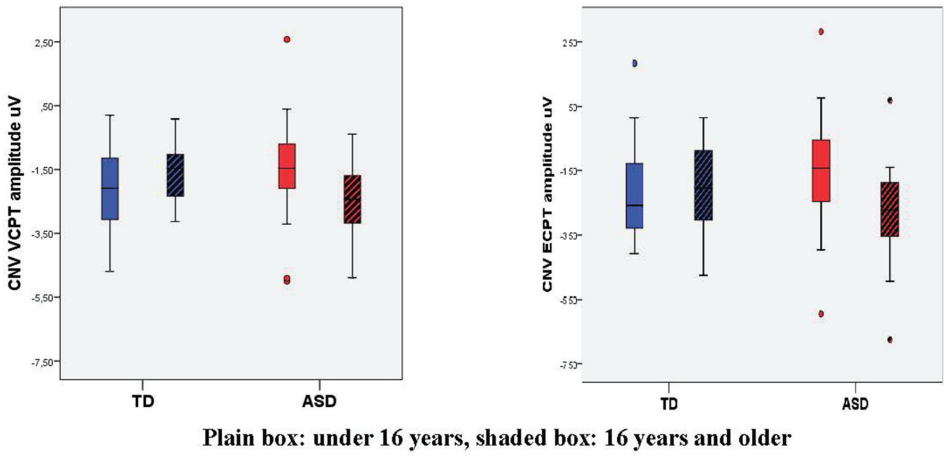

FIGURE 3 | Box plot of Contingent Negative Variation, CNV, in VCPT/ECPT. Mean CNV VCPT and ECPT increases from young to old in TD, decreases in ASD, giving a significant age-group × diagnosis interaction.

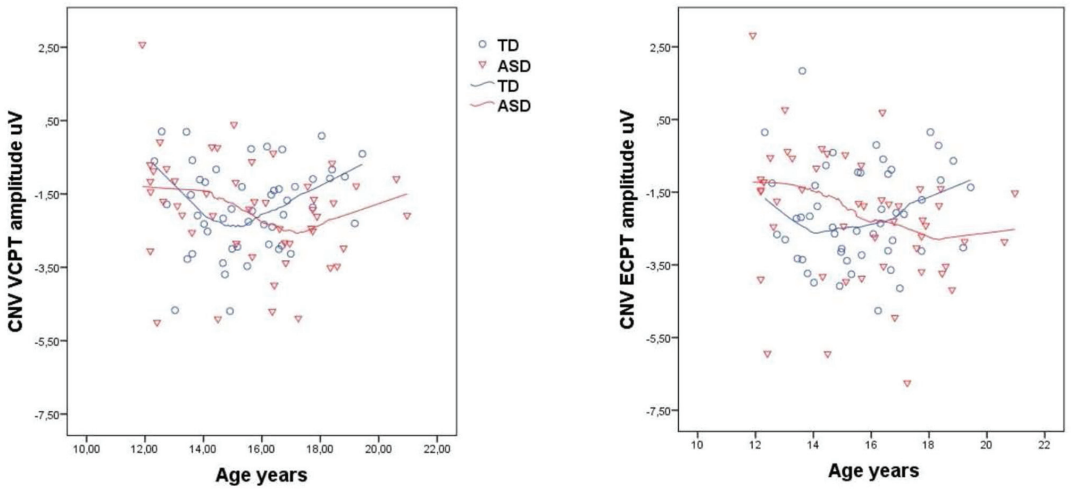

FIGURE 4 | Contingent negative variation, CNV, in VCPT/ECPT vs. age in typical developing adolescents (TD) and adolescents with autism spectrum disorders (ASD). Scatterplots with loess curves fitted to each diagnostic group.

the opportunity to find significant differences in our study, leading to Type II error. All participants were tested by the same technician in the same lab to reduce variations caused by testing conditions.

CONCLUSION

The current study of ERPs during a cued Go-NoGo task indicates age-dependent alterations of CNV (related to response preparation), and N2 (related to conflict monitoring) in ASD. These neurophysiological abnormalities during an executive function task may be related to Insistence of Sameness, a core clinical feature in ASD. Our results also underscore the importance of controlling for ADHD comorbidity when interpreting ERPs in an ASD sample. The pathophysiological underpinnings of executive dysfunction in ASD should be further investigated to learn more of how this phenomenon is related to core characteristics of ASD.

AUTHOR CONTRIBUTIONS

AH, GØ, TN, and OA contributed to the design of the work, the analyses and interpretation of data. SL, SH, and TT contributed to interpretation of the data. AH and ME carried out EEG-analyses and contributed to interpretation of the data. All authors drafted the manuscript and revised it and gave their final approval of the version to be published. All authors also agreed to be accountable for the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnins.2017.00393/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL - 2

Event-Related Potentials in a Cued Go-NoGo Task Associated with Executive Functions in Adolescents with Autism Spectrum Disorder; A Case-Control Study

Figure S1. Task Stimuli

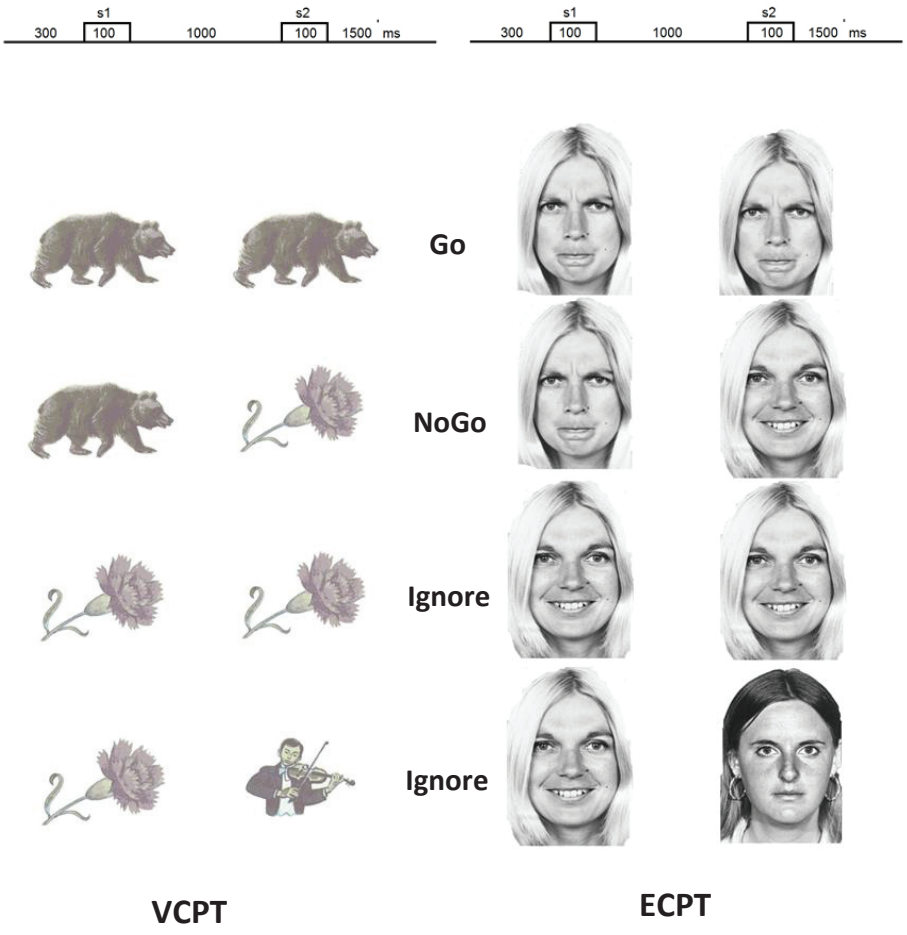
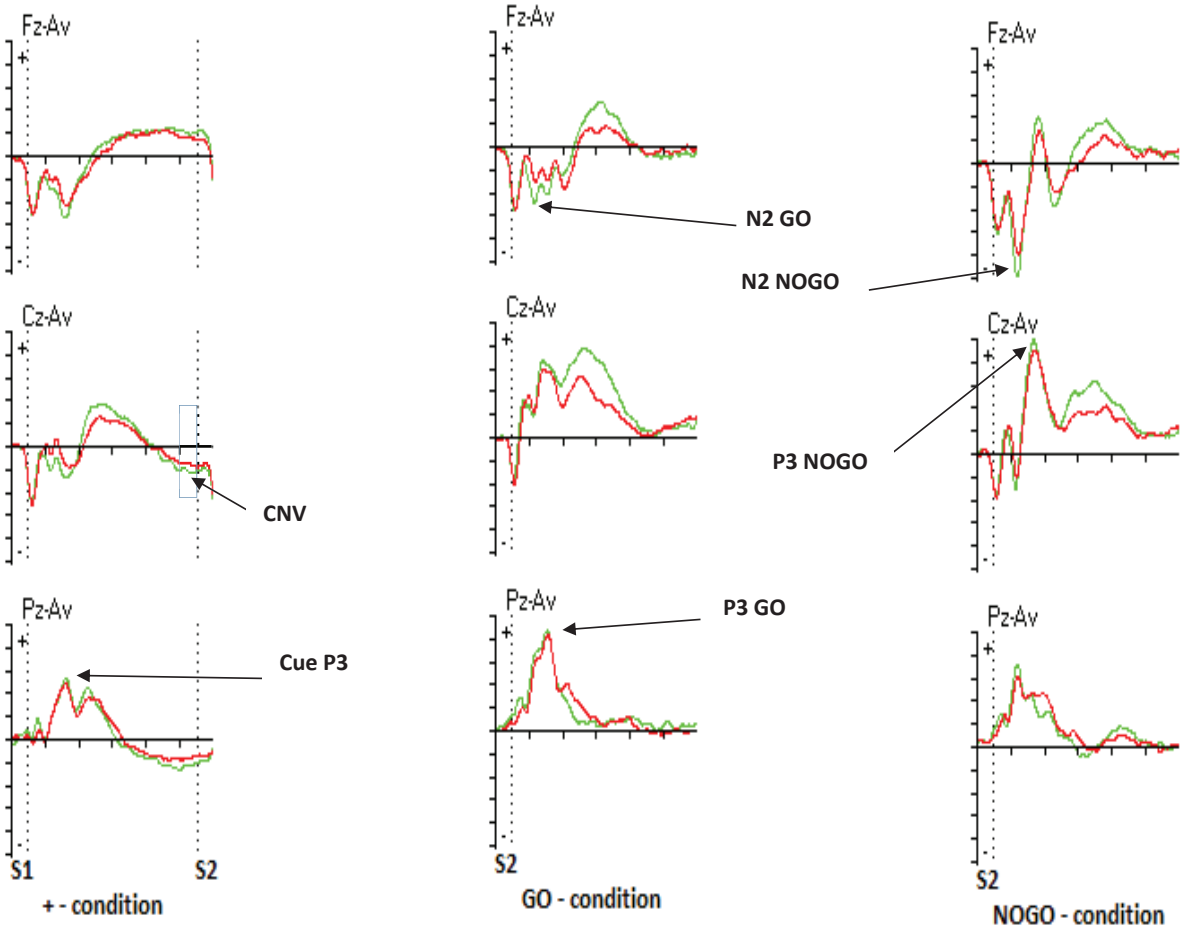
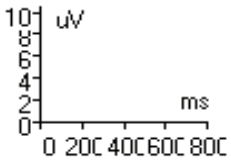


Figure S2. Event Related Potentials, ERPs, from midline electrodes from participants under 16 years of age



Typical developing

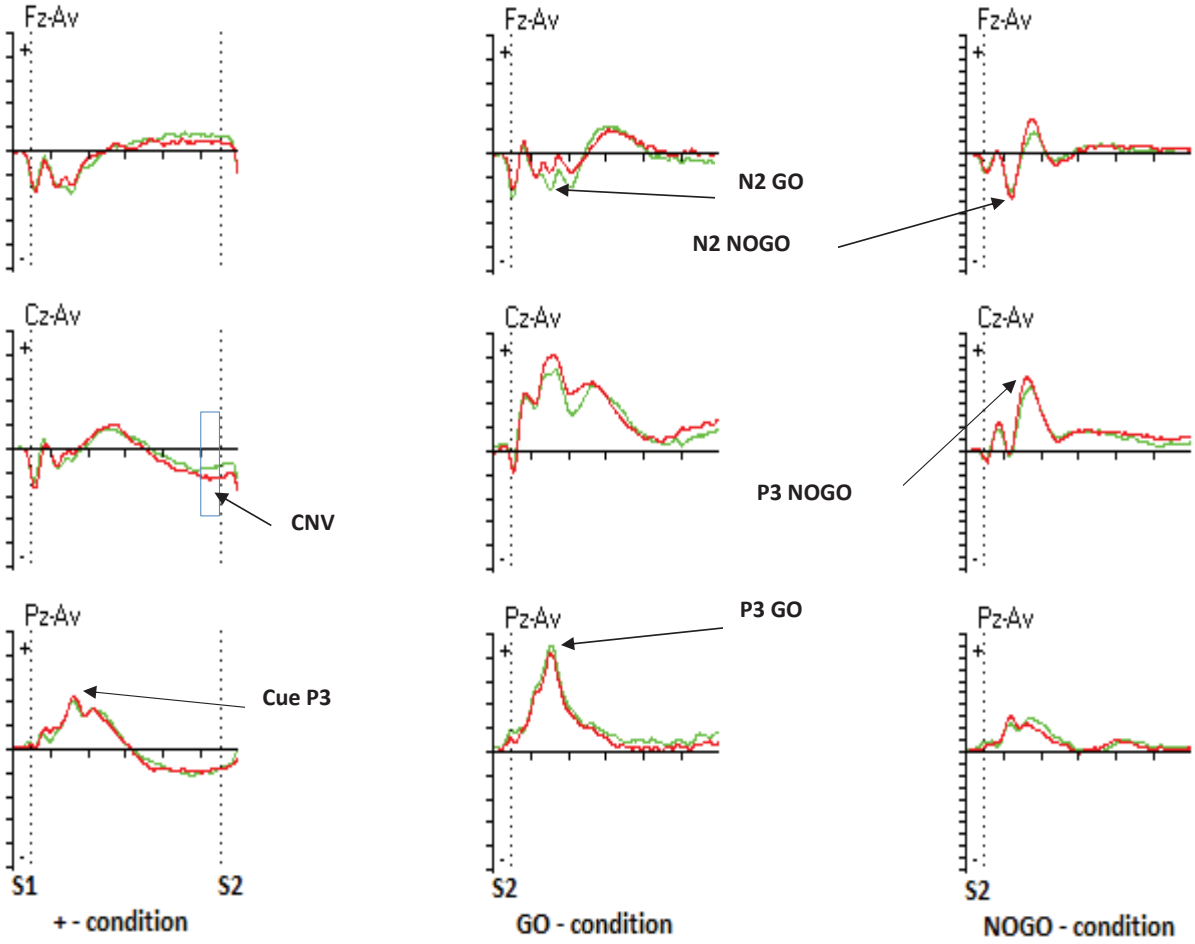
Autism Spectrum disorder, ASD



Scale y-axis 2 µV

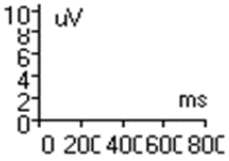
Scale x-axis 200 msec

Figure S3. Event Related Potentials, ERPs, from midline electrodes from participants 16 years of age and older



Typical developing

Autism Spectrum disorder, ASD



Scale y-axis 2 µV

Scale x-axis 200 msec

Paper III

Is not included due to copyright