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Gender specific sensory processing in ASD

An attempt to explain the male predominance in ASD and the need for a gender adapted assessment procedure

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SOFIA ÅKERLUND is a clinical psychologist with a special interest in the female perspective of Autism Spectrum Disorder (ASD).

The main aim of this thesis is to provide a global explanation of the gender differences seen in ASD and raise awareness of the importance in recognizing female ASD as a different phenotype than male ASD.

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Sofia Åkerlund

LUND UNIVERSITY

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Abstract: The male predominance in ASD has been widely discussed amongst researchers, some suggesting the female additional set of x-gene works protectively, others it is a lack of understanding of the female phenotype in ASD. While there is scientific evidence supporting both theories, few attempts have been made to integrate the theories into a more comprehensive understanding of ASD. Being a sensory processing disorder ASD has sometimes been referred to as the “extreme male brain syndrome” implying those affected show extreme male brain charachteristics such as an enhanced visual ability. However, it is well documented that females are superior in language processing partly due to an enhanced auditory processing. We hypothesized that an extreme female brain in ASD would be portrayed with an auditory enhancement perhaps being related to social ability. The aim of this thesis was to explore gender differences in audio-visual sensory processing in relation to parental ratings of social ability and auditory brainstem response. By separating between unisensory and multisensory processing we hoped to differentiate between less complex social settings and more complex social settings. In the first two studies patients already diagnosed with ADHD (paper I) and ASD (paper II) were included as well as control groups to explore gender differences in Auditory Brainstem Response (ABR). In paper III and IV all patients being referred for an ASD assessment were invited to participate in the study as we looked into ASD gender differences in audio-visual processing in relation to ABR and parental ratings of Social Responsiveness. In paper I and II, two regions in the brainstem were identified and later used in study IV. In paper IV an enhanced auditory ability in the female ASD group was associated with lower ABR activity in unisensory processing. In multisensory processing a visual dominance was associated with lower ABR-activity. In paper III an enhanced auditory ability was related to better social skills in unisensory processing, and more social difficulties in multisensory processing. In the male ASD group, an enhanced visual ability was associated with lower ABR activity in unisensory processing whereas no relation could be seen in multisensory processing. An enhanced visual ability showed no association to parental ratings in the unisensory measurments whereas in multisensory processing an association with social difficulties was seen. The findings confirm gender specific differences in sensory processing being related to different aspects of ASD, suggesting an *“extreme female brain”* is related to a feminine phenotype of ASD.

Key words: “ASD”, “child- and youth”, “gender differences”, “extreme female brain”, “audio-visual temporal processing”, “sensory processing”.

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MADE IN SWEDEN

Till minne av Lena Åkerlund

Table of Contents

Populärvetenskaplig sammanfattning

Introduktion: Sett ur ett historiskt perspektiv så har kvinnor under lång tid missgynnats i samhället. Hundra år tillbaka i tiden var varken rösträtt eller fri utbildning en självklarhet för svenska kvinnor. Även om dagens samhälle ser väldigt annorlunda ut så finns det fortfarande tydliga könsskillnader som väcker misstankar om att ett könsdiskriminerande synsätt fortfarande påverkar dagens vård av kvinnor.

Ett sådant område är psykiatrisk ohälsa. I dagens Sverige löper kvinnor en betydligt högre risk att utsättas för alvarlig vård skada eftersom bland annat neuropsykiatriska diagnoser ställs allt för sent i livet. Med tanke på att ångestrelaterade diagnoser är betydligt högre hos kvinnor kan man fråga sig om en Freudiansk kvinnobild fortfarande lurar kvar under ytan?

De färre AST diagnoser som ges till kvinnor förklaras av en del forskare med att kvinnor genom sin biologi är skyddade från neuropsykiatrisk problematik. Andra forskare menar att det snarare handlar om att det finns för lite kunskap om hur autismspektrumtillstånd tar sig uttryck hos kvinnor och att de därför ofta missas inom vården. Det finns gott om vetenskapligt stöd för båda sidor men sällan har någon försökt att förena de båda perspektiven i en mer enhetlig förklaring av AST.

AST kallas ibland för det *”extremt manliga hjärnsyndromet”* som syftar på att många med AST uppvisar en extrem variant av den typiskt manliga hjärnan som bland annat är överlägsen i bearbetning av visuella stimuli. Kvinnor å andra sidan har visat sig vara överlägsna i auditiv signaldetektion vilket bidrar till fördelar i språkutvecklingen.

Syftet med denna avhandling är att utforska om en *”extremt kvinnlig hjärna”* hos flickor med AST, skulle kunna kopplas till föräldraskattningar av social förmåga och hjärnstamsaktivitet. Vår hypotes är att en överlägsen auditiv förmåga ger flickor en bearbetningsfördel i mindre komplexa sociala sammanhang medan de mer komplexa sociala sammanhangen är lika svåra för flickor som för pojkar.

Metod: Genom att jämföra hjärnstamsaktivitet, audio-visuell bearbetningsförmåga och föräldraskattningar av Social Förmåga har de specifika syftena varit att identifiera (1) könsskillnader i ABR vid ADHD; (2) könsskillnader i ABR vid AST. (3) könsskillnader i ASD i sambandet mellan audio-visuell bearbetning och föräldraskattningar; (4) könsskillnader i ASD i sambandet mellan audio-visuell bearbetning och ABR.

Resultat: I de två första studierna identifierades två olika områden i hjärnstammen med avvikande ABR-aktivitet som kunde kopplas till ASD. De två områdena undersöktes sedan mer noggrant i de två sista studierna. Resultaten från studie III och IV bekräftar könsspecifika skillnader i audio-visuell bearbetning som är kopplade till både föräldraskattningar och hjärnstamsaktivitet. I gruppen med AST-flickor såg man att en överlägsen auditiv förmåga kunde kopplas till bättre social förmåga i mindre komplexa sammanhang men med fler sociala svårigheter i komplexa sammanhang. En högre signaldetektionsförmåga var också kopplat till lägre ABR-aktivitet en-sensoriska sammanhang. I multisensoriska sammanhang fanns en koppling mellan en Visuell dominans i snabbhet och lägre ABR aktivitet.

I gruppen med AST-pojkar kunde en visuell styrka kopplas till sämre social förmåga i mer komplexa sammanhang och med en lägre nivå av ABR-aktivitet i en-sensoriska sammanhang.

Slutledning: Specifika könsskillnader kunde ses i audio-visuell bearbetning både kopplat till en-sensoriska och multisensoriska sammanhang. Resultaten stöder könsspecifika fenotyper inom AST, vilket innebär att bedömningsinstrument, skattningsskalor samt diagnoskriterier kan behöva revideras för att även anpassas efter den kvinnliga fenotypen.

List of Papers

Paper I

Claesdotter Hybbinette, E., Cervin, M., Åkerlund, S., Råstam, M., & Lindvall, M. (2016). Gender specific differences in auditory brain stem response in young patients with ADHD. Neuropsychiatry 2016 Mar 30; 6(1):28 - 35

Paper II

Claesdotter-Knutsson, E., Åkerlund, S., Cervin, M., Råstam, M., & Lindvall, M. (2019). Abnormal auditory brainstem response in the pons region in youth with autism. *Neurology, Psychiatry and Brain Research 32*: 122-125

Paper III

Åkerlund, S., Håkansson, A., & Claesdotter-Knutsson, E., (2023). An auditory processing advantage enables communication in less complex social settings. Signs of an extreme female brain in children and adolescents being assessed for Autism Spectrum Disorders. *Frontiers in psychology.* Vol 13.
Doi: *10.3389/fpsyg.2022.1068001*

Paper IV

Åkerlund, S., Håkansson, A. & Claesdotter-Knutsson, E. (2023). Gender Specific Differences in Audio-Visual Processing Related to Auditory Brainstem Response in Children Assessed for an Autism Spectrum Disorder. *Submitted.*

Abbreviations

ABR	Auditory Brainstem Response
ADHD	Attention Deficit Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
AN	Acoustic Nerve
ASD	Autism Spectrum Disorder
AST	Autismspektrumtillstånd
CAP	Compound Action Potential
CN	Cochlear Nucleus
DS	Dorsal Stream
HF	High Functioning
IC	Inferior Colliculus
IVA-CPT	Integrated Visual and Auditory Continuous Performance Test
LL	Lateral Lemniscus
RRBI	Restricted, Repetitive Behaviour and Interests
SIT	Sensory Integration Theory
SOC	Superior Olivary Complex
TBW	Temporal Binding Window
TW	Time Window
TD	Typically Developed
VS	Ventral Stream

Introduction

History of female mental health

While the history of female psychiatric health is well documented throughout time (mostly by males), starting with the old Greek philosophers (Tasca, Rapetti & Fadda, 2012) the documentation of male psychiatric health has been almost non-existing (Hagget, 2014). This is explained by “males” being seen as the “norm” and consequently anything differing from the norm, such as “femaleness” was seen as deviant behaviour (Hagget, 2014). Besides denouncing females as mentally ill the causes of women’s psychiatric illnesses were often attributed to some form of sexual need (Hagget, 2014).

Females have been disadvantaged in many aspects of society throughout time. To mention a couple, the right to vote and study were denied Swedish women only 100 years back. The society of today is obviously much different, however sometimes one might wonder if there are some Freudian thinking still luring around, making life a little bit more difficult for women.

For example, in the Swedish psychiatric health care system women run a much higher risk of being exposed for a care injury due to receiving neuropsychiatric diagnoses at a much later time in life than males (Sveriges Kommuner och Regioner, January 2021). The risk of women with ASD developing anxiety related disorder due to not being properly understood in the psychiatric care is well documented (Dean, Harwood & Kasari, 2017; Hull et al., 2017; Rynkiewicz et al., 2016; Green et al., 2019; Rynkiewicz, Janas-Kozik & Słopień, 2019). According to the latest report from the Swedish Agency for Civil Protection and Emergency Planning, the female population between the ages of 10-19 show 3-4 times more self-harm behavior than males in the same age range (Myndigheten för samhällsskydd och beredskap, 2014). Considering many of the alternative diagnoses given to females are anxiety related it is highly plausible an outdated Freudian School of thinking is still being present in todays’ society.

In 1798 Sir Alexander Crichon, a Scottish physician published one of the first books focusing on mental issues from a physiological or medical perspective in which he makes a polar distinction between two possibilities of abnormal inattention: *increased* or *decreased* sensibility of the nerves (Crichton, 1798). The descriptions of patients showing these kinds of symptoms were often described as young boys unable to behave morally correct (Lange et al., 2010). In 1902 studies of attention did include some female children but they were in minority, justified by the believe that medical mental deficiencies were not as common in females as in males, a belief that is still living with us today (Lange, et al., 2010).

During the past 20 years more females have indeed been included in both ADHD and ASD studies, however, it has often been done without consideration to the fact that females included are most likely those passing through the current screening instrument for such disorders, hence, showing the male phenotype of ADHD and ASD (D'mello et al., 2022). Despite more females being included in studies, skewed research in neuropsychiatric disorders is still dominating the research field using mainly male participants and lacking in gender perspective (D'mello et al., 2022).

Recently the Swedish Radio (SR) reviewed the decision basis for placing teenagers in compulsory care (Velasco, 2023). The review revealed several examples of discriminating thoughts around females that had been sexually molested, justifying the placement by claims such as: "through her behaviour she put herself at risk of being molested". This is just one example of how the history of female mental health still seem to affect todays' society. In a study from 2022, 15% of females diagnosed with bipolar disorder met the diagnostic criteria for ASD (Belcher, 2022), a proof of females being wrongly diagnosed.

Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a neurodevelopmental sensory processing disorder characterized by difficulties within social interaction and repetitive and stereotyped behaviour (American Psychiatric Association, 2013 [APA]). Around 1-2 percent of the population is affected (Rødgaard et al., 2019) and the gender distribution is 1:3, favouring males (Loomes, Hull & Mandy, 2017; Chiarotti & Venerosi, 2020; Saito et al., 2020). The heritability of ASD is high, approximately 80% (Sandin et al., 2017; Bai et al., 2019) and while 10-25% of all patients with ASD can be related to a genetic disorder the remaining 75-90% are so called non-syndromic ASD, having ASD as their main diagnosis (Bhandari, Paliwal & Kuhad, 2020).

Diagnostic assessment of ASD

The ASD diagnostic assessment is made by professional clinicians using cognitive tests, rating scales, parental interviews, and clinical observations to assess the severity and degree of autistic traits. The ASD diagnostic criteria of DSM-5 are used when assessing if the patient meets the ASD criteria or not. The golden standard assessment of ASD includes the Revised parental Autism Diagnostic Interview

(ADI-R) (Lord, Rutter & Couteur, 1994) and the Autism Diagnostic Observation Schedule (ADOS) (Gotham et al., 2006) made with the patient.

ASD diagnostic criteria of DSM-5

The diagnostic criteria of ASD are categorized from A to E where the A -criteria constitutes three different aspects of difficulties within social-communication and social interaction; 1 – behaviours related to deficits in social emotional reciprocity. 2 – behaviours related to deficits in nonverbal communication. 3 – behaviours related to deficits in developing, maintaining, and understanding relationships and the B-criteria constitutes four different aspects of restricted, repetitive patterns of behaviour, interests, or activities: 1 – Stereotyped or repetitive behaviour. 2 – Insistence of sameness, inflexibility. 3 – Restricted, fixated interests. 4 – Hyper- or hypoactivity to sensory inputs or unusual interests in sensory aspects. The C-criteria states *"Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life"*. The D-criteria states that symptoms must cause clinically significant impairments whereas the E-criteria states that the symptoms must not be better explained by an intellectual disability (APA, 2013).

Several studies in ASD show that both genders struggle with an equal number of impairments within social communication and interaction whereas restricted, repetitive behaviour/ interests/ activity (RRBI) are predominantly seen in males (Van Wijngaarden-Cremers, Eeten & Groen, 2014; Wang et al., 2017; Tillman, Ashwood & Absoud, 2018) Lately it has been discussed whether females show other kinds of RRBI not being picked up by Golden standard measurements (Moseley, Hitchiner & Kirkby, 2018; McFayden, Antezana & Albright, 2019) which is supported in a study from 2019 showing increased compulsivity, insistence in sameness and self-injurious behaviour was associated with female ASD whereas the classical RRBI was mainly related to males (Antezana et al., 2019).

Complicating factors

ASD are often overlapping with other disorders such as language disorders, ADHD, sleep problems, epilepsy, aggression, anxiety, gastrointestinal abnormalities, and dyslexia (Geschwind, 2009). ADHD alone is believed to affect 50-70 % of the ASD population (Rong et al., 2021). The lack of biological markers for ASD in combination with a symptom overlap with other psychiatric disorders makes the clinical assessment of ASD difficult (Fernández, Mollinedo-Gajate & Peñagarikano, 2018).

Another complicating factor relates to the diagnostic criteria changing over time as the knowledge of ASD has increased (Lyall et al., 2017). In 2013 the new DSM-5 was published including sensory processing difficulties to make it better adapted for females (APA, 2013). Still, all the ASD assessment tools used today are based on the old DSM-IV criteria, that includes ADI-R (Lord, Rutter & Couteur, 1994) and

ADOS-2 (Lord et al., 2012), as well as rating scales such as *"The Social Communication Questionnaire"* (SCQ) (Rutter et al., 2003) the *"Autism Quotient"* (AQ) (Baron-Cohen et al., 2001) and *"Autism Spectrum Screening Questionnaire"* (ASSQ) (Posserud, Lundervold & Gillberg, 2006), still commonly recommended and used in the screening process of ASD in Sweden and worldwide (Zander, 2021a; Zander, 2021b).

A third complicating factor are when scales such as *AQ* and *ASSQ* claim to be normally distributed over the population, (Wing, 1988; Constantino & Todd, 2003; Posserud, Lundervold & Gillberg, 2006). A study of gender differences in the normal population showed a skewness towards more autistic traits in males whereas females showed a skewness toward less autistic traits (Ruzich, et al., 2015). It is important to bear in mind that the autistic so called "traits" being rated in these scales are the result from research mainly made on males and therefore, most likely represents the male phenotype of ASD.

A fourth factor concerns the diversity of cognitive traits in ASD, some subjects showing high verbal skills, others low (Vogindroukas et al., 2022), some showing a low level of empathy compared to TD (Mensi et al., 2019) others the same level (Stroth et al., 2019). For that reason, we might ask whether the scales and instruments used for ASD assessments of today are indeed a true representative of all people within the autism spectrum?

Explaining the male predominance in ASD

The male predominance in ASD is still a question in need to be fully understood although there are several theories suggested. The theories can be divided into two categories, those meaning women are genetically protected from ASD and those meaning there is a lack of knowledge about the female phenotype of ASD.

The theory of female protective effect against ASD reasons that if females are affected by ASD at the same level as males, ASD females should have the same level of polygenetic risk for ASD as ASD males have. Since that has shown to not be the case, they argue females are genetically protected against ASD (Jacquemont et al., 2014; Wigdor et al., 2022). The female protective effect theory is built upon the assumption that females show the same genetic ASD structure as males (Wigdor et al., 2022) which some mean has been disputed and disproved (Bai et al., 2020). Another genetic explanation for the male predominance in ASD is the belief that women are biological protected by their extra set of x-chromosome (Baron-Cohen et al., 2011; Werling, 2016) providing them with extra resources. They describe ASD as being a form of *"male brain syndrome"* mostly affecting males (Asperger and Frith, 1991; Baron-Cohen, 2003; Baron-Cohen et al., 2011) which is also supported in studies of brain structure and function, showing ASD females have cognitive similarities to the male cognitive style (Greenberg et al., 2018;

Kozhemiako et al., 2019). On the other side of explanations are those meaning there is a lack of theoretical knowledge and clinical understanding in how ASD is portrayed in females (Moseley, Hitchiner & Kirkby, 2018; Young, Oreve & Speranza, 2018).

From the perspective of social communication there is support for both explanations. In the normal population it is well documented that females are superior in language developing (Ramos-Loyo et al., 2022) partly explained by them being superior in *Auditory Acuity* (Mc Givern et al., 2019) which is related to language comprehension (Ayasse, 2019). Males have shown to be superior in visual processing more specifically in spatial and motional processing (McGivern et al., 2019). These are gender differences that can be seen in as young children as newly born (Alexopoulos et al., 2022).

In the normal population the gender differences in language processing are very small but in those on the 10^{th} percentile and below, it is much higher, males being more than twice as likely to be diagnosed with a language disorder (Wallentin, 2020).

Since language difficulties as well as language disorders are common in ASD, some argue we should see the same diagnostical pattern in ASD, however that is not the case. Contrary to language processing, ASD gender differences are much lower in those on the 10th percentile and below while much larger in those above the 10^{th} percentile (Yeargin-Allsopp et al., 2003; Brugha et al., 2016; Salomone et al., 2016). The contrasting gender distribution patterns generate believes that we are failing in detecting ASD in High functioning (HF) ASD females (Moseley, Hitchiner & Krikby, 2018; Young, Oreve & Speranza, 2018). In addition, concerns have been raised around the fact that in subjects with HF ASD both genders show an equal number of impairments in social understanding but differ in social behaviour, leaving females less likely to meet the diagnostic criteria of ASD (Hiller, Young & Weber, 2014; Rynkiewicz et al., 2016; Dean & Kasari, 2017; Parish-Morris et al., 2017; Ratto et al., 2018; Cola et al., 2020). There are also studies showing the age of receiving an ASD diagnosis is positively related to a verbal IQ of 70 and above in both genders, but far stronger in girls (Salomone et al., 2016; McDonnel et al., 2021).

ASD prevalence on the rise

In 2017 the World Health Organization (WHO) reported that the worldwide prevalence of ASD was one of 160 children. In Sweden as in many other developing countries the prevalence of ASD has increased over the years. Between the years of 2010 and 2016 the prevalence of ASD in Stockholm went from 1 to 3%, females showing a somewhat higher rise than males (Centrum för Epidemiologi och Samhällsmedicin, 2017 [CES]).

The increase is mainly explained by the more allowing diagnostic criteria of DSM-5 replacing the previous edition of DSM-IV in 2013 (APA, 2013). A better understanding of female ASD is also considered to contribute to the increase (Rødgaard et al., 2019).

An aspect brought up by several journalists via social media, is the complexity of todays' modern society, including the school system, and the social demands it puts on children. They argue it creates a higher likelihood for a child with autistic traits to meet the DSM-5 specific diagnostic criteria of ASD stating that besides showing autistic traits there must also be the presence of a prolonged suffering on a clinical level (Karlsson, 2014; CES, 2017; Flygt, 2017; Jansson, 2017; Kriisa, 2021). This is contradicted by research in genetics showing the true ASD prevalence to be around 5 % rather than 1%, mainly caused by genetic factors, showing environmental aspects to be of negligible impact (Tick et al., 2016; Yip et al. 2018; Bai et al., 2019). Studies showing environmental factor are significant in ASD are accused of using a too low estimated prevalence causing skewed results (Tick et al., 2016).

The impact of an ASD diagnosis

The difference between receiving a neuropsychiatric versus anxiety-related diagnosis lies within the explanation as to why the person is affected by psychiatric illness. A neuropsychiatric diagnosis will provide a biological explanation for the patient, granting support and interventions whereas anxiety-related diagnoses will leave a patients open for their own interpretation as to why the anxiety has developed.

In Sweden, the diagnosis of ASD, legislated under the "law of support and service" (Lagen om stöd och Service [LSS]) (SFS nr 1993:387) grants access to interventions and tailored accommodations not typically given to other psychiatric disorders. In 2019, 64% of the total LSS interventions given to people between 0-19 years of age[1], were given to males (Statistiska Centralbyrån [SCB], 2019a). A diagnosis of ASD also allows the parent of the patient to apply for a care-allowance (SFS nr 1993:387). In 2019, 67% of the care-allowance in Sweden were given to males (SCB, 2019b).

[1] ”Persongrupp 1” to which patients with ASD belongs.

Cognitive predictors

According to the American Psychiatric Association (APA, 2020), cognition constitutes one of three components of mind along with affect and conation. Cognition is defined as being “all forms of knowing and awareness, such as perceiving, conceiving, remembering, reasoning, judging, imagining and problem solving” (APA, 2020).

Sensory processing

Sensory processing refers to the ability to detect, regulate, interpret, and respond to sensory stimuli (Brown et al., 2001) whereas *temporal processing* is the ability to integrate contemporary sensory inputs into an adequate global interpretation (Wallace and Stevenson, 2014). According to the Sensory Integration Theory (SIT) (Ayres, 1979) temporal integration of multisensory information is paramount for human development, in particular language development (Foss-Feig et al., 2017; De Nier et al. 2018; Jain, Priya & Joshi, 2020; Meilleur et al. 2020) and the construction of a coherent perception of the world (De Nier et al., 2018).

By differing between *Unisensory* and *Multisensory* processing, SIT separates between complexity levels of sensory processing. While unisensory processing requires the process of one or more stimulus from *the same sensory modality* such as auditory *or* visual stimuli, multisensory processing involves processes requiring an integration of stimuli received *from different modalities* such as auditory *and* visual stimuli (Zhou et al., 2018; Meilleur et al., 2020).

The Temporal Binding Window (TBW) refers to the duration of time that elapses between the presentation of two stimuli that are perceived as being bound together.

Difficulties integrating multisensory information are often associated with one sensory modality dominating over another by responding faster or stronger, blocking out information from other modalities (Shams, Kamitani & Shimojo, 2000; Alais & Burr, 2004).

Sensory processing in ASD

Being a sensory processing disorder, atypical sensory experiences are estimated to be present in 90 % of people with ASD (Tomchek & Dunn, 2007; Tavassoli et al., 2014). Clinical symptoms have been noticed in as young children as 6 months of age and has shown to precede (Estes et al., 2015) and predict (Turner-Brown et al., 2013) social-communication deficits. As a reduced audio-visual temporal acuity is well established in ASD, mostly affecting audio-visual speech stimuli (Bebko et al., 2006; Foss-Feig et al., 2010; Kwakye et al., 2011), it has been suggested that social difficulties seen in patients with ASD are a result of an inaccurate representation of the environment caused by an inability to properly integrate contemporary sensory inputs from different kind of modalities such as auditory and visual stimuli (Wallace and Stevenson, 2014).

There is plenty of support showing children with ASD are superior in visual acuity (Jolliffe & Baron-Cohen, 1995; Joseph et al., 2009; Kaldy et al., 2016). Considering the heterogeneity in autistic behaviours as well as the lack of gender perspective in studies of ASD (Feldman et al., 2018; D'mello et al., 2022), we should be careful when relying too much on research findings describing autistic features to be portrayed in a certain way. In research of unisensory processing in ASD, studies have yielded varied results. Some suggesting individuals with autism have a larger visual TBW (impaired visual discrimination), others that it is smaller (better visual discrimination) (Zhou et al., 2018; Meilleur et al., 2020). In auditory processing, children with ASD exhibit impaired auditory discrimination, indicating they have a larger auditory TBW than their typically developing peers (Kwakye et al., 2011). As ASD adults are better in visual discrimination than their typically developed counterpart it has been suggested that the differences most likely are due to age; in ASD children sensory integration matures later than in TD (Falter, Elliott & Bailey, 2012). It should however be noted that the studies mentioned above predominantly featured male subjects and did not account for gender as a factor. In a study from 2017 DiCriscio and Troiani could show that an enhanced visual ability was only associated with ASD symptoms in ASD males (DiCriscio & Troiani, 2017) which was supported in a study from 2018, providing evidence for an *"Extreme female brain"* in ASD claiming that the *"male brain syndrome"* only represents a sub-group of the ASD population (Floris et al., 2018).

Sensory processing in speech comprehension

The process of speech comprehension involves sensory processing on many different levels, from the subcortical areas of the brain to executive functioning in cortical levels of the brain (Friederici, 2011).

The Dual Stream Theory of speech comprehension explains how audio-visual sensory information are passed on and integrated through two distinct streams, the *Ventral Stream* (VS) and the *Dorsal Stream* (DS). The VS is responsible for making decisions about the most relevant information to transmit, while the DS unconsciously prioritizes immediate information (Hickok & Poepple, 2004; Mostert-Kerckhoffs, 2015; Zeki, 2016). The streams interact by passing on relevant information while blocking others (Zeki, 2016; Hickok & Poepple, 2004; Mostert-Kerckhoffs, 2015; Fu et al., 2020).

There are gender differences associated with language processing. Females in the normal population have shown to be superior in processing of tonal stimuli in the VS (McGivern et al., 2019; Siedlecki et al., 2019; Thornton et al., 2019) which is highly associated with speech comprehension (Ayessa, Penn & Wingfield, 2019). Females have also shown to have a higher degree of bilateral processing using bimodal sources of information to a greater extent than males. Males in turn, have a visual-spatial information processing advantage in the DS (DiCriscio & Troiani, 2017). They are also more lateral in their language processing than females, relying mostly on auditory information from the DS (Koles et al., 2010) (Figure 1).

The left hemisphere dominates in language processing (Rasmussen and Milner, 1975; Vingerhoets, 2019), it reflects incoming information, compares with previous knowledge to interpret, and grasp the overall meaning of the situation (Corballis, 2012). In contrast, the right hemisphere processes contemporary non-verbal information such as tonal stimuli and visual information (Corballis, 2012). The VS is more connected to the right hemisphere and exhibits a left ear advantage, while the DS is more connected to the left hemisphere and has a right ear advantage (Hickok & Poepple, 2004; Mostert-Kerckhoffs, 2015; Zeki, 2016). A right ear advantage is therefore seen in speech perception and a left ear advantage for tonal stimuli (Kimura, 1961, 1963, 1964, 1973).

A lesion in the VS often causes auditory comprehension deficits (Kümmerer et al., 2013) whereas DS lesions are associated with repetition deficits and stereotyped speech (Kümmerer et al., 2013). When the DS is impaired, the VS work as a compensatory function with suboptimal performance as a result (López-Barroso et al., 2011). ASD has been associated with various impairments in the Ventral Stream (VS) (Greenway & Plaisted, 2005; Chan & Naumer, 2014), resulting in a sensory overload and challenges related to comprehending the overall meaning of text or social interaction (Gomot & Wicker, 2012; Robertson & Baron-Cohen, 2017).

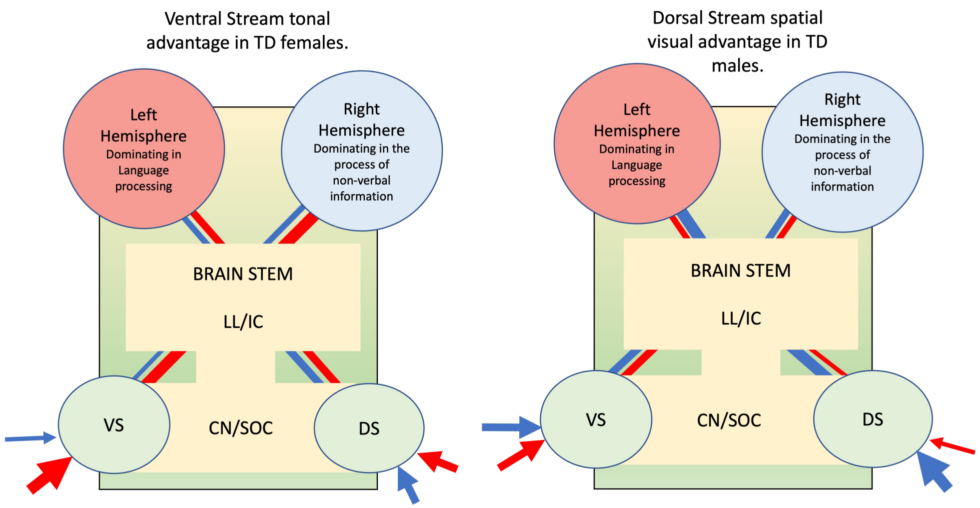

Figure 1. Simplified explanation of language processing in Typically Developed (TD) females and males. Auditory (red) vs Visual (blue)

Empathizing-systemizing (E-S) theory of sex differences in cognition.

The *Empathizing-Systemizing* (E-S) theory of psychological sex differences was proposed as an attempt to explain the *"extreme male brain"* often seen in subjects with ASD (Baron-Cohen, 2003; Baron-Cohen, 2009). According to the E-S theory the male brain is more inclined to analyse and predict behaviours of system whereas a female brain is more inclined to analyse and predict behaviours of other people's mental states (Baron-Cohen, 2003). People are divided into five different *empathy-systemizing* dimensions: those having an equal amount of empathizing and systemizing are categorized as *Type B* (E=S). *Type E* show a stronger ability of empathizing than systemizing (E>S) and the reversed situation is represented by *Type S* (E<S). *Extreme Type E* represent those with an extreme ability for empathizing and is more common in females whereas *Extreme Type S* represent those with an extreme ability for systemizing and is more common in males (Greenberg et al., 2018). In ASD *Extreme Type S* is commonly seen whereas the *Extreme Type E* is rare to find (Greenberg et al., 2018).

Social cognition

Social cognition refers to the ability to pick up and integrate social cues, make an interpretation of collected information and produce a response adequate to the specific setting (Mitchell, 2009). Besides being one of the primary criteria of ASD, deficiencies in social communication are also the most prominent difficulties associated with ASD (Fernández, Mollinedo-Gajate, & Peñagarikano, 2018). Several studies of ASD show both genders have an equal number of impairments in social understandings but differ in social behavior, leaving females less likely to meet the diagnostic criteria of ASD (Hiller et al., 2014; Rynkiewicz et al., 2016; Dean, Harwood & Kasari, 2017; Parish-Morris et al., 2017; Ratto et al., 2018; Cola et al., 2020). In literature about ASD, females are often mentioned to engage in reciprocal conversations, share interests and to integrate verbal and nonverbal expressive behaviours to a higher degree than males (Hiller, 2014).

The theory of Social Motivation differentiates between a complex social setting and a less complex social setting where the first refers to a social situation where multiple sensory modalities need to be integrated to grasp the global understanding of the situation and the second, to social settings where only one source of sensory information is needed to be processed (Tamir and Hughes, 2018).

Camouflaging

"Camouflaging" is a commonly used strategy among females with ASD. It refers to the ability to appear socially adapt, despite experiencing challenges with social communication (Hull, 2017). Camouflaging strategies correlate with signal detection ability in females. While the use of camouflaging strategies may be perceived as a strength; it is known to cause exhaustion and increase the risk of developing depression- and anxiety-related disorders (Rynkiewicz, Janas-Kozik & Slopien, 2019). Camouflaging strategies is also known to cause misunderstandings and inaccuracies in ASD assessments despite children being rated accurately in contextually relevant situations by those who know them well (Hull et al., 2017; Young, Oreve & Speranza, 2018). Additionally, the use of camouflaging strategies has been associated with delayed diagnosis of ASD in females (Belcher et al., 2022).

The brainstem

The brainstem is composed of three sections, the midbrain, the pons and the medulla oblongata. Besides being responsible for vital functions such as breathing, consciousness and heart rate the brainstem is also where sensory information is registered, sorted out and passed on for further processing in cortical areas (Angeles-Fernandez-Gil et al., 2010; Fernández, Mollinedo-Gajate, & Peñagarikano, 2018). Being the first receiver of acoustic input, the brainstem has been pointed out as a possible area of impairment causing difficulties in ASD (Pollak, 2013).

The auditory path through the brainstem can be divided into five parts. The Acoustic Nerve (AN), the first receiver of auditory information, the Cochlear Nucleus (CN) where acoustic information is processed at a first stage, sorted out and passed on to different streams (DS vs VS), the Superior Olivary Complex (SOC), responsible for converging binaural ascending inputs from the CN, the Lateral Lemniscus (LL), innervated by the contralateral dorsal stream, having excitatory and inhibitory inputs to the Inferior Colliculus (IC) which serves as a switchboard and an integration station for multisensory information as well as for converging all sound stimuli before passing it on to the cerebral cortex (Pickles, 2015; Peterson, Reddy & Hamel, 2020).

Executive functioning (EF)

The executive functioning (EF) are cognitive skills needed for planning and flexibility, enabling a “top-down” process to take place (Rabinovici, Stephens & Possin, 2015). In regards of social competence, the EF facilitate a correct interpretation and understanding of a person’s thoughts and emotions (Jones et al., 2018; Kouklari, Tsermentseli & Auyeung, 2018). The EF, located in the prefrontal regions of the frontal lobes, has constant interaction through neural connections with other cortical, subcortical and brainstem regions (Lalonde, 2017). In ASD, common EF deficiencies include cognitive flexibility, working memory, inhibition, and planning (Craig et al., 2016; Kouklari et al., 2019). Compared to TD children, patients with ASD score significantly lower in all aspects of EF measured with a computerized Continuous Performance Tests (CPT). Compared to children with ADHD, ASD children also show a significantly lower performance within auditory and visual response control, whereas the audio and visual attention scores are at the same level (Corbett & Constantine, 2006).

Rationale

This thesis is an attempt to converge two conflicting theories into one; The believe of females being genetically protected from ASD and the believe that female ASD is not properly understood.

Communication, being one of the building blocks for social functioning is highly depending on language processing. In the normal population females have shown to be superior in language processing, having a superior *Auditory Acuity* and using bilateral processing as well as bimodal information to a higher degree than males whereas males are superior in visual spatial processing and have a more lateral language processing mostly relating on auditory information.

The *"Extreme male brain"* theory of ASD is based on the belief that subjects with ASD show extreme male brain thinking causing ASD difficulties. Sensory integration difficulties, common in ASD, are often caused by one sensory modality responding faster or stronger than the other. Since the male brain is superior in visual processing, we reason auditory information will be blocked out, having a severe impact on language since the male language process is mostly depending on auditory information and also lack compensating abilities.

Assuming an *"Extreme female brain"* is constituted by a superior *Auditory Acuity* in the VS blocking out visual information, it would not be causing that much of a damage in unisensory processing considering auditory information is vital for language processing. A loss of visual information can be compensated for by females using an alternative stream or gathering information from an alternative modality. In multisensory processing a blockage of visual information should cause more problems as both auditory and visual information will be necessary, hence, no alternative processing stream or modality to gather information from will be available.

Since camouflaging strategies are more common in females than in males and has been associated with better signal detection ability as well as with stress and anxiety related problems, we suggest a *Superior Auditory* processing in ASD females enables social communication in less complex social settings (unisensory) while leaving more complex social settings (multisensory processing) as difficult to process as they are for males.

Aim

The main aim of this present thesis is to explore whether an *"extreme female brain"* can be related to ASD females and if so, can it also be related to communication abilities in less complex social settings or in more complex social settings or perhaps to both?

Is the male predominance in ASD diagnoses a correct representation of reality or might there be aspects that are important to take into considerations before we decide that females are not as affected by ASD as males?

By looking at gender characteristics in three different aspects of functioning. 1 – Auditory Brainstem Response (ABR) 2- Integrated Auditory and Visual processing, 3 - Child/youth behaviour rated by parent, we aimed to gain a more global understanding of ASD.

In paper I and II the specific aim was to identify potential gender differences in ABR in patients with ADHD (paper I) and ASD (paper II) respectively and to compare them with control groups to identify regions of interests in the brainstem. In paper III the specific aim was to look at ASD gender differences in associations between audio-visual processing and parental ratings of child behaviour. In paper IV the specific aim was to look at ASD gender differences in the association between audio-visual processing and ABR in the two areas identified in study I and II.

Method

Design and ethics

This thesis consists of four papers based on three separate clinical studies. In the first two clinical trials, resulting in paper I and II, gender differences in auditory brainstem response were investigated in children diagnosed with ADHD and Autism respectively. In both studies control groups were used.

In the third clinical study, resulting in paper III and IV, all patients triaged for an ASD assessment were included, regardless of them meeting up to the ASD criteria or not. Paper III explores ASD gender differences related to associations between parental ratings of child autistic behaviour and child performance in audio-visual sensory processing. In paper IV audio-visual sensory processing performance is explored in relation to ABR functioning.

All parents were given written information about each study before deciding whether they wanted to participate or not. All children were also given written information adapted for a child to understand. Before any material was collected a written consent was collected from both parents and patients. A gift card of 200SEK was given out to each child when all material was collected.

In the third clinical trial, children wanting to leave the study in advance were also given a gift card as an encouragement for trying. However, since the leaving often occurred in the middle of the ABR or IVA-testing which might be hard for impatient and sensitive children we also encouraged them to continue with the last part of the test by offering an extra reward of a second gift card of 200SEK. Out of 11 children who wanted to leave 9 took the opportunity to gain a second gift card.

The studies were approved by the regional ethics committee of Lund University. Paper 1: Dnr: 2010-120. Paper 2: Dnr: 2010-120, Dnr: 2015/11. Paper III and IV: Dnr: 2016/964.

Participants

Paper I

Study I included patients diagnosed with ADHD and control subjects between the ages of 7-17 years. All patients were recruited during the year of 2015 from the Child and Adolescent Psychiatry outpatient departments of Eslöv and Lund, two cities in the south of Sweden. All patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). The diagnoses were confirmed by a senior psychiatrist. Patients with other concurrent psychiatric diagnoses were excluded to avoid comorbidity. On the day of testing all patients were instructed to come unmedicated. The control groups were recruited from schools in Lund and did not have any previous record of psychiatric disorders. Subjects with any kind of hearing impairment were excluded from the study. Sixty-three females diagnosed with ADHD (age mean 13.8 years, SD 2.5) and 48 males diagnosed with ADHD (age mean 13.1 years, SD 1.8), 26 female control subjects (age mean 13.8 years, SD 2.7), and 20 male control subjects (age mean 12.8 years, SD 1.7) were included in the study. The age difference between boys and girls were not statistically significant.

Paper II

Study II included patients diagnosed with ASD and control subjects between the ages of 7-17 years. All patients were recruited during the year of 2016 from the same clinics as in the first study. The patients were assessed in clinical settings by a senior psychologist using the Autism Diagnostic Observation Schedule (ADOS) (Lord, Rutter, DiLavore, & Rishi, 2001) and Autism Diagnostic Interview – Revised (ADI-R) (Rutter, Le Couteur, & Lord, 2003) (mean females 27.83, SD 16.34; mean males 33.00, SD 14.77). The ASD diagnoses were confirmed by a senior psychiatrist. All ASD patients had an IQ of 70 or above, as measured by either the Wechsler Intelligence Scale for Children–Fourth edition (WISC-IV) (Wechsler, 2003) or the Wechsler Adult Intelligence Scale–Fourth edition (WAIS-IV) (Wechsler, 2008). The control groups were recruited from the same area as in study I and they had no prior record of psychiatric disorders or any known intellectual disabilities. Any child, belonging to either of the groups were excluded if they had a previous contact with the ear, nose, and throat clinic to avoid including children with hearing impairments. Twenty-one females with ASD (mean age 12.71 years, SD 3.36) and 18 males with ASD (mean age 11.50 years, SD 3.09), 24 female control subjects (mean age 13.12 years, SD 3.47) and 23 male control subjects (mean age 13.18 years, SD 3.22) were recruited into the study.

Paper III and IV

In study III and IV all patients triaged for an ASD assessment during the year of 2017, were invited to participate in the study. Fifty-seven patients between the ages of 7-17 (29 females mean age 12.97 years, SD 3.168 and 28 males, mean age 11.71 years, SD 2.904) were recruited from the child and adolescent psychiatric out-patient clinic in Eslöv, Sweden. The patients were all from the same socioeconomic area, the communities of Eslöv, Höör and Hörby where the median wage is around 74% of the Swedish median wage and an unemployment rate of 20% of compared to 9.4% for all of Sweden (Statistiska Centralbyrån [SCB], 2021).

The triaging process is a part of the clinics own screening procedure done by clinical psychiatric nurses using the structured Brief Child and Family Phone Interview (BCFPI) (Boyle et al. 2009; Cunningham et al. 2009). A patient could also have been triaged by a direct referral from a medical clinician working at another medical clinic, school or by staff working in social services. Four girls and seven boys were diagnosed with ADHD and were included in the study unmedicated. The remaining 46 children had no prior neuropsychiatric diagnosis. To be included in the study an IQ -level of 85 and above was required. IQ was measured with Wechsler Intelligence Scale for Children (WISC-V). Exclusion criteria were diagnosis of mental retardation, a diagnosis of any hearing disabilities including tinnitus, difficulties communicating in Swedish and any form of substance abuse. In study III 40 patients were included, 20 females (mean age = 13.90 years, SD= 2.34) and 20 males (mean age = 12.15, SD= 2,83). In study IV 36 patients were included 19 females (mean age=13.95 years, SD=2,094) and 17 males (mean age = 12.41 years, SD=2.917) (Table 1).

Table 1. Group statistics for recruited subjects in paper III and IV.

	Females		**Males**	
Recruited	29		28	
Age (SD)	12.97 (3.168)		11.71 (2.904)	
Paper	**III**	**IV**	**III**	**IV**
Excluded	8	7	7	7
Outliers	1	3	1	4
Remained	**20**	**19**	**20**	**17**
Age of included subjects (SD)	13.90 (2.34)	13.95 (2.094)	12.15 (2.83)	12.41 (2.917)
WISC-V Intelligence quotient	>85			

Measurements

Tests

Auditory Brainstem Response (ABR)

Auditory brainstem response (ABR) is a form of Electroencephalography (EEG) used in the detection of aberrant activity in the brainstem in reaction to auditory stimuli (Eggermont, 2019). It was used in study I, II and IV.

As nerve fibres in the brainstem activates in response to acoustic input, the electrical activity created in a specific area of the brain can be measured. The more activation the higher will the weighted average activity (the Compound Action Potential [CAP]) be (Eggermont, 2019).

CAP responses are collected during the first 10 milliseconds after an auditory stimulus has been presented. It generates an output of seven waves, each representing a specific area of the brainstem, with the two last waves being more difficult to define, hence only the first five are used within research (Eggermont, 2019).

It has been debated as to what extent it is possible to define the exact area of the brainstem each wave represents, but today there is a general acceptance of the following interpretation: Wave I – Acoustic Nerve (AN), wave II – Cochlear Nucleus (CN), wave III - Superior Olivary Complex (SOC), wave IV - Lateral Lemniscus (LL) and wave V – Inferior Colliculus (IC) (Wilson, 2004; Xie et al., 2018) (Figure 2).

Transmission delayals, a high or low wave amplitude and desynchrony of binaural activity are all seen as aberrant activity. Previous research investigating resting state functional connectivity (RSFC) in the SOC-area has shown it to be less activated in children with ASD (Mansour & Kulesza, 2020). A hypo connectivity has also been seen in the IC area (Baldwin et al. 2016). Findings on pathological brainstem activity in children with ASD are highly inconclusive but two main trends seem to be consistent, deviances occur mainly at higher levels of auditory processing in the brainstem and are more common in younger than older children (Pillion, Boatman-Reich & Gordon, 2018).

In paper I and II ABR frequencies, latencies and amplitudes in left and right ear were analysed in correlation to a norm curve and compared to control groups.

In paper IV the amplitude from left and right ear was analysed.

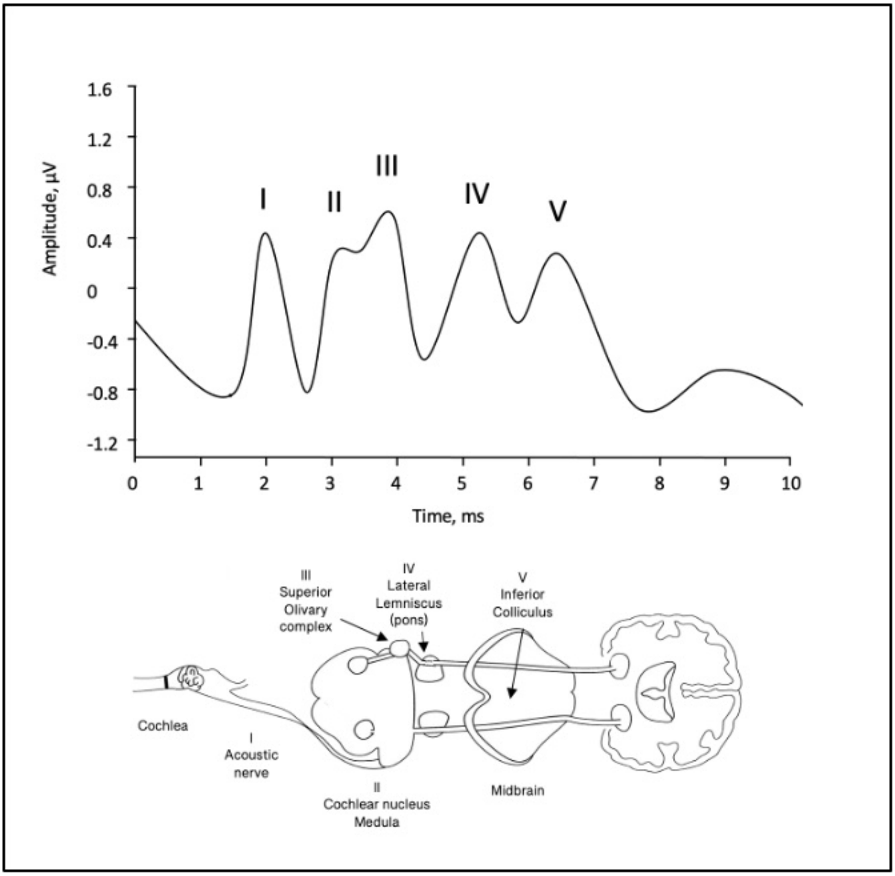

Figure 2. ABR waves and corresponding areas in the brainstem.

Integrated Auditory and Visual Continuous Performance Test (IVA-2 CPT)

IVA-2 (Sanford & Turner, 2000) is a computerized continuous performance test integrating visual and auditory sensory processes. The test was distributed to the patients in study three and the results were used in paper III and paper IV.

The output consists of 20 basic measurements, each providing a separate auditory and visual measure as well as a combined audio-visual measurement. Four primary scales representing: *Attention*, *Sustained Attention*, *Response Control* and *Symptomatic Problems* are built up by different combination of selected basic measurements as are seven sub-scales providing measurements of *Self-control*, *Presence*, *Resilience, Agility*, *Accuracy, Competence* and *Maintainability*. Each subscale also provides separate measures of *Auditory* and *Visual* performance as well as combined audio-visual scores enabling explorations of the balance between the two modalities (Table 3).

The test is made to produce errors such as omissions (i.e., inattentiveness), errors of commission (i.e., impulsiveness) and idiopathic errors enabling a better understanding of the deviant result. The *Validity Scales* control for lack of comprehension, unwillingness to participate or other misconduct behaviour. The unisensory measurements used in study III were *Elasticity*, *Focus* and *Acuity*, in study IV the same measurements were used although *Agility* was also added. The *Scales of Competence* and *Maintainability* were used as measures of a complex unisensory measures. As measurements of multisensory processing the audio-visual difference score were used in *Focus* and *Agility* (paper III) and in *Elasticity, Focus, Acuity,* and *Agility* (paper IV) (Table 2). All measurements used were chosen to represent common difficulties seen in ASD.

The IVA-2 profile is summarized quantitatively through standard scores that are familiar to most clinical practitioners. An IVA-testing not passing the validity scales shows no results. Test time: 15 minutes.

Compared to TD, children with ASD have a significantly lower performance on the IVA-test in all aspects and compared to patients with ADHD they have a significant lower performance within auditory and visual response control, whereas the auditory and visual attention scores are at the same level (Corbett & Constantine, 2006).

Table 2. The Iva-measurements used in paper III and IV.

<table>
<tr><td rowspan="5">Uni-Ensory measur-ements.</td><td rowspan="2">Specific</td><td>Auditory Elasticity</td><td>Visual Elasticity</td><td>Auditory Focus</td><td>Visual Focus</td><td>Auditory Acuity</td><td>Visual Acuity</td><td>Auditory Agility</td><td>Visual Agility</td></tr>
<tr><td colspan="2">III, IV</td><td colspan="2">III, IV</td><td colspan="2">III, IV</td><td colspan="2">IV</td></tr>
<tr><td rowspan="3">Complex</td><td colspan="2">Auditory Scale of Competence</td><td colspan="2">Visual Scale of Competence</td><td colspan="2">Auditory Scale of Maintenance</td><td colspan="2">Visual Scale of Maintainance</td></tr>
<tr><td colspan="4">High demanding tasks
(Prudence, Steadiness, Stability, Quickness)</td><td colspan="4">Low demanding tasks
(Reliability, Acuity, Dependability, Swiftness)</td></tr>
<tr><td colspan="4">III, IV</td><td colspan="4">III, IV</td></tr>
<tr><td rowspan="5">Multi-sensory measur-ements (Difference score)</td><td rowspan="3">Biased</td><td colspan="2">Elasticity</td><td colspan="2">Focus</td><td colspan="2">Acuity</td><td colspan="2">Agility</td></tr>
<tr><td colspan="8">Audio-visual balance</td></tr>
<tr><td colspan="2">IV</td><td colspan="2">III, IV</td><td colspan="2">IV</td><td colspan="2">III, IV</td></tr>
<tr><td rowspan="2">Un-biased</td><td colspan="2">Elasticity</td><td colspan="2">Focus</td><td colspan="2">Acuity</td><td colspan="2">Agility</td></tr>
<tr><td colspan="2">IV</td><td colspan="2">III, IV</td><td colspan="2">IV</td><td colspan="2">III, IV</td></tr>
</table>

Table 3. The IVA-testbattery output measurements.

						PRIMARY SCALES					
	MENTAL CONCENTRATION SCALES					Attention Scales		Validity Scales			
SCALES BASIC MEASUREMENTS	Self-control	Presence	Reciliance	Agility	Accuracy*	Attention Quotient	Sustained Attention	Response Controll	Symptomatic Problems	Competence High demand	Maintainability Low Demand
Vigiliance		X				X					
Focus			X			X					
Speed				X		X					
Prudence	X									X	
Reliability	X						X				X
Stamina	X										
Acuity		X					X				X
Elasticity		X					X				
Steadiness		X					X			X	
Consistency			X								
Dependability			X				X				X
Stability			X							X	
Quickness				X						X	
Swiftness				X			X				X
Readiness								X			
Comprehension									X		
Sensory/motor								X			
Persistance									X		
Fine Motor hyperactivity								X			
Accuracy*					X						
Balance									X		

Parental Rating Scales

The Swanson, Nolan and Pelham Scale (SNAP-IV).

The Swanson, Nolan and Pelham scale (Swanson et al., 2012) is a widely used rating scale (Hall et al., 2020) providing measures of ADHD symptoms related to inattention, hyperactivity as well as Opposite Defiant Disorder (ODD). The scale consists of 26 questions divided into three different groups, the first nine questions are related to inattention, the following nine to impulsivity/ hyperactivity and the remaining eight to ODD. The rating span from 0-3 corresponds to the child showing a certain behaviour "not at all", "just a little", "quite a bit" and "very much". The average score for each measure is calculated providing a score ranging from 0.0 – 3.0. A score above 1.0 indicates deviances. Test time: 10 min. This test was only used in paper III.

Social Responsiveness Scale (SRS-1).

The Social Responsiveness Scale (Constantino et al., 2003) is a parental rating scale measuring social behaviour in a child or adolescent between the ages of 4 and 18. It consists of 65 questions (17 of which are reversely scored) divided into five subscales measuring *social cognition social communication*, *social awareness*, *social motivation,* and *autistic mannerisms* (Constantino & Gruber, 2011). The rating span 0 to 3 represents, in corresponding order: Not true, somewhat true, often true, always true. The total score in each category is compared to a norm curve that provides a final t-scale score. A T-score above 60 indicates a low level of difficulties whereas a score above 70 indicates severe difficulties. Test time: 30 min. Social Responsiveness Scale (SRS) is one of the mostly used standardized assessments of ASD both internationally and in Sweden (Zander, 2021b) and surveys core symptoms of autistic traits (Constantino & Todd, 2003). The test was used in paper III. serving as an index of severity of social deficits in ASD.

Procedure

ABR

The test procedure in ABR have previously been described by our research team (Claesdotter-Hybbinette et al., 2016; Claesdotter-Knutsson et al., 2019; Åkerlund, Claesdotter-Knutsson & Håkansson, 2023). All ABR tests were performed and administered by trained staff. Participants were seated with a neck brace to make sure the neck was fixed and relaxed during testing. Two reference electrodes were placed on the mastoid bone behind the left and right ear, respectively, with two active electrodes and one ground electrode placed on the forehead. To ensure good transmission the sites were washed with disinfectant. Abrasive paste was used to fasten the electrodes. Absolute impedances and inter-electrode impedances were measured before and after the experiments to verify that electrode contact was maintained (below 5000 Ω). Earphones were fitted to cover both ears and the subjects were instructed to turn off their mobile phones and relax with their eyes closed. The test required no active participation.

The ABR was administered at the child's first appointment to the clinic. In cases where the family did not have the time to do the testing during the first appointment another test time was booked in a couple of days later, just for the purpose of participating in the study.

The measuring system used was SensoDetect® BERA (Brainstem Evoked Response Audiometry) A1000. The stimuli were presented via TDH-50P headphones with Model 51 cushions (Telephonics, Farmingdale, New York, USA). Presentations were made binaurally with the stimuli in phase over headphones. In total, 4 sound stimuli were used (Figure 3). The sound stimuli included square-shaped click pulses, high frequency varied pulses, forward masking, and backward masking stimuli. The click pulses were repeated until a total of 1024 accepted evoked potentials had been collected for each sound stimulus. Thus, each ABR waveform represents an average of the responses to 1024 stimulus presentations. TTL (transistor-transistor logic) trigger pulses coordinated the sweeps with the auditory stimuli. A TTL pulse is the signal which tells the ABR system to measure. With a correctly timed TTL pulse, all ABR representations will be synchronized. Aberrant activity, such as extremely high amplitudes due to extraordinary movements was rejected. Sound levels were calibrated using a Bruel and Kjaer sound level meter and Type 4152 artificial ear (Bruel & Kjaer S & V Measurement, Naerum, Denmark). The acoustic output from the earphones corresponded to SPL: 80 dB HL or 109 peSPL (peak equivalence). A square-shaped click pulse was used as probe in the auditory masking stimuli [32]. The sound stimuli included square-shapedre click pulses (0.136 ms duration, including 0.023 ms rise and fall; 192 ms interstimulus interval), high pass filtered pulses (a Butterworth high-pass filtered square shaped click pulse with a cutoff of 3000Hz), forward masking (12.3 ms gap from masker to click pulse) and backward masking (12.3 ms from click pulse to the masker) stimuli as previously described. A 1500-Hz Butterworth low-pass filtered white noise, with 15 ms duration (including 0.4 ms rise and fall times) was used as masker for both forward and backward masking stimuli. All stimuli were constructed using MATLAB Signal Processing Toolbox (The MathWorks, Inc., Natick, Massachusetts, USA) and stored in a flash memory in the SensoDetect® BERA system.

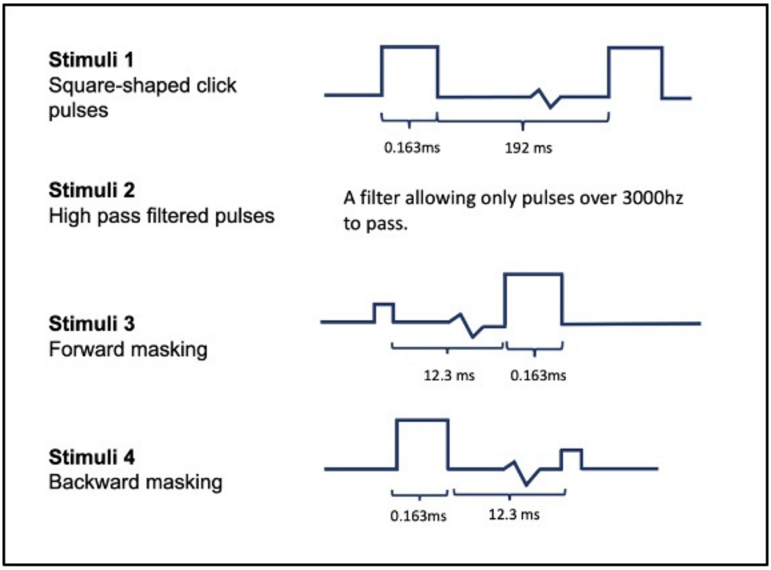

Figure 3. ABR-sounds used in study I, II and IV.

IVA-2 CPT

The IVA-test procedure has previously been described by our team (Åkerlund, Claesdotter-Knutsson & Håkansson, 2023; Åkerlund, Håkansson & Claesdotter-Knutsson, 2023). The IVA tests were performed and administered by trained staff. Participants were seated on a comfortable chair, adjusted to give the patient a comfortable and easy-to-reach position. The participant was presented with the auditory stimuli through tight fit headphones with ear cushions to reduce eventual disturbing sounds. The test room was empty, and the windows were covered up to shut out possible disturbing visual stimuli outside. The participants were presented with a session of 2 x 1 minute of responding to auditory and visual stimuli one at a time. After that a training session of 1.5 minutes started where the patient got to practice responding to both kinds of stimuli in a random order. The test starts when the computer has registered a proper response pattern in the practice part. The main test consists of either a written number 1 or 2 on the computer screen or a voice reading “one” or “two”. The computer voice tells the participants when they are to click on the mouse and when they are not to. The test continues for 13 minutes. As with the ABR-testning the IVA-test was also administered at the child’s first appointment to the clinic. In cases where the family did not have the time to do the test at that time another appointment was booked as soon as possible just for the purpose of participating in the study.

Parental ratings

The rating scales were handed out to the parents at the first appointment. The scales as well as the envelope they were given in were all marked with the patient code. The parents were asked to fill in the scales while the child was doing the tests. In those cases where the child could not make the test at the time of first appointment or if the child was accompanied by someone not being their caregiver the scales were allowed to be taken home for completion. Those ratings were either returned by a pre stamped and pre-addressed return envelope included in the first envelope, or at the patients next appointment.

Analytical and Statistical Methods

Paper I and II

The analytical method of ABR has been described in two previous studies from our research team (Claesdotter-Hybbinette et al., 2016; Claesdotter-Knutsson et al., 201). Prior to further analysis all the audiogram was correlated to ABR data, derived from a normative database to depict general audiogram quality, a standard operating procedure to grant audiogram quality. A low correlation led to exclusion of the patient due to risk of erroneous measurement (e.g. loose electrodes or head phones). The Sensodetect system rejected all evoked potentials being of abnormally high voltage (i.e. aberrant activity), typically trigged by patient movement, coughing or tension. Collected evoked potentials for each sound stimulus from each individual was imported to Microsoft Excel (Microsoft Corp, Redmond, WA, USA) and analysed using SensoDetect. BAS. Aberrancies in the ABR were denoted traits (TR).

For measuring differences between young males with ADHD/ASD compared to age matched control group and young females with ADHD/ASD compared to age matched control group, the nonparametric test Mann–Whitney U was used.

Paper I

Frequencies, latencies, amplitudes, and correlation coefficients was compared to a normed ABR curve, respectively, were investigated. Amplitudes were measured from the positive peak of a given wave to the bottom of the previous wave. Since the amplitude values obtained were not read in µV, microvolt outputs were indexed (i.e., normalized by adding constants to avoid negative values, then all amplitude values were divided by the highest observed amplitude). Thus, relative linear amplitudes are used in this study.

To identify specific pathologies along the auditory pathway, correlation values to a normative ABR curve were calculated for different sections of the ABR. Values ranging from -1 to +1 were obtained using Spearman rho. High, positive values indicate similarity (e.g. no pathology) values around zero indicate no relation, and low values close to -1 indicate inverse relationship. After the r-values for all sections of the total ABR curve (0-10 ms) had been computed, the results were ranked. Thus, the test subject's most aberrant ABR region, when compared with the norm curve, depicts a high number, and vice versa. The same principle was used to identify occurrence of high frequencies in the ABR curves of the test subjects. A mathematically constructed artificial ABR (a sine wave with the frequency 3500Hz) was used as norm. Norm population median values for every data point in the ABR were used to construct the artificial ABR. Every patient's ABR curve was correlated to this artificial ABR. The correlation value was calculated for each possible starting point in the ABR and the r (max) was used to indicate occurrence of the specific frequency. As the ambition with this operation was to see whether the test person had an occurrence of the frequency or not, the outcomes were ranked from 1 for all values between r=-1 to r=+0.1 and thereafter 2 for r=0.1 to r=0.2 and so forth, with 10 for r=0.9 to r=1, indicating a perfect match to the normed ABR.

Paper II

ABR in two predefined windows were analysed: amplitude in time window 2.5ms-4.0ms as well as the interaural correlation in time window 3.3ms - 4.4ms Correlations between the data collected from the left and right ear were calculated using Pearson rho to discriminate differences between ABR wave sections. Pearson rho results in r-values between -1 to +1 where a positive value indicates similarities, a negative the opposite relation whereas a value of 0 indicates no association.

Paper III and IV

Analyses were done using the Statistical Package for Social Sciences (SPSS) (IBM Corp., 2019) using a significance level of 0.05 in all tests. Before further analysing, the IVA-data was screened for unusual cases above 3 x the interquartile range. The descriptive statistics were used for calculating group mean score and standard deviations of age. The Kolmogorov-Smirnov test was used to test for normal distribution. The independent samples t-test was used when calculating group mean differences in age. Levene's test of variance was used to explore the homogeneity of variances. An analysis of covariance (ANCOVA) test was used to examine group mean differences within the measurements from the parental scales and the a priori chosen IVA measurements, controlling for the covariate of Age. The Bonferroni correction was used to adjust for multiple correlations. The Pearson correlation test was used when determining relationships between the parental ratings and the selected IVA-measurements using age as a control variable.

Paper III

The IVA-scores were correlated with each of the subscales of the parental SRS assessment. All the correlations were calculated using Pearson rho. The results are presented in r-values between -1 to +1. A positive value indicates a positive correlation, and a negative value indicates an inverse relation. A value around 0 indicates no correlation.

Paper IV

ABR data were screened for unusual cases where the average ABR amplitude from all four sounds were above the 3 x interquartile range in any of the ears which was then excluded.

The average amplitudes from each of the four sounds added up and divided by four in left and right ear, in two different time windows (TW) were extracted. TW I: 2.5ms - 4.0ms representing the CN/SOC area of the brainstem. TW II: 4.5ms - 6.5ms representing the LL/IC area of the brainstem.

The IVA-scores were then correlated with each of the four ABR measurements extracted. All the correlations were calculated using Pearson rho. The results are presented in r-values between -1 to +1. A positive value indicates a positive correlation, and a negative value indicates an inverse relation. A value around 0 indicates no correlation.

Results

Paper I

Females with ADHD showed a lower correlation to the norm curve in the CN/SOC (3.3ms -4.3ms) area (p=.0004) as well as in the Thalamus (6.0ms-7.0ms) area of the brainstem compared to TD females (p=.000064). In the area ranging from SOC to the Thalamus (4.0ms -7.5ms) a higher frequency of 3500 Hz compared to TD was seen (p=0006).

In the male group a lower correlation to the norm curve compared to TD males was seen in the IC to Thalamus (3.5ms -7.5ms) area (p=.0011). In the SOC to Thalamus (4.0ms -7.5ms) area there was a higher presence of 3500 Hz than in the TD group (p=.00013). In the early auditory pathways (2.5ms - 4ms) a lower correlation to nom curve was seen in backward masking (complex sounds) (p=.0003).

Both genders with ADHD showed significantly lower correlations to the norm curve in the later part of the brainstem compared to males and females without ADHD. Both genders in subjects with ADHD also showed a higher presence of 3500 Hz-frequencies in the SOC- Thalamus area, than respective control group. In the CN/SOC area ADHD females showed a lower correlation to the norm curve compared to TD females. In the male group the area of AN- CN/SOC showed a significantly lower correlation to the norm curve in backward masking, a more complex sound, compared to males without ADHD.

Paper II

In the area of the Acoustic Nerve (AN) to the CN/SOC area a higher amplitude was seen in the female ASD group compared to the control group (p=.0002). This was not seen in the male group (p=.015). The male control group also showed a lower correlation between left and right ear compared to the ASD males (p=.006), and the ASD females as well as the female control group.

Paper III

No significant gender differences were found in the parental ratings of Social Communication.

In the female ASD group, a higher performance in *Auditory Acuity* was associated with less rated problems within *social communication* (r=-.535, p=.022). In multisensory processing an *Auditory Dominance* in *Agility* was associated with a higher number of rated problems within *Social Awareness* (r=.541, p= .017) (Figure 4).

In the male group no associations were found between the unisensory measurements and the parental ratings of social responsiveness. In multisensory processing a *Visual Dominance* in *Focus* was associated with a higher number of rated problems within *Social Rigidity* (r=-.601, p=.007) (Figure 5).

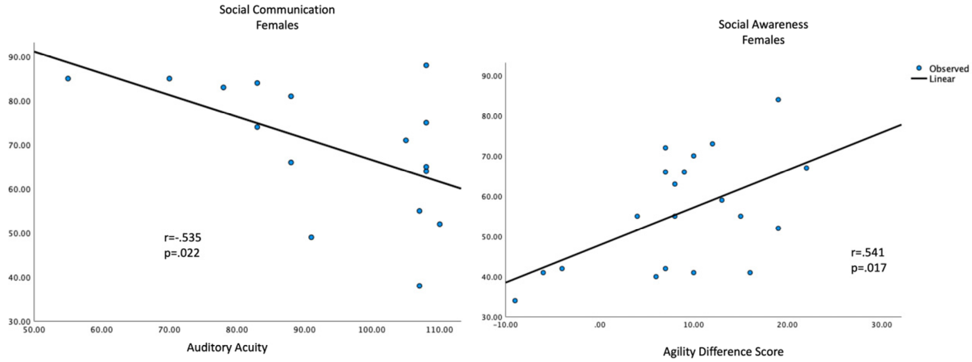

Figure 4. Regression table of significant results from paper III between unisensory versus multisensory processing and Social Responsiveness in the female group.

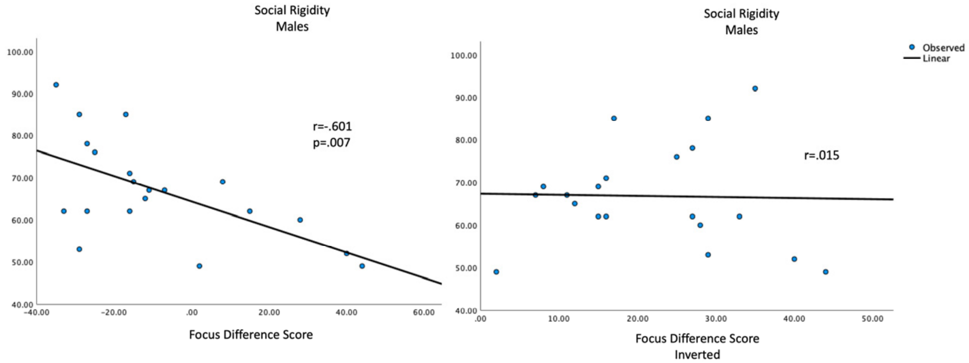

Figure 5. Regression table presenting results from paper III between Social Rigidity and Focus Difference Score versus Focus Difference Score inverted in the male group.

Paper IV

In unisensory processing the female ASD group showed associations between a better *Auditory Acuity* and a lower activity in left ear ABR (r= -.478, p=.045) in the CN/SOC area whereas no associations at all was seen in the LL/IC area. In the male group a better *Visual Acuity* was associated with lower ABR-activity in both left (r=-.602, p=.014) and right (r=-.555, p=.026) ear in the CN/SOC area, as well as in right ear ABR (r=-.527, p=.036.) in the LL/IC area. In the female group a better performance in *Auditory* (r= .513, p=.030) and *Visual Agility* (r=.565, p=.015) was related to a higher activity in right ear ABR of the CN/SOC area. In the male group a better performance in *Visual Elasticity* was associated with a higher activity in right ear ABR in the CN/SOC (r=.502, p=.048). A better performance in *Auditory*

Agility was associated with a higher ABR in left ear of the CN/SOC area (r=.503, p=.047) (Figure 6).

In multisensory processing a *visual* dominance in *Agility* was associated with a lower ABR activity in left ear in the LL/IC (r=-.590, p=.010). In the male group no significant associations were seen (Figure 7).

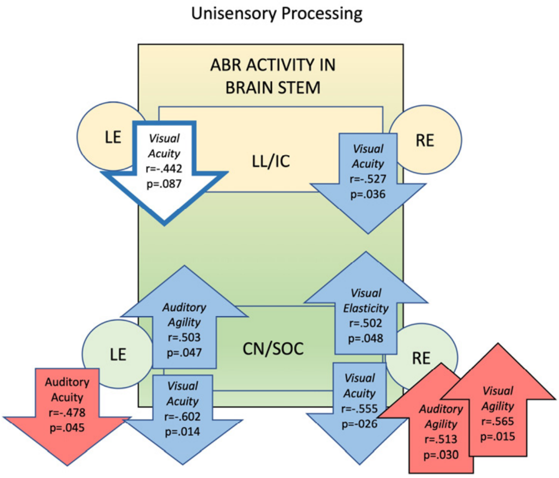

Figure 6. Results from paper IV. Significant associations as well as trending towards being significant findings in associations between unisensory versus complex unisensory processing and ABR activity in males (blue) and females (red).

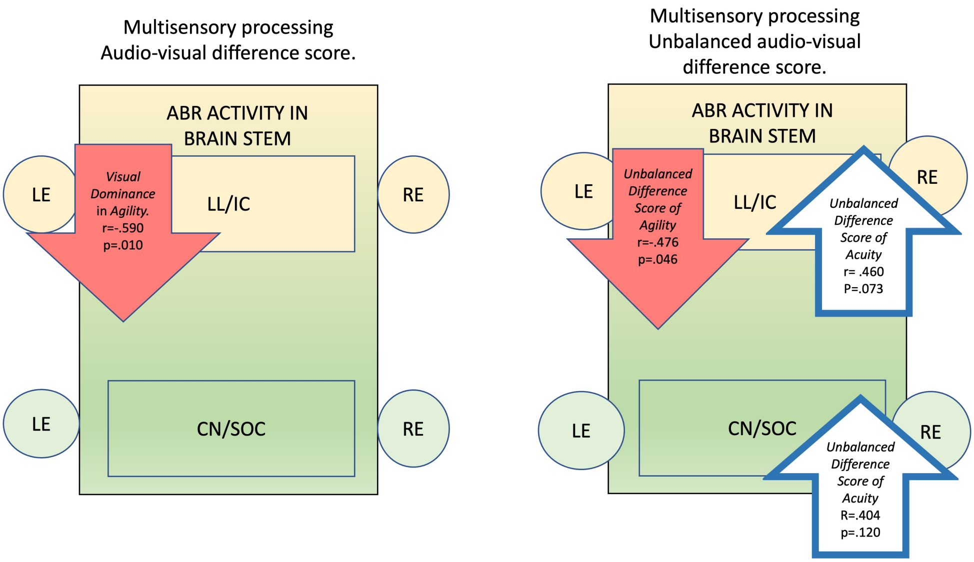

Figure 7. Results from paper IV. Significant as well as trending towards being signficant findings of associations between multisensory processing and ABR in males (blue) and females (red).

General discussion

This thesis aimed to gain a better understanding of the gender differences seen in ASD. The troublesome history of female psychiatric health in combination with difficulties still associated with diagnosing and treating female psychiatric disorders was the main source of inspiration. The methods used can be divided into three steps, each providing information on a different aspect of human functioning: auditory brainstem activity, audio-visual performance, and parental ratings of child's behaviour. This was done as an attempt to get a more global perspective of gender differences in ASD.

While the findings in each of the studies confirm gender differences in sensory processing, the overall, global perspective of this thesis suggests society must change its relation to female functioning, not only for a better understanding of female ASD, more importantly, for the understanding of females', period. If we continue to use the male brain as the norm, we cannot expect to reduce the number of females suffering from mental health issues.

Our findings suggest there are gender specific differences in audio-visual processing that can be related to ASD symptoms. It raises the need for more studies focusing on females. We need to start from scratch, investigating female functioning on a much deeper level, catching up to all the research that has already been made on males.

The main findings will be presented below as the conclusions of this thesis along with clinical implications will be discussed in a separate section at the end.

Main findings

Identification of brainstem areas significant for analysing in ASD

In the first two studies we got a better understanding on what areas in the brainstem are deviant in children and youth with ADHD and ASD in comparison to control groups. Since the ADHD children showed ABR deviances in the very late part of the brainstem as well as a higher presence of 3500Hz frequencies that was not seen in the ASD children we could exclude such analyses from our future studies of ASD.

Based on the findings in paper I and II we decided to go further with the investigation of amplitudes in two specific areas of the brainstem representing the CN/SOC as well as the LL/IC area as they also represent different stages of sensory processing.

No gender differences in parental ratings indicates the same level of difficulties in both genders.

As the parental ratings of *Social Communication* showed no significant gender differences, meaning parents of both genders reported the same number of difficulties we must assume both groups show the same level of difficulties.

In the measure of "*Social Rigidity"* there was a trend toward a significant (p=.085) difference between the groups, females being higher rated than the males. Considering *Rigidity* is more associated with male ASD (Hattier et al., 2011; Werling & Geschwind, 2013; Tofani et al., 2022) this finding might seem strange., however it seems reasonable that female children referred for an ASD assessment will be those showing more symptoms related to male ASD as they will be easier to spot compared to ASD females showing more of a female ASD phenotype (Rynkiewicz, Janas-Kozik & Słopień, 2019). It should be mentioned thought, that it has been suggested ASD females show the same number of rigid behaviours as ASD males, just portrayed differently (Lai & Baron-Cohen, 2015; Green et al., 2019; Antezana et al., 2019). In a study from 2019 restricted behaviours in ASD females were found to have more of a social quality compared to restricted behaviours seen in males, meaning females were more likely to be having a restricted interest in people or relations rather than in an object (McFayden, Antezana & Albright, 2019).

Just as in SRS, no gender differences were seen in the ratings of ADHD symptoms. The lack of externalized behaviour in girls have previously been pointed out as one reason to why girls are diagnosed with ASD much later than boys (Lindbom, 2020) however, gender differences in *ODD* behaviours do only apply to situations outside of home (Chapline & Aldao, 2013). As our ratings are made by parents the results are very much in line with previous research showing ASD females to have the same numbers of social difficulties as ASD males (Hiller et al., 2014; Rynkiewicz et al., 2016; Dean, Harwood & Kasari, 2017; Parish-Morris et al., 2017; Ratto et al., 2018; Cola et al., 2020).

In previous studies of ODD, identified risk factors are mostly connected to family factors such as socio-economic status, parent-child communication, and child ability to stay focused (Lin et al., 2022), aspects all relying on an adequate language processing. Considering no gender differences are seen in the parental ratings of ODD we believe gender differences in ODD are better related to audio-visual sensory processing. In previous studies, language and flexibility have been identified as risk factors impacting ODD in males, whereas in girls only flexibility was identified as a risk factor (Kerekes et. al. 2014).

As *Auditory Elasticity*, a form of flexibility showed a negative correlation with ODD in the male group as did *Auditory Acuity*, a measurement which has shown to be associated with speech comprehension (Lee et al., 2018; Ayasse et al., 2019) our findings are in line with previous research. The results indicate that a more female-like sensory processing profile is related to less ODD. In the female group an enhanced *Visual Elasticity* was significantly associated with a higher rating of ODD indicating that a more male-like sensory processing is associated with higher ratings of ODD in the female group. This is giving further support to our belief that the audio-visual balance is important when understanding social functioning.

Enhanced Auditory Acuity reduces ODD in males whereas in females it is associated with less problems in Social Communication.

A “social quality” is often attributed ASD females (Cola et al., 2022), especially when referring to the concept of “camouflaging”, i.e., the ability mask social difficulties and behave in a seemingly social accepted way (Hull, 2017). In our study *Auditory Acuity* was associated with less rated problems within *Social Communication* in ASD females whereas in ASD males it was associated with less rated problems within *ODD*. While the results are supportive of our hypothesis of an “extreme female brain” being associated with better communication skills in unisensory processing, the association to ODD in the male group was nothing we predicted.

Basically, in both groups *Auditory Acuity* is related to a positive effect in communication with another person, however, only the female group show associations with the measure of Social Communication. A possible explanation could be related to the questions in Social Responsiveness perhaps being too complex to be relatable to unisensory processing in males?

In a study from 2019 very similar results are reported in the association between receptive language and parental ratings of *Social Responsiveness* (Rodgers et al., 2019).

As *Auditory Acuity* is associated with language comprehension (Lee et al., 2018; Ayasse, Penn & Wingfield, 2019) it is fair to say that a measure of receptive language can be used as a comparison to *Auditory Acuity.* Just as in our study, despite no gender differences in SRS-ratings, ASD females showed associations between a better receptive language and ratings in *Social Communication* while no correlation at all was seen in the male ASD group. The authors suggested receptive language play a unique role in social functioning in ASD females (Rodgers et al., 2019).

Since the lateral and unimodal language processing in males is very limited compared to the language processing seen in females (Koles et al., 2010; DiCriscio & Troiani, 2017) it is possible that an enhancement in Visual Acuity will leave males with such a lack of auditory information that they are not able to communicate and therefore are left with using externalizing behaviours and hence SRS questions will not be relatable.

As an "extreme female brain" will be blocking out visual information it will not cause as much damage as in males, allowing females to still be communicating in unisensory social settings. This is in line with results from a study showing ASD females to be advanced in pragmatic and semantic language processing compared to ASD males. The authors of the study suggest a female phenotype of ASD needs to be considered as language processing difficulties might lie above sentence-level language processing (Sturrock, Adams & Freed, 2021).

Possible gender differences in ability to compensate when sensory information is lost?

If we assume that a *Visual Acuity* causes language processing difficulties in males by blocking out Auditory information, an enhanced Visual Acuity should also be associated with less ABR activity which is exactly what our findings show. An enhanced Visual Acuity is associated with lower ABR in both left and right ear of the CN/SOC. In the LL/IC area of the brainstem an enhanced *Visual Acuity* is only associated with lower ABR activity in the left ear.

Since there is a constant exchange of information between the VS and DS, a lack of information in one stream can easily be compensated for information from the other stream (López-Barroso et al., 2011). Considering the LL gathers and sort out information from both streams, and passes it on to the IC which in turn converges all sound stimuli as well as integrates auditory information with other sensory information such as visual information before passing it on to the cerebral cortex (Pickles 2015; Peterson, Reddy & Hamel, 2020) we might assume that the lack of association with ABR in left ear of the LL/IC area are due to some male ability to compensate for a loss of information. As the left hemisphere is dominating in the process of language (Rasmussen and Milner, 1975; Vingerhoets, 2019) and males are mainly relying on auditory information in the DS it seems reasonable that it is the right ear ABR (DS) that shows association to an enhanced *Visual Acuity.*

In the female group an enhanced *Auditory Acuity* was only associated with lower ABR in left ear of the CN/SOC area. No associations were seen in the LL/IC area of the brainstem. Since females have a more bilateral language processing than males, also using bimodal information to a higher degree than males (Koles et al., 2010) it seems reasonable to believe that the information being "blocked out" from the VS by an enhanced *Auditory Acuity* in the left ear of the first stages of processing will be compensated for by auditory and visual information collected from the DS.

These findings are in line with our theory of males being more affected by an enhanced *Visual Acuity* in unisensory processing than females will be by an enhanced *Auditory Acuity*.

The female ASD group also showed associations between a better performance in *Auditory* and *Visual Agility* and a higher ABR activity in right ear of the CN/SOC area indicating a higher level of processing. The fact that a higher ABR activity is associated with *Visual* Agility is also supportive of females using bimodal information when processing language. (Koles et al., 2010).

The paradox of an enhanced Auditory Acuity being associated with lower ABR activity as well as less rated problems in Social Communication

In study IV the female ASD group showed an enhanced *Auditory Acuity* to be related with a lower ABR activity in the left ear ABR. As TD females have shown a tonal detection advantage in the VS (McGivern et al., 2019; Siedlecki et al., 2019; Thornton et al., 2019) this is quite in line with our hypothesis of ASD females showing the same (or stronger) sensory processing as TD females do. However, the paradox of an enhanced *Auditory Acuity* being associated with less ABR activity in one study and with less rated problems in Social Communication in another, might seem a difficult one to explain. Nevertheless, if we consider a lower ABR activity to be representative of some sort of processing difficulty the results are quite in line with a study from 2017 exploring gender differences in adult ASD related to camouflaging behavior (Lai et al., 2017). In the study, a better signal detection ability in ASD females was associated with a higher number of camouflaging behaviors and significantly lower ratings of autistic features from both professionals and parents. As signal detection is just another name for *Auditory Acuity* the studies can be compared, although the study does not show a lower activity in the brainstem, it does show associations to the use of camouflaging strategies, strategies used by those having some form of social communication difficulty (lower ABR). Signal detection ability was also associated with significantly lower number of autistic features within social communication and RRB while the self-ratings of autistic behaviors were significantly higher in the female ASD group compared to the ASD male group. Further evidence is found in studies showing that ASD females using camouflaging strategies are often exhausted and run the risk of developing anxiety related disorders (Rynkiewicz et al., 2016; Dean, Harwood & Kasari, 2017; Rynkiewicz et al., 2019), indicating ASD females do not have adequate communication skills.

Specific sensory modality measures are better related to language processing than are global measures.

The two measures "*Scale of Competence"* and "*Scale of Maintainability"*, are unisensory measures of more complexity, comprising several aspects of *auditory* versus *visual* abilities. In the female group an enhanced *Auditory Maintainability* was associated with a lower ABR activity in left ear whereas in the male group an enhanced *Visual Competence* was associated with a lower ABR in left ear. Since these correlations are lower and non-significant compared to those seen with the specific measures it indicates that the specific measures of *Auditory* and *Visual* abilities are better related to brainstem activity than are the wider more including measure. This would mean that it is important to pay notice to different aspects of Auditory versus Visual abilities, as they seem to relate to different aspects of functioning.

This is supported by previous studies showing *Auditory Acuity* to be associated with language comprehension (Lee et al., 2018; Ayasse, Penn & Wingfield, 2019), whereas *Auditory Agility* was associated with vocabular comprehension, vocabular expression, speech articulation and phonological awareness bimodally (Demopoulos et al., 2023). This implies that an enhanced *Auditory* or *Visual* ability might not just be blocking out information from other modalities but also other types of information from the same modality.

Multisensory processing as difficult in females as in males?

Just as in the measures of unisensory processing, multisensory processing showed gender differences associated with audio-visual processing.

In the male group a *Visual dominance* in *Focus* was associated with a higher number of rated problems within Social Rigidity. Since no association between audio-visual processing and *Social Responsiveness* was seen in unisensory processing in the male group, it can be interpreted as *Social Rigidity* in ASD males are better explained by the *Visual Dominance* in relation to *Auditory* performance rather than visual strength on its own. This is in line with our previous reasoning around the questions of SRS perhaps being too complex to be related to unisensory processing in males.

However, one might question why a multisensory measure such as *Visual* dominance in *Focus* is better related to ratings of *Social* Rigidity than to brainstem activity? Should not high ratings of Social Rigidity result in some processing difficulty that can be seen in ABR activity? We cannot answer that question with the result from our study, however we might suspect that there is a mediating variable involved somehow. An interesting aspect is that the same pattern was seen in the female group as the multisensory measure of Agility showed an *Auditory* dominance to be associated with higher ratings of problems within *Social*

Awareness, still showing no association with ABR. In the female group a visual dominance in Agility showed associations to a lower ABR which will be discussed further down. In the male group no association between ABR and audio-visual sensory processing was seen.

The lack of association between the multisensory measurements and ABR in the male group is most likely related to the limited language processing seen in males. When an enhanced *Visual Acuity* is blocking auditory information out from both streams, males are not able to compensate in any way, reducing the ability to relate to a multisensory measure.

As said before, in the female ASD group, an *Auditory Dominance* in *Agility* was associated with a higher number of rated problems within *Social Awareness* supporting our hypothesis of an "*Extreme female brain"* causing processing difficulties in multisensory processing in ASD females. Since *Agility* is a combined measure of rapid processing one might suspect that it is a measure better connected with attention deficits rather than ASD processing difficulties, however no significant association was found between an *Auditory dominance in Agility* and the symptoms of *ADHD* in either of the groups.

In multisensory processing the female group showed a dominant *Visual Agility* to be associated with lower ABR activity in the left ear, indicating *Auditory Agility* is defected in the VS. The same was not seen in the male group. As said before, a lesions in the VS often causes auditory comprehension deficits whereas DS lesions are associated with repetition deficits and stereotyped speech (Kümmerer et al., 2013).

In a study from 2017 (Foss-Feig et al., 2017) rapid auditory processing deficits were associated with clinical assessments of receptive language impairments in ASD children. Since the authors of the study do not declare whether the ASD group consists of male or female children or perhaps a mix, it is difficult to draw any conclusions other than that *Auditory Agility* is related to language processing difficulties in some children (perhaps all) with ASD.

The findings of this thesis suggest females are having VS lesions in both unisensory and multisensory processing although in unisensory processing they are able to compensate for the information being lost. In males there are both VS and DS sensory processing difficulties in unisensory processing. Their lateral and unimodal language processing do not provide any alternative ways to gain access to lost information leaving them with much more severe processing difficulties. The multisensory measurements seem to not be of any relevance in males.

Looking at the unbiased difference score in the male group, a tendency to association can be seen in both areas of the brainstem showing a higher difference score associated with a lower ABR activity, although non-significant, which proves it is not the audio-visual balance that can explain activity in the later parts of the brainstem in males, rather it is better explained by a single measure of *Visual Acuity*.

Discussion

The main aim of this present thesis is to explore whether an *"extreme female brain"* can be related to ASD females and if so, can it also be related to communication abilities in different levels of social processing.

The lack of gender studies in ASD is profound (D'mello et al., 2022) and probably sustained by the common belief that ASD, is a form of "*extreme male brain syndrome",* directing research towards the male phenotype of ASD, away from females, leaving them to be more vulnerable in the Swedish psychiatric care system (Sveriges kommuner och regioner, 2021).

Some researchers break the trend though, paying more attention to the feminine aspects of ASD, trying to find out what signifies the female characteristics of ASD (Beggiato et al., 2017; Dean, Harwood, Kasari et al., 2017; Hull et al., 2017; Lai et al., 2017; Hull, Petrides & Mandy, 2020; Cola et al., 2020; Lockwood et al., 2021; McDonnell et al., 2021). Typically, female ASD is portrayed as someone with better social skills (Rynkiewicz et al., 2016), no externalizing behaivour (Lindbom, 2020), masking their communication difficulties well (Hull et al., 2017), hence the portrayal of an individual that is difficult to detect in an ordinary ASD assessment.

In a study published just recently, 100 adult females are revisited 17-20 years after receiving their ASD diagnosis, showing 89% are still meeting up to the criteria of ASD (Kopp et al., 2023). In another article from March 2023 a Swedish researcher raises concerns over the many ASD diagnoses given out today and requests clinicians to stop over diagnosing ASD (Gillberg, 2023).

The discussion of ASD rates being too high is a completely different story than the content of this thesis, but still highly important when discussing female ASD. As female patients are being under diagnosed due to having the appearance to be socially skilled despite having social difficulties, it is unfortunate that Gillberg do not clearly state exactly what he believes is significant for a patient that he means is wrongly diagnosed with ASD. Without further directions female patients will be the first to go.

The findings of this thesis support the belief of an "*extreme female brain"* being. present in ASD females as several aspects of an enhanced *Auditory* processing in ASD females is related to unisensory processing advantages as well as less rated problems in Social Communication. No such relation could be seen in multisensory processing. As the enhanced Auditory ability is associated with advantages one could also claim that our findings support the belief that females are protected from

ASD. Looking at the IVA scores, the females often show higher average scores than the males, however, the female scores are most of the time also well below the average score found in the normal populations (Figure 8) which implies they are advantaged in comparison to ASD males, but when compared to TD their difficulties become clearer.

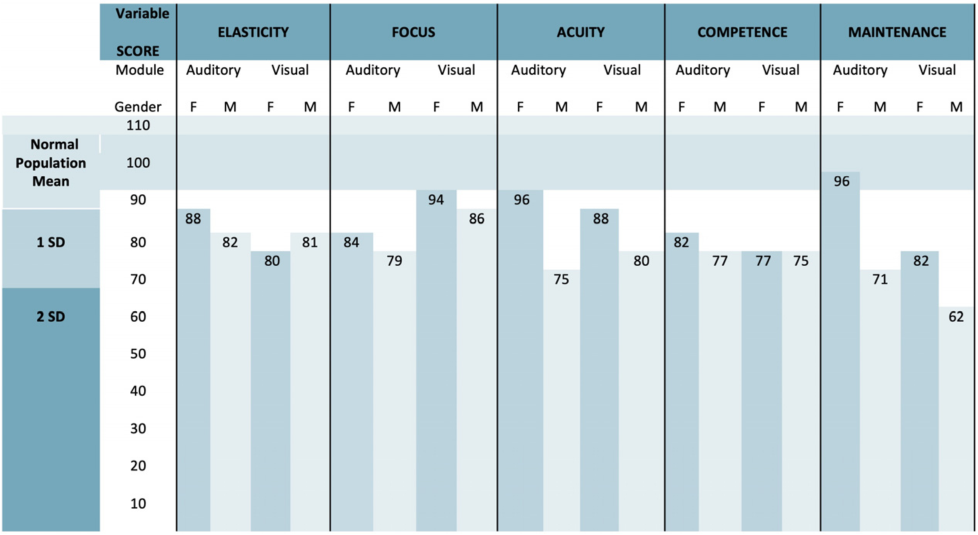

Figure 8. Average IVA scores in the female versus male group from study III.

The question that needs to be answered is rather at what point we consider a person (any gender) to need the help that is offered people with ASD? What aspects of a child's functioning need to be assessed to rate the child's need of help?

Today the DSM-5 criteria are used when we diagnose ASD (APA, 2013). The description of behaviours found under category A and B are all based on behaviours associated with rigid thinking pattern. Behaviours that might not be very well associated with the female phenotype of rigid thinking patterns. In category C the criteria states: "*Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life*". This is a disclaimer mainly relating to those using camouflaging strategies, a disclaimer trying to reach out to those female patients not showing typical male ASD symptoms. However, it does not say how to separate between someone who has learned strategies later in life from TD. Neither does it tell us what kind of behaviour we should expect from someone that are masking their difficulties.

In order to answer the question as to who shall be given an ASD diagnosis we first have to understand if there are different rigid thinking patterns in males and females and if so, how do we identify them in our patients?

A healthy social functioning should be associated with the ability to make flexible and healthy judgements when to adapt to others and when to prioritize oneself. In male ASD it is common to see behaviours in line with not wanting to adapt, causing ODD and externalizing behaviour (Lindbom, 2020) in females we see the opposite behaviour, when they adapt to everybody and make no notice of themselves, resulting in exhaustion, depression, and anxiety related disorders (Rynkiewicz et al., 2016). Both groups have the same problem with adapting in social settings, they just deal with it in different ways. Males chose to adapt in favour of them self while females chose to adapt in favour of others.

Our findings show that the portrayal of an *"extreme female brain"* in ASD females becomes an advantage in settings requiring unisensory processing, meaning they will be able to understand and react to less difficult social interaction. In ASD males, our findings show that the portrayal of an *"extreme male brain"* will be causing processing difficulties even in less complex settings.

Considering less complex social settings are often presented to us in younger years it seems reasonable to believe that ASD girls will go undetected for quite a while before showing symptoms that are more obvious. As ASD male are faced with communication difficulties already in less complex settings the externalizing behaviour might be their only option.

As ASD females get older, they might just be schooled into adapting in social settings, however, as social settings get more complex the adaption solution is not working that well. Our findings indicate that a superior *Visual Agility* is associated with less activity in the VS in the LL/IC area in ASD females. VS lesions are known to cause comprehension difficulties (Kümmerer et al., 2013). Since *Agility* is a measure of rapid processing (Sandford and Turner, 2000) a dominant Visual Agility should be blocking out Auditory Agility. Deficits in rapid auditory processing have shown to be associated with clinical assessments of receptive language impairments in ASD children (Foss-Feig et al., 2017).

The findings of this thesis imply we should be able to design assessment tools to include more complex social settings, enabling female ASD to be easier identified. Our findings also support the need for different assessment tools for different phenotypes of ASD. For those with a female phenotype of ASD more complex social settings need to be evaluated as the less complex settings might not be able to pick up female ASD. In males, less complex settings seem to be enough as more complex social settings might be too much for them to even be able to participate.

The visual dominance being associated with lower ABR in female ASD was quite the opposite to what we expected to find. We believed all ASD difficulties in females would be related to an enhanced Auditory processing. However, the fact that we see associations with a visual dominance might just be an indication of how complex our brains are. As argued above, the *Visual* dominance in *Agility* is not seen in the male group meaning it is most likely related to a female ASD profile.

The fact that a dominant *Auditory Agility* was associated with a higher rating of problems within *Social Awareness* in females is also a hard one to explain, but it is telling us that there is no easy way to understand or describe sensory processing in ASD. In males two trends toward significant associations were seen in the unbalanced multisensory processing measure of *Acuity* showing that the bigger the audio-visual difference the higher the ABR activity of right ear in both areas of the brainstem. All these findings need to be further explored before we know for sure but a possible explanation for the male associations is perhaps related to difference scores where auditory ability outperforms visual ability in the male group.

The gender differences found in our studies are based on group level, it does not exclude the fact that some ASD males and females can show a sensory processing profile that is more in line with the opposite gender (Werling & Geschwind, 2013; Werling, 2016). Prenatal testosterone levels have been associated with language lateralization in 6-year-old children, showing a higher level of testosterone to be associated with more lateralized language processing whereas lower levels were associated with bilateral processing in both genders (Lust et al., 2010). Considering homosexuality is much higher in subjects with ASD (George & Stokes, 2018a) compared to in TD it is reasonable to believe an extreme male brain in females as well as an extreme female brain in males will be related to homosexual preferences. It is therefore also fair to suggest homosexual males might be just as discriminated in ASD assessment as are females which is also supported in a study showing a higher percentage of homosexual preferences in ASD females compared to ASD males (George & Stokes, 2018b), implying males are being discriminated when showing more feminine ASD profiles.

DSM-5 Autism Diagnostic Criteria

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

1-Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

2-Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.

3-Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

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

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

1-Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

2-Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).

3-Highly restricted, fixated interests that are abnormal in intensity or focus (e.g, strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).

4-Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

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

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

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

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

Figure 9. DSM-5 Autism diagnostic criteria (APA, 2013).

Clinical implications

The knowledge that female ASD is considered difficult to assess, leaving females vulnerable to developing severe anxiety related disorders, makes the findings of our research highly important. The gender specific differences seen in audio-visual processing relating to ASD deserves attention, especially from those clinicians' working with assessment of ASD.

When faced with patient who seem to be social adequate although exhausted in social settings, pulling away from social settings, perhaps sleeping every day after school or having other kind of anxiety-related disorders, it must ring a bell. It should be the signal that makes us suspect difficulties in social flexibility.

The ASD assessment instruments mostly used today (ADOS, ADI) must be used with care. Clinicians must start questioning the assessment tools of today, are they able to detect autistic traits in those also showing a feminine ASD profile?

In the best of worlds, the ASD criteria in DSM-5 would be rewritten to include more concrete functioning rather than just including behaviours indicating ASD difficulties. However, if that is not happening at least they should be rewritten to be more adapted for female ASD. As of today, criteria 1 and 2 under category A, (figure 2.) is difficult to meet for someone who uses camouflaging strategies as a routine.

Until that is happening, clinicians need to be creative when using the DSM-5 criteria assessing female ASD. They cannot rely on clinical observations and parental assessments of social abilities, they need to put themselves in the patient's situation figuring out what is actually dysfunctional in their patient's seemingly perfect social behaviour? Why is it not working for them?

When asking questions about their patients social functioning they must make sure to cover different aspects of social settings and not be satisfied with an answer indicating that a patient is able to have a best friend, or that a patient do not argue with classmates. Rather clinicians need to focus on social settings requiring a bit more from the patient, such as a new social setting, making new friends, keeping friendships, being able to flexibly participate in a group work in school, stand up for their own rights in school and so on.

Being able to diagnose female ASD at an earlier stage in life than is done today will provide the patients and their caregivers with a better understanding of the problem, giving them the correct tools for providing support and therefore also increase the probability of them developing psychologically in a better direction than before.

Knowing that females more so than males turn their mental illness toward themselves a neuropsychiatric diagnosis very likely would prevent the developing of a low self-esteem and reduce the number of anxiety related diagnosis given to young females today.

Strengths and limitations

The strength of our study lies within the global perspective used. Today it is very common to keep research within one or two fields of subjects which of course has its advantages by making it easier to control. However sometimes we need to take a wider perspective to understand a full concept. By including theories of language processing, brainstem activity and audio-visual processing as well as parental ratings of social behaviour and finding the common factor we were able to build up a proposal for an understanding of gender differences in ASD.

Another strength is related to the use of undiagnosed patients in the two last studies, including all patients being referred for an ASD assessment rather than those already diagnosed with ASD. In that way we reduced the risk of females being disqualified to participate due to not receiving an ASD diagnosis. Still, since we used patients referred for an ASD assessment it means someone previously have made an ASD screening using biased ratings which of course must have screened out some females incorrectly.

A third strength is related to the relatively even number of males and females used in all the studies included in the thesis, enabling a more equal analysis.

There are also some limitations, one being the power of the study, due to the low number of subjects participating in the studies. While the number of recruited subjects were quite high, the number of subjects finally included were far lower. The testing procedures used in the studies required endurance and patience which was quite difficult for some of the subjects, resulting in dropouts as well as invalid test-results. It cannot be excluded that these patients represent a specific kind of functioning that possibly caused our results to be skewed.

Another limitation in this study is the lack of control group in study III and IV. The biggest reason for not using a control group was the complexity of testing so many children. We reasoned that we were mostly interested in gender differences between ASD patients and even if a control group could have added information about the severity of processing difficulties in ASD females it is such a big question that it deserves a study by itself.

Further, the use of some verbal measure might have been interesting to gain a better understanding of how verbal ability is related to ASD, on the other hand, adding another perspective might also have made the analysis much more complicated and therefor better analysed separately.

Future directions

If we want men and women to be equally cared for in society, we must pay greater attention to gender differences, not only when they are obviously present in the aspect of wage and work hierarchy, but also in areas denounced by some professionals to be a true reflection of reality such as the gender differences in neuropsychiatric diagnoses.

Since the field of psychiatric health is highly influenced by social factors such as the developmental stage of society as well as the specific believe system of a certain society there is a high probability of researchers being too entangled in the system that they fail to detect the discriminative thought patterns supporting their believes.

This means we need to take a more global perspective of gender differences in ASD and give ASD female the same research resources as male ASD has been given during the past 70 years. We need to stop using the male brain as the norm.

Does that mean the male predominance in ASD is wrong? Not necessarily. Future research needs to find that out in a fair way, starting from scratch rather than using previous research from males directing focus. It is possible that a female kind of ASD should be called something completely different, also requiring a different kind of treatment. But we will not know until such research are made.

There is also a need for future research to go further into the investigation of gender differences in sensory processing related to social functioning. Since our findings show different aspects of auditory and visual ability have different functions in social processing, a deeper analysis of audio-visual sensory processing might be of aid in defining sub-categories of ASD. Perhaps categories that should be renamed to something else, those that some means are being over diagnosed.

If an enhanced auditory or visual ability is causing processing difficulties it would also be interesting to investigate whether children can be trained to be more attentive to certain kind of information and if so, can be aided in social communication.

We also need to investigate real social settings of different complexity levels to see whether associations to audio-visual processing still can be made. We need to clarify what constitutes a complex social setting compared to a less complex social setting. In our study we make the same division as is made in Sensory Integration Theory, differentiating between unisensory and multisensory tasks. However, we must consider the possibility that there might be other aspects of a social situation adding to the complexity level, for example the subjects' own emotions, which is also relevant to investigate in future research.

A final need for future research is to get a better understanding of ASD males and females showing sensory processing that is more in line with the opposite gender making sure we are not missing out on any people in need of help.

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tack för allt vad du beskär.
Tack för tiderna som farit,
tack för stund som inne är.
Tack för redan glömda tårar,
tack för friden i mitt bröst.
Tack för vad du uppenbarat,
tack för vad jag ej förstår.
Tack för bön som du besvarat,
tack för vad jag inte får.
Tack för livets hemligheter,
tack för hjälp i nödens stund.
Tack för prövningar och strider,
tack för hopp som uppfyllts väl.
Tack för dagen som framskrider,
tack för hopp som slagit fel.
Tack för rosorna vid vägen,
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tack för himmelsk salighet.
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August Ludvig Storm, 1891

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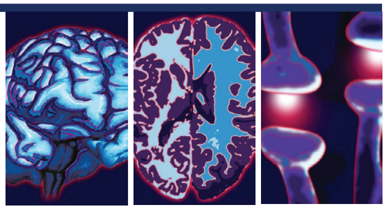
Paper I



Gender specific differences in auditory brain stem response in young patients with ADHD

Emma Claesdotter-Hybbinette*, Matti Cervin, Sofia Åkerlund, Maria Råstam, Magnus Lindvall

Abstract

Objective: The auditory brainstem response (ABR) is often affected in neurodevelopmental disorders. The aim of this study was to investigate gender differences in ABR between young females and young males with ADHD, compared to control subjects.

Method: We studied 63 females with ADHD (mean 13.8years), 26 female controls (mean 13.8years), 48 males with ADHD (mean 13.1 years), and 20 male controls (mean 12.8years). All patients were diagnosed according to the DSM-IV. An ABR consists of seven positive peaks (wave I–VII) 10 ms following a stimulus, recorded by electrodes on the mastoid processes of each ear and on the forehead.

Results: When analysing the ABRs of the female ADHD patients 3 traits were identified; TR6, TR14 and TR15. The higher value in TR6 (p=0.000064) is explained as an aberrant thalamus profile. In TR14 (p=0.00059) presence of 3500 Hz-frequencies in the region from superior olivary complex to thalamus. TR15 (p=0.00035) represents more aberrant curve profiles in the region of the lateral leminiscus. In the ABR of the male patients we found we 3 traits; TR4, TR5 and TR14. TR 4 (p=0.00105) is a lower correlation to a norm curve in inferior colliculus and thalamic area. TR5 (p=0.00027) identifies irregular curve profiles representing the nucleus cochlea. TR14 (p=0.00013) presence of 3500 Hz-frequencies in the region from superior olivary complex to thalamus.

Conclusion: Young females with ADHD exhibited a significantly different ABR in a region between cochlear nucleus and superior olivary complex and in the thalamic region. In the male ADHD group ABR aberrancies were found in the midbrain region and in the more peripheral part; nucleus cocleus. The only trait that was significantly different between the ADHD group and the control subjects, for both male and females, was TR14. These data indicate both gender specific aberrations in the ABR in ADHD subjects as well as specific differences between ADHD subjects and normal controls.

Keywords: ABR; ADHD; Child and adolescent psychiatry; Diagnostics; Gender; Young patients

Introduction

Attention deficit hyperactivity disorder (ADHD) has been recognized as one of the most common neurodevelopmental disorders in childhood [1]. It is a heterogeneous condition with persistent symptoms of hyperactivity, inattention and impulsiveness which impair functioning in multiple settings [2, 3]. ADHD is a highly heritable disorder and twin studies have shown a heritability rate of approximately 80 % [4]. The estimated worldwide prevalence of ADHD in children is around 5% [5]. The symptoms frequently persist into adulthood and are associated with functional limitations as well as psychiatric and somatic morbidity. ADHD is a considerable burden

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to the affected individual and to society [1, 6]. ADHD is affecting both sexes, with a male to female ratio approaching 1:1 [7] contrasting to previous studies showing a gender ratio (girl:boy) ranging from 1:3 to 1:16 [8]. Over the years research has been trying to find differences in symptoms to explain the gender differences in prevalence. It has been proposed that girls with ADHD may be more likely to have the inattentive type of ADHD and may suffer more from internalizing symptoms and inattention while, boys on the other hand have more hyperactive and aggressive symptoms [9-12].

An ADHD diagnosis should be based on neurodevelopmental and clinical history [1, 2]. In addition, neuropsychological testing and rating scales are often used as a supplement. There is a great need for objective measures to improve the diagnostic accurancy and to guide clinical interventions. There are recent studies that have focused on trying to find objective neuropsychological testing methods for the diagnostics of ADHD [13-17].

Auditory brainstem response (ABR) was first described in 1971 [18] and refers to the particular kind of event related potential (ERP) where the stimulus is sound, in this case, in the shape of distinct clicks at given intervals. In ABR, electrodes are placed and calibrated to study the processes that occur in the basic auditory pathways, situated in the brainstem [19] **(Figure 1)**. ABR reflects the subcortical neuronal electrical activity in the auditory pathway within 10 milliseconds (ms) after brief auditory stimuli.

The ABR wave-pattern provides information in terms of the latencies and amplitudes of these peaks. Analysis of the ABR wave patterns normally comprises measurements of inter-peak latencies as well as ratios of peak amplitudes [20, 21]. ABR is an objective method that does not require active patient participation and is considered an objective approach to investigate brainstem function. In addition, complex stimuli may reveal aberrations, which may not be assessed by standard audiological ABR procedures. Complex click stimuli (e.g. forward masking) were therefore used in the present study to increase the possibility of detecting variances in comparison with matched healthy children. The importance of using complex stimuli is also stated for autism spectrum disorder, ASD [22].

Several studies have shown that ABR is often affected in ASD [23-28] adults with ADHD [29, 30], schizophrenia [28, 31, 32] and bipolar disorders [33]. Possible ABR abnormalities in young patients with ADHD need more studies [34, 35].

We have previously presented a study on ABR in young females with ADHD where we found ABR traits specific for young females with ADHD compared to control subjects [14]. The aim of the present study is to investigate possible gender differences in ABR between young females and young males with ADHD, compared to control subjects.

Methods

■ Subjects

This study included a total of 63 females with ADHD (age mean 13.8 years, SD 2.5), 26 female control subjects (age mean 13.8 years, SD 2.7), 48 young males with ADHD (age mean 13.1 years, SD 1.8), and 20 male control subjects (age mean 12.8 years, SD 1.7). Patients and control subjects were in the age range of 7-17 years. The age difference between boys and girls were not statistically significant. All patients were instructed to not take any medication the day of the testing.

All patients were recruited from the Child and Adolescent Psychiatry outpatient department of Eslöv and Lund, two cities in the south of Sweden. All patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). The diagnoses were confirmed by the same senior psychiatrist. The control groups were recruited from schools in Lund and recruited subjects had no previous record of any psychiatric disorder. Patients with other concurrent psychiatric diagnoses were excluded to avoid comorbidity. Subjects with hearing impairment were excluded from the study.

Written informed consent was obtained from all the subjects and their parents/guardians. The study was approved by the regional ethics committee at the Lund University (Dnr: 2010-120).

■ Apparatus and stimulus

The evoked potentials were recorded using auditory brainstem response, ABR. The ABR consists of a sequence of seven positive peaks (wave I–VII) that normally occur within 10 ms following the onset of a stimulus recorded by surface electrodes on the mastoid processes of each ear and on the forehead. Waves I and II are produced by the auditory nerve, whereas the subsequent peaks are due to the combined electrical activity of nuclei at gradually higher levels of the ascending auditory pathway in the brainstem. Waves III and IV are believed to be generated in the cochlear nucleus and superior olivary complex (SOC), respectively, whereas wave V is thought to represent activity at the levels of lateral lemniscuses and inferior colliculus [36, 37]. The measuring system used was SensoDetect® BERA (Brainstem Evoked Response Audiometry) A1000. The stimuli were presented via TDH-50P headphones with Model 51 cushions (Telephonics, Farmingdale, New York, USA). Presentations were made binaurally with the stimuli in phase over headphones.

In total, 4 sound stimuli were used. The sound stimuli included square-shaped click pulses, high frequency varied pulses, forward masking and backward masking stimuli. The click pulses were repeated until a total of 1024 accepted evoked potentials had been collected for each sound stimulus. Thus, each ABR waveform represents an average of the responses to 1024 stimulus presentations. TTL (transistor-transistor logic) trigger pulses coordinated the sweeps with the auditory stimuli. A TTL pulse is the signal which tells the ABR system to measure. With a correctly timed TTL pulse, all ABR representations will be synchronized. Aberrant activity, such as extremely high amplitudes due to extraordinary movements was rejected. Sound levels were calibrated using a Bruel and Kjaer sound level meter and Type 4152 artificial ear (Bruel & Kjaer S & V Measurement, Naerum, Denmark). The acoustic output from the earphones corresponded to SPL: 80 dB HL or 109 peSPL (peak equivalence). A square-shaped click pulse was used as probe in the auditory masking stimuli [32]. The sound stimuli included square-shaped click pulses (0.136 ms duration, including 0.023 ms rise and fall; 192 ms interstimulus interval), high pass filtered pulses (a Butterworth high-pass filtered square shaped click pulse with a cutoff of 3000Hz), forward masking (12.3 ms gap from masker to click pulse) and backward masking (12.3 ms from click pulse to the masker) stimuli as previously described. A 1500-Hz Butterworth low-pass filtered white noise, with 15 ms duration (including 0.4 ms rise and fall times) was used as masker for both forward and backward masking stimuli. All stimuli were constructed using MATLAB Signal Processing Toolbox (The MathWorks, Inc., Natick, Massachusetts, USA) and stored in a flash memory in the SensoDetect®BERA system.

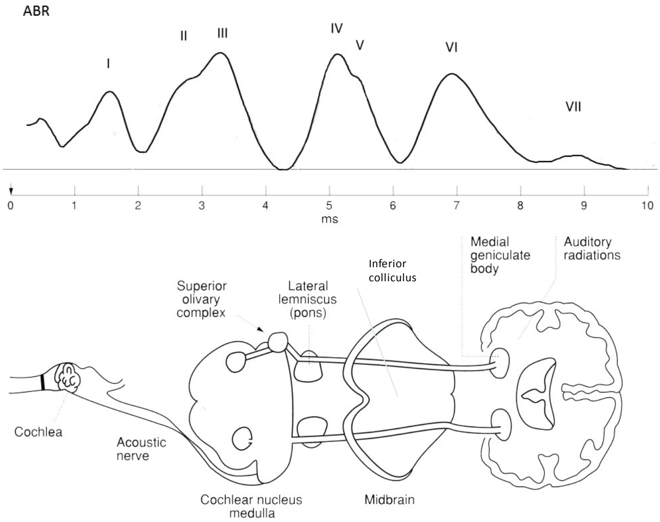

Figure 1: Illustration of wave pattern of the standard ABR and corresponding anatomical structures within the first 10 ms after stimulation.

■ Procedure

All tests were performed in a soundproof slightly darkened room. Participants were comfortably seated in an armchair with their legs on a small footstool to assure a resting position. Five surface electrodes were applied: two reference electrodes on the mastoid bone behind the left and right ear, respectively, and two active electrodes and one ground electrode placed on the forehead. To make sure a good transmission the sites were washed with disinfectant and abrasive paste was used to stick the electrodes. Absolute impedances and inter electrode impedances were measured before and after the experiments to verify that electrode contact was maintained (below 5000 Ω). Earphones were fitted to cover both ears. The subjects were instructed to turn off their cellular phones and relax with their eyes closed and were permitted to fall asleep. The test requires no active participation other than being subjected to sound stimulation. Before the test situation written information had been sent home to the subject's parents or guardians as well as to the subject. On site of the test session, subjects were again verbally informed of the nature of the experiments. The click sounds were presented to the subjects beforehand to make them acquainted with stimuli. The subjects were tested one at a time and the duration of the testing procedure was approximately 30 minutes.

Data analysis

Prior to further analysis the audiogram was correlated to ABR data, from a group of healthy and normal hearing individuals, derived from a normative database to depict general audiogram quality. This is a standard operating procedure of this method in order to grant audiogram quality. A low correlation led to exclusion of the patient due to risk of erroneous measurement (e.g. loose electrodes or head phones). The Sensodetect system rejected all evoked potentials being of abnormally high voltage (i.e. aberrant activity), typically trigged by patient movement, coughing or tension. Collected evoked potentials for each sound stimulus from each individual was imported to Microsoft Excel (Microsoft Corp, Redmond, WA, USA) and analyzed using SensoDetect® BAS. Frequencies, latencies, amplitudes and correlation coefficients to a normed ABR curve, respectively, were investigated. Amplitudes were measured from the positive peak of a given wave to the bottom of the previous wave. Since the amplitude values obtained were not read in µV, microvolt outputs were indexed (i.e., normalized by adding constants to avoid negative values, then all amplitude values were divided by the highest observed amplitude). Thus, relative linear amplitudes are used in this study. In order to identify specific pathologies along the auditory pathway, correlation values to a normative ABR curve were calculated for different sections of the ABR. Values ranging from -1 to +1 were obtained using Spearman rho. High, positive values indicate similarity (e.g. no pathology) values around zero indicate no relation, and low values close to -1 indicate inverse relationship. After the r-values for all sections of the total ABR curve (0-10 ms) had been computed, the results were ranked. Thus, the test subject's most aberrant ABR region, when compared with the norm curve, depicts a high number, and vice versa **(Figure 2)**.

The same principle was used in order to identify occurrence of high frequencies in the ABR curves of the test subjects. A mathematically constructed artificial ABR (a sine wave with the frequency 3500Hz) was used as norm. Norm population median values for every data point in the ABR were used to construct the artificial ABR. Every patient's ABR curve was correlated to this artificial ABR. The correlation value was calculated for each possible starting point in the ABR and the r (max) was used to indicate occurrence of the specific frequency. As the ambition with this operation was to see whether the test person had an occurrence of the frequency or not, the outcomes were ranked from 1 for all values between r=-1 to r=+0.1 and thereafter 2 for r=0.1 to r=0.2 and so forth, with 10 for r=0.9 to r=1, indicating a perfect match to the normed ABR.

Aberrancies in the ABR were denoted traits (TR). The ABR trait numbering emanated from the fact that a higher number of potentially interesting traits were originally investigated. However, not all of these qualified in terms of test-retest prediction values. Thus, the traits presented in this study shows gaps in numbering.

For measuring differences between young males with ADHD compared to age matched control group and young females with ADHD compared to age matched control group, the nonparametric test Mann–Whitney U was used.

Results

When analysing the ABRs of the female ADHD patients we found aberrancies in three wave areas these included wave VI (i.e. denoted TR6: Aberrant thalamus profile ranging from 6.0-7.0ms), wave IV-VI (i.e. denoted TR14: Presence of 3500 Hz-frequencies in the region 4.0-7.5ms ranging from SOC to thalamus) and waves III-IV (i.e. denoted TR15: Aberrant profile in the region 3.3-4.3ms ranging from cochlear nuclei to SOC). In the ABR of the male patients we found aberrancies in three areas; wave IV-VI (i.e denoted TR4: Low correlation to norm curve in the region 3.5-7.5 ms ranging from inferior colliculus to thalamus and i.e denoted TR14: Presence of 3500 Hz-frequencies in the region 4.0-7.5ms ranging from SOC to thalamus) and wave III (i.e denoted TR5: Low backward masking correlation to norm curve in the region 2.5-4 ms indicating a peripheral function deficit in the early auditory pathway.

Comparing the ABR of 63 girls with ADHD to 26 age correlated control subjects three traits were identified, denoted TR6, TR14 and TR15 **(Figure 3a-e)**.

The higher value in TR6, specific for the ADHD females (p=0.000064), as compared with the female controls, is explained by more aberrant curve profiles in the thalamic region at 6.0-7.0 ms. In TR14, a higher presence of 3500 Hz-frequencies in the midbrain region at 4.0-7.5 ms (ranging from SOC to thalamus), was observed for the ADHD group as compared with controls (p=0.00059). The higher value in TR15, specific for the ADHD females at 3.3-4.3 ms (p=0.00035), as compared with the female controls, is explained by more aberrant curve profiles in the region of the lateral leminiscus **(Table 1)**.

When looking at the ABR from 48 young males with ADHD and comparing them to their 20 age correlated control subjects we found three traits; TR4, TR5 and TR14 **(Figure 3a-e)**. TR4 is described as a lower correlation to a norm curve in inferior colliculus and thalamic area at 3.5-7.5 ms (p=0.00105). TR 5 identifies irregular curve profiles within peak III, ranging from at 2.5-4.0 ms, representing the cochlear nucleus (p=0.00027). TR14 is described as a higher presence of 3500 Hz-frequencies in the region at 4.0-7.5ms (ranging from SOC to thalamus), was observed for the ADHD male group as compared with controls (p=0.00013).

The only trait that was significantly different between the ADHD group and the control subjects, for both male and females, was TR14 **(Table 1)**.

Discussion

Due to the major rise in reported ADHD prevalence during the past decades [38], the public debate concerning the need for more objective ADHD diagnosis has been vivid [19, 39, 40]. We have recently published an article with results showing specific ABR differences in the young female group with ADHD compared to healthy controls [14].

The aim of this study was to identify differences in brainstem responses, ABR, in young patients diagnosed with ADHD compared to a control group. To our knowledge this is the first ABR study done on young patients (7-18 years) with ADHD trying to find gender specific ABR differences. In this study we compared the young females with ADHD both to a young female control group but also to young males with ADHD and their male control group. In the group of young males with ADHD we found three traits specific for ADHD compared to healthy controls; TR4, TR5 and TR14. In the young female group we found three traits not present in the healthy controls; TR6, TR14 and TR15. One trait co-occurred in both gender groups; TR14.

Looking at the ABR findings from a biological view, two of the female traits (TR6 and TR14) and one of the male traits (TR4) were found in the thalamic area or in the near proximity. This

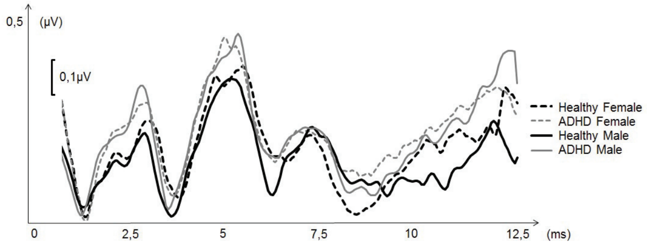

Figure 2: Median Curves of all Healthy females, ADHD females, Healthy males and ADHD females. Sound 1, left ears.

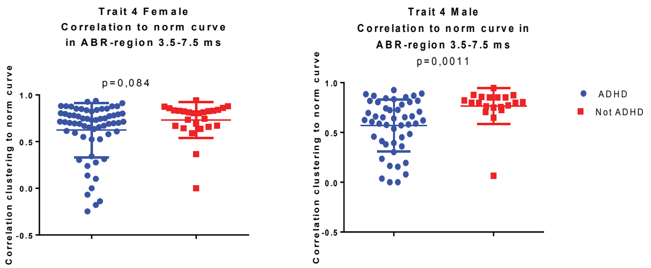

Figure 3a: Trait 4, 5, 6, 14 and 15 and their p values. Mean and Standard Deviation is indicated in the figures.

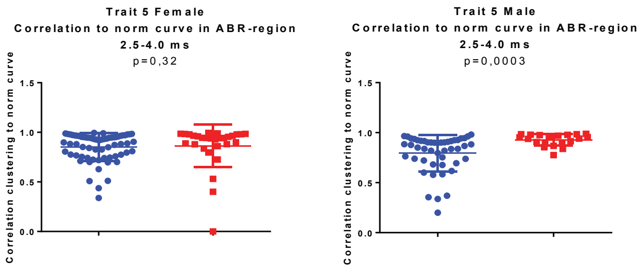

Figure 3b: Trait 4, 5, 6, 14 and 15 and their p values. Mean and Standard Deviation is indicated in the figures.

supports other studies that have shown structural and functional abnormalities in the deep parts of the brain of young patients with ADHD [41-43]. It has been described earlier that thalamic dysfunction leads to symptoms of hyperactivity, inattention and dysregulation of sleep and wakefulness all of which are symptoms of ADHD [44, 45]. The only trait that is not in the thalamic area is TR5 representing the cochlear nucleus, a more peripheral part of the brain. The cochlear

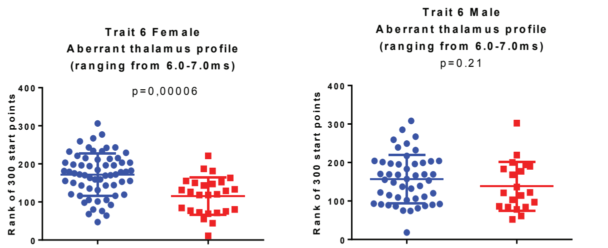

Figure 3c: Trait 4, 5, 6, 14 and 15 and their p values. Mean and Standard Deviation is indicated in the figures.

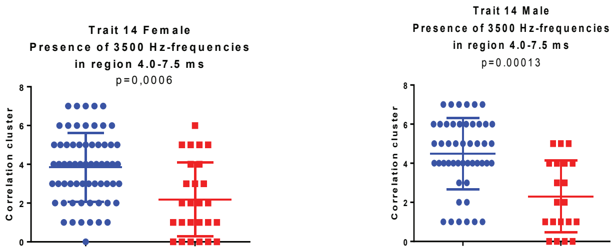

Figure 3d: Trait 4, 5, 6, 14 and 15 and their p values. Mean and Standard Deviation is indicated in the figures.

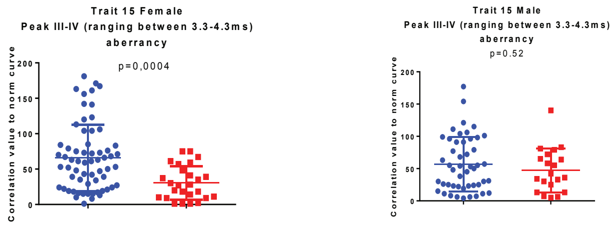

Figure 3e: Trait 4, 5, 6, 14 and 15 and their p values. Mean and Standard Deviation is indicated in the figures.

nucleus is where parts of the auditory temporal processing occurs. It is an important component in sound detection in noisy environments and in selective auditory attention [46], deficits in these aspects of sound processing are frequent symptoms in ADHD.

TR15, only present in the young female ADHD group is located in lateral leminiscus; pons area. Previous studies regarding brain activity have shown higher resting-state activity in young patients with ADHD compared to controls in this area [47].

TR14 which is present in both gender groups is located in the midbrain ranging from SOC that is the first major site of convergence of auditory information from both ears important for localization of sound to thalamus. In Thalamus, transformation of soundsource acoustics (frequency, time and amplitude) into perceptual features (i.e. acoustic features) begins to form [48].

It is possible that these different traits found represent different subgroups of ADHD. Further research areas would be to link the person with a specific ABR trait to its reported symptoms. For example do patients with prominent TR5 report more ADHD symptoms involving hearing and sound detection?

Early studies have shown age and gender differences in ABR [49], whereas there are other more modern studies that demonstrate that the aging process is essentially a peripheral phenomenon which does not involve the central part of the acoustic pathways [50-52]. Neurodevelopmental differences may, at least partially, explain why girls are diagnosed so much later than boys [53]. Since our patients are age matched we believe that we have fully controlled for this factor in our study.

It is clear from our material that ABR in young patients with ADHD is gender specific. Only one trait namely TR14 overlapped; the others are gender specific.

Our findings support the fact that ADHD needs to be looked upon as a diagnosis composed of subgroups [9-12, 54, 55] a view that DSM5 and its subgrouping of ADHD supports. Our study shows that ABR has the potential to be the objective diagnostic instrument child and adolescent psychiatry has been looking for. ABR is a non-invasive method that is easily administered to patients; it is not dependent on language skills or cultural background [19]. Our findings suggest that ABR could be used as a complement and a support when diagnosing young patients with ADHD. By means of our ABR findings we have got a deeper understanding of the biological nature of ADHD and its subgroups. The present study suggests that the ABR method might provide useful biomarkers to support the clinical diagnoses of ADHD.

Many reports show possible regulation of locus coeruleus activity by metylphenidates and by atomoxetin [56-59]. Future research areas of interest would be to investigate whether medication would decrease the ABR differences

Tabel 1: ABR results for young patients with ADHD compared to controls. Mann-Whitney U test was used. Female ADHD group (N=63), female controls (N=26), male ADHD group (N=48) and male controls (N=20).

Trait	Female ADHD mean (S.D.)	Female controls mean (S.D.)	Female p-value	Male ADHD group mean (S.D.)	Male controls mean (S.D.)	Male p-value
	median	median				
TR4	0.62 (0.29); 071	0.73 (0.19); 0,81	0.084	0.57(0.26); 0,62	0.77 (0,18); 0.80	0.00105
TR5	0.85 (0.14); 0.90	0.85 (0.22); 0.94	0.321	0.80 (0.18); 0.87	0.93 (0,06); 0.95	0.00027
TR6	172 (56); 174	116 (49); 123	0.000064	157 (63); 156	139 (64); 122	0.208
TR14	3.8 (1.8); 4	2.2 (1.9); 2	0.00059	4.5 (1.8); 5	2.3 (1.8); 2	0.00013
TR15	66 (47); 61	31 (24); 27	0.00035	57 (42); 52	47 (34); 39	0.518

between the group of children with ADHD and healthy controls, and if it is possible to predict choice of medical treatment according to trait match. There is also a need for longitudinal studies with child and adolescent control subjects with other psychiatric diagnoses to further substantiate our findings. We have therefor recently initiated a study of ABR and ASD in young patients. Another study regarding ABR and OCD has started in the autumn of 2015 at the University of Lund. Findings from these studies will be of great interest to investigate possible overlap with ADHD traits and the possible role of comorbidity.

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Paper II

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Abnormal auditory brainstem response in the pons region in youth with autism

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ABSTRACT

Purpose of the article: Autism spectrum disorder (ASD) is an impairing neurodevelopmental disorder with an unknown etiology. The present study aims to investigate if the auditory brainstem response (ABR) to complex stimuli in children and adolescents diagnosed with ASD can be a possible objective biomarker in autism.
Materials and methods: The ABR of 39 youth with ASD (7–18 years) were compared to the ABR of 34 typically developed youth (TD). The ABR consists of seven positive peaks (waves I–VII) that occur during 10 Ms following a sound stimulus.
Results: The amplitude of wave III (region 2.5–4.0 Ms) was higher in the ASD group compared to the TD group. The TD males showed a significant lower degree of correlation, between left and right ear compared to the ASD groups and the TD females.
Conclusions: Altered auditory processing was evident in the pons region of the brainstem for the ASD group when compared to the TD group. Implications of the findings are discussed in relation to the neurobiology and assessment of autism spectrum disorder in youth.

1. Background

Autism spectrum disorder (ASD) is an impairing and heterogeneous neurodevelopmental disorder with an early onset (Volkmar, Reichow, & Mcpartland, 2014). ASD is characterized by social impairments, communication difficulties, altered sensory processing, and repetitive and restricted behaviours (American Psychiatric Association, 2013) and affects 1%–3% of the population (Baron-Cohen, Scott, & Allison, 2009; Kim, Leventhal, & Koh, 2011; Baxter, Brugha, & Erskine, 2014).

Individuals with ASD show abnormal cortex activation when processing acoustic stimuli (Blasi, Lloyd-Fox, & Sethna, 2015; Hames, Murphy, & Rajmohan, 2016) and it is proposed that subcortical structures might be involved in this process (Orekhova, Tsetlin, & Butorin, 2012). In line with this, abnormal brainstem processing responses to auditory stimuli has been found in adults with ASD (Källstrand, Olsson, & Nehlstedt, 2010). Further, it has been suggested that brainstem abnormalities may be partly responsible for the difficulties with language, cognitive and social development in children with ASD (Baranek, David, & Poe, 2006). One study showed that the brainstem in children with ASD is smaller and has a slower growth rate than in TD children (Jou, Frazier, & Keshavan, 2013). Brainstem functioning is also strongly related to the development of behaviour and emotion regulation in infants. Hence, further exploration of possible alterations in subcortical and brainstem systems in individuals with ASD is warranted (Geva & Feldman, 2008).

Auditory brainstem response (ABR) was first described by Jewett and Williston in 1971 (Jewett & Williston, 1971). The ABR method measures the subcortical neuronal electrical activity in the auditory pathways 10 ms (Ms) after sound stimuli. The seven positive waves (wave I–VII) of a ABR each represent a different part of the auditory pathway (Fig. 1). The ABR wave-pattern provides information in terms of the latency (speed of transmission), amplitudes of the peaks (number of neurons firing), inter-peak latency (the time between peaks) and interaural correlation (correlation between left and right ear) (Musiek & Lee, 1995). During the 1980s and early 1990s several studies were published with a focus on ABR in populations with ASD (Gillberg, Rosenhall, & Johansson, 1983; Klin, 1993; Rosenblum, Arick, & Krug, 1980; Tanguay, 1982). Subsequent studies have confirmed that ABR is often affected in children with ASD (Cohen, Gardner, & Karmel, 2013; Dabbous, 2012; Miron, Ari-Eve, & Gabis, 2016; Rosenhall, Nordin, &

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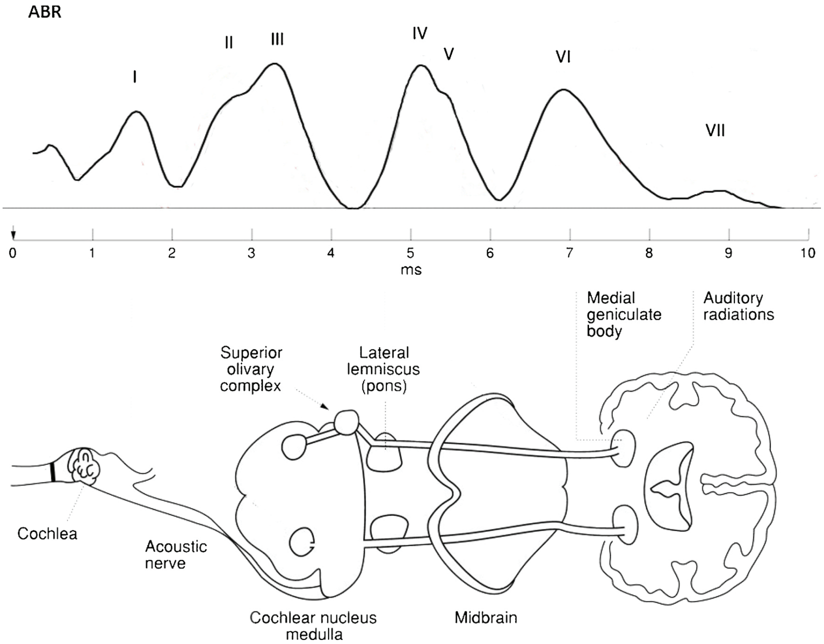

Fig. 1. Illustration of wave pattern of the standard ABR and corresponding anatomical structures within the first 10 ms after stimulation.

Brantberg, 2004). ABR has also been studied in other diagnostic groups such as ADHD (Baghdassarian, Markhed, & Lindström, 2017; Johnston, Mwangi, & Matthews, 2014), schizophrenia (Källstrand, Nehlstedt, & Sköld, 2012; Nielzén, Olsson, & Källstrand, 2008) and bipolar disorders (Sköld, Källstrand, & Nehlstedt, 2014) with evidence for both intact and altered auditory processing in populations with mental disorders (Baghdassarian et al., 2017; Manouilenko, Humble, & Georgieva, 2017).

The aim of the present study is to investigate brainstem response to complex stimuli in children with ASD. We will explore possible deviations in amplitude and interaural correlation.

2. Method

2.1. Subjects

The study included 39 children with ASD and 34 TD children. Twenty-one females with ASD (mean age 12.71 years, SD 3.36) and 18 males with ASD (mean age 11.50 years, SD 3.09). The TD group consisted of 24 females (mean age 13.12 years, SD 3.47) and 23 males (mean age 13.18 years, SD 3.22). The children with ASD were assessed in clinical settings by a senior psychologist using the ADOS (Lord, Rutter, DiLavore, & Rishi, 2001) and ADI-R (Rutter, Le Couteur, & Lord, 2003) (mean females 27.83, SD 16.34; mean males 33.00, SD 14.77) (Table 1). ADOS and ADI are diagnostic tools considered the “gold standard” in ASD diagnostics (Falkmer et al., 2013). To participate in the study, the ASD children were not allowed to have had any previous contact with the ear, nose and throat clinic to exclude hearing impairment. All ASD patients had an IQ of 70 or above, as measured by either the Wechsler Intelligence Scale for Children–Fourth edition (WISC-IV) (Lord et al., 2001) or the Wechsler Adult Intelligence Scale–Fourth edition (WAIS-IV) (Rutter et al., 2003). The ASD diagnoses were confirmed by a senior psychiatrist. To exclude TD participants with mental diagnoses or hearing impairment, the control group were not allowed to have any previous contact with mental health or ENT services. No participant in the TD group had a known intellectual disability or other NDD. Written informed consent was obtained from all participants and their parents/guardians. The study was approved by the regional ethics committee at the Lund University (Dnr: 2010/210, Dnr: 2015/11).

Table 1
Age distribution among the ASD patients and the TD. Age in years.

Sex	N	Age(Mean)	SD
Female (ASD)	21	12.71	3.36
Female (TD)	17	13.12	3.47
Male(ASD)	18	11.50	3.09
Male(TD)	17	13.18	3.22

2.2. Apparatus and stimuli

The ABR was measured with SensoDetect BERA (Brainstem Evoked Response Audiometry) A1000. The sound stimuli were presented via TDH-50 P headphones with Model 51 cushions (Telephonics, Farmingdale, New York, USA). Presentations were made binaurally with the stimuli in phase over headphones. The click pulses were repeated until a total of 1024 accepted evoked potentials had been collected for each sound stimulus. Transistor-transistor logic (TTL) trigger pulses coordinated the sweeps with the auditory stimuli. With a correctly timed TTL pulse, all ABR representations will be synchronized. Sound levels were calibrated using a Bruel & Kjaer 2203 sound level meter and Type 4152 artificial ear (Bruel & Kjaer S&VMeasurement,

Table 2
Deviation (DV) 1 and 2.ABR results for young patients with ASD compared to TD.

Sex	DV	Diagnos/TD	N	Mean	Median	SD	P-value
Female	DV 1	ASD	21	0.56	0.57	0.09	0.0002
Female	DV 1	TD	17	0.42	0.43	0.12	
Male	DV 1	ASD	18	0.52	0.53	0.08	0.02
Male	DV 1	TD	17	0.45	0.47	0.09	
Female	DV 2	ASD	21	0.67	0.63	0.17	0.15
Female	DV 2	TD	17	0.75	0.8	0.17	
Male	DV 2	ASD	18	0.73	0.77	0.19	0.006
Male	DV 2	TD	17	0.52	0.61	0.26	

DV 1 showing wave amplitude. DV 2 showing interaural correlation. Mann-Whitney U test was used.

Naerum, Denmark). The acoustic output from the earphones corresponded to SPL: 80 dB HL or 109 peSPL (peak equivalence). The collected evoked potentials for each sound stimulus from each ear of each individual was imported to Microsoft Excel (Microsoft Corp, Redmond, WA, USA) and analyzed using SensoDetect® BAS. Theparticipants were presented either a forward masked sound (FM) or a standard sound (Table 2) during a 30 min period of time. The sound stimuli were square-shaped click pulses (0.136 Ms duration, including 0.023 MS rise and fall; 192 Ms interstimulus interval. The forward masked sound had a 12.3 Ms gap from masker to click pulse. A 1500-Hz Butterworth low-pass filtered white noise, with 15 Ms duration (including 0.4 Ms rise and fall times) was used as masker for both forward and backward masking stimuli. All stimuli were constructed using MATLAB Signal Processing Toolbox (The MathWorks, Inc., Natick, Massachusetts, USA) and stored in a flash memory in the SensoDetect® BERA system.

2.3. Procedure

All ABR tests were performed and administered by trained staff. Participants were seated with a neck brace to make sure the neck was fixed and relaxed during testing. Two reference electrodes were placed on the mastoid bone behind the left and right ear, respectively, with two active electrodes and one ground electrode placed on the forehead. To ensure good transmission the sites were washed with disinfectant. Abrasive paste was used to fasten the electrodes. Absolute impedances and inter-electrode impedances were measured before and after the experiments to verify that electrode contact was maintained (below 5000 Ω). Earphones were fitted to cover both ears and the subjects were instructed to turn off their mobile phones and relax with their eyes closed. The test required no active participation.

2.4. Data analysis

Prior to further analysis, the audiogram was correlated to a norm ABR. A low correlation of $r \leq 0.35$ resulted in exclusion of the recording since there is a high risk the measurement is based on erroneous measurements du to coughing or tension (Källstrand et al., 2010, 2012). Due to poor audiogram quality 9 ASD males, 10 ASD females, 6 TD males and 7 TD females were excluded from the study resulting in the remaining subjects, 18 ASD males, 21 ASD females, 17 TD males and 17 TD females.

We analyzed the ABR in two predefined windows: amplitude in time window 2.5 Ms-4.0; 2; Ms interaural correlation in time window 3.3 Ms.- 4.4 Ms. Correlations between the data collected from the left and right ear were calculated using Pearson rho in order to discriminate differences between ABR wave sections. Pearson rho results in r-values between -1 to +1 where a positive value indicates similarities and a negative value indicates an inverse relationship whereas values around zero indicate no relation at all. To identify specific alterations along the auditory pathway, correlations with a normative ABR curve were made. An aberrancy was denoted as a deviation (DV). Since the data was not normally distributed, the nonparametric test Mann–Whitney U was used.

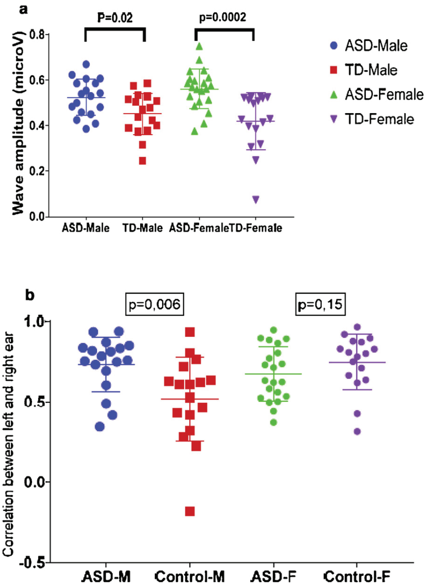

Fig. 2. (a) DV 1 and its p-value. Mean and Standard Deviation are indicated in the figure. (b) DV 2 and its p-value. Mean and Standard Deviation are indicated in the figure.

3. Results

The amplitude of wave III (region 2.5–4.0 Ms) was higher in the ASD group compared to the TD group (denoted deviation 1 (DV 1)) (Table 2) (Fig. 2a).

The TD males showed a significant lower degree of correlation, between left and right ear compared to the ASD groups and the TD females (denoted deviation 2 (DV 2) (Table 2) (Fig. 2b).

4. Discussion

The aim of this study was to explore possible altered auditory processing in the brainstem in youth with ASD. The ABR in 39 youth with ASD were compared with the ABR for 34 TD youth.

We found that the amplitude of wave III was higher in the ASD group compared to the TD (DV 1) in the FM sound. From a neuroanatomical point of view, the DV 1 corresponds to the pons region. Hence the ASD group had more neurons firing in the pons region than the TD group as a response to acoustic stimuli (Falkmer et al., 2013). The pons region is involved in the processing of sensory information from hearing, taste, facial sensation, touch and pain as well as facial expression, chewing, swallowing, and secretion. Depending on the severity of ASD, autistic children can show difficulties within all of these areas (American Psychiatric Association, 2013). Difficulties with hyper- or hypo-sensitivity to touch and pain and limited facial expression are also common in children with ASD. More severely autistic children often report difficulties with salivation, choking and chewing (Baranek et al., 2006). The simplest interpretation of more neurons firing in this specific area would be that we measured a hyper sensitivity to sound. Still it could be argued that the deviation of sound could represent a larger dysfunction of the pons area. Our finding is well in line with research showing increased pontine activity in children with ASD (Di martino, Kelly, & Grzadzinski, 2011; Sajdel-Sulkowska, Xu, & McGinnis, 2011; Suzuki, Sugihara, & Ouchi, 2013).

The TD males differed significantly from all the other groups by having a lower correlation between the left and right ear in the ABR in a neuroanatomical region corresponding to the midbrain. Interaural differences have for a long time been considered to represent brainstem pathology (Hall, 1984), although later studies show that healthy humans use *small* interaural differences to locate sound (Undurraga, Haywood, & Marquardt, 2016). However, the TD females did not exhibit this pattern of correlation. The high correlation between the auditory processing of the left and right ear in the ASD group could be related to difficulties in the processing of everyday sounds, an impairment often reported by children with ASD (Alcantara, Weisblatt, & Moore, 2004). This theory is supported by (Lepistö, Kultunen, and Sussman (2009) who concluded that children with ASD have difficulties segregating concurrent sound streams. However, this deviation (DV2) has to be confirmed in a future study.

The results in this study are based on group differences. Other obvious limitations are the small number of participants and the fact that no clinical comparisons group were included. Further, around 30% of the total number of children participating (ASD and TD) were excluded due to low quality ABR. Several of the ASD youth had complaints during testing about the sound level and having sensors attached to their foreheads. Hence the ASD youth with the most sensory processing difficulties have been excluded due to tensions and movement during testing, which might have impacted our results.

In sum, the results of this study support the notion of altered auditory brainstem processing in youth with ASD. However, the results need to be replicated and extended to further explore the potential of ABR as a possible biomarker in ASD.

Conflict of interest

None of the authors declare any conflict of interest.

Ethical statement

The study was approved by the regional ethics committee at the Lund University (Dnr: 2010/210, Dnr: 2015/11).

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An auditory processing advantage enables communication in less complex social settings: Signs of an extreme female brain in children and adolescents being assessed for Autism Spectrum Disorders

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Background: The underlying factors of the male predominance in Autism Spectrum Disorders (ASD) are largely unknown, although a female advantage in social communication has been pointed out as a potential factor. Recently, attention has been given to ASD as a sensory processing disorder, focusing on the audio-visual temporal processing paramount for the development of communication. In ASD, a deviant audio-visual processing has been noted, resulting in difficulties interpreting multisensory information. Typically Developed (TD) females have shown an enhanced language processing in unisensory situations compared to multisensory situations. We aim to find out whether such an advantage also can be seen in girls within the ASD population, and if so, is it related to social communication skills?

Method: Forty children (IQ>85), 20 females (mean age=13.90years, SD=2.34) and 20 males (mean age=12.15years, SD=2.83) triaged for an ASD assessment were recruited from a child and youth psychiatric clinic in Sweden. Using The Social Responsiveness Scale (SRS) we looked at associations with child performance on the Integrated Visual and Auditory Continuous Performance Test (IVA-2).

Results: An auditory advantage in the female group was associated with less rated problems in social communications in unisensory processing whereas in multisensory processing an auditory dominance was associated with more rated problems in Social Awareness. In the male group, a visual dominance was associated with more rated problems in Social Rigidity.

Conclusion: A female unisensory processing advantage in ASD could very well be explaining the male domination in ASD. However, the social difficulties related to multisensory processing indicate that ASD females might be struggling as hard as males in more complex settings. Implications on the assessment procedure are discussed.

KEYWORDS

ASD, "gender differences", "sensory processing", "child and adolescent psychiatry", auditory, "extreme female brain", "processing advantage"

Introduction

Autism Spectrum Disorder (ASD) is a set of heterogeneous neurodevelopmental conditions characterized by difficulties in social communication and restricted, repetitive behavior and interests [American Psychiatric Association (APA), 2013]. Historically, ASD was considered a male disorder, although the view has changed there is still a male dominance with a 3:1 ratio (Hull et al., 2017; Loomes et al., 2017; Chiarotti and Venerosi, 2020; Saito et al., 2020). The male predominance in ASD is far from being fully understood, however, since the domination is mostly prominent in the group of High Functioning patients, those with an Intelligence Quotient (IQ) of 75 and above, some mean it is insufficient theoretical knowledge and clinical insight about the ASD female profile that is a part of the explanation (Moseley et al., 2018; Young et al., 2018). Others mean the female double set of x-genes provides a biological protection from ASD (Baron-Cohen et al., 2011; Werling, 2016).

In terms of communication, there is support for both theories. A female superiority in language development is well established although the gender difference in the normal population is very small, larger differences have been seen in those on the 10th percentile and below, boys being twice as likely to be diagnosed with a language disorder (Wallentine, 2020). In support for there being a lack of knowledge of female ASD, there are studies showing autistic girls to generally be more positively rated by a novel conversation partner than autistic boys despite an equal level of autism severity (Rynkiewicz et al., 2016; Dean et al., 2017; Parish-Morris et al., 2017; Cola et al., 2020).

"Camouflaging" refers to the ability to meet social demands by mimicking behavior in a seemingly flexible way and is more common in ASD girls than boys. While the use of camouflaging strategies requires some understanding of social communication, the lack of flexibility typically leaves the individual exhausted and in risk of developing various depression- and anxiety-related disorders (Rynkiewicz et al., 2019). Camouflaging strategies are said to blur important distinctions and inadvertently contribute to misconstruing important clinical and eligibility decisions even though these children/adolescents are insightfully rated by those who know them well in contextually relevant situations (Hull et al., 2017; Young et al., 2018).

A verbal IQ of 70 and above has shown to be positively related to age of diagnosis in both genders when controlling for demographic factors. The association has shown to be far stronger for girls which means that being a female with good verbal skills will be putting you at risk for a delayed autism diagnosis (McDonnell et al., 2021) which, in turn, increases the risk of the patient developing more severe psychiatric symptoms (Rynkiewicz et al., 2019).

In the past few years, the view of ASD as a sensory processing disorder has received more attention (Robertson and Baron-Cohen, 2017; Posar and Visconti, 2018; Zhou et al., 2021), specifically the audio-visual temporal processing and its effect on language development (Ocak et al., 2018; Tanigawa et al., 2018; Jain et al., 2020; Meilleur et al., 2020), social abilities (Wallace and Stevenson, 2014), and to form a coherent perception of the world (De Niear et al., 2018). Sensory processing difficulties, defined as hyper- and hypo-sensitive responses to sensory information, are reported in more than 96% of children with ASD (Marco et al., 2011; Robertson and Baron-Cohen, 2017).

While sensory processing refers to the ability to detect, regulate, interpret, and respond to sensory stimuli (Dunn, 2001), temporal processing refers to the ability to integrate contemporary sensory inputs into an adequate global interpretation of the whole (Wallace and Stevenson, 2014). The Sensory Integration Theory (SIT; Ayres, 1979) states that the human development is strongly affected by the process and integration of sensory inputs. It differs between *Unisensory* and *Multisensory* processing, the first referring to the process of one or more stimulus from one sensory modality such as auditory *or* visual stimuli, whereas the second refers to the integration process of stimuli received from different modalities such as auditory *and* visual stimuli.

The Temporal Binding Window (TBW) is used to describe the period of time passing between the exposure of two stimuli in order for them to still be perceived as bind together. In terms of auditory and visual unisensory temporal processing, studies of ASD show varying results, some indicating that there is a larger TBW in people with autism whereas others indicate that it is smaller (Zhou et al., 2018; Meilleur et al., 2020). However, age seems to be affecting the results as adults with ASD showed to be better in visual discrimination than TD, indicating a smaller visual TBW than TD (Falter et al., 2012), whereas children with ASD showed no enhanced visual discrimination but rather an impaired auditory discrimination, indicating a larger auditory TBW than TD (Kwakye et al., 2011). However, both studies are largely dominated by male subjects, and neither considered gender as a factor.

Research of audio-visual temporal processing in ASD shows more consistent findings. A reduced audio-visual temporal acuity is well established (Shams et al., 2000; Alais and Burr, 2004; Zhou et al., 2021). Several studies show that the audio-visual TBE in children and youths with ASD is larger than in TD, however, the results are restricted to audio-visual speech stimuli (Woynaroski et al., 2013; Stevenson et al., 2014; Noel et al., 2018). One study showed no audio-visual temporal processing impairments in youth with ASD (de Boer-Schellekens et al., 2013); however, subjects in this study were young adults including adults and mainly of male gender which might have skewed the results. In a review article covering studies of temporal processing in ASD (Meilleur et al., 2020) lack of age as a developmental variable is noted. Still, it is concluded that the collected material points toward a delayed maturation of multiple sensory integration in children with ASD, since studies of adults with ASD show better audio-visual integration performance than studies with ASD children presented with the same task.

It is common for children with ASD to have one sensory modality that is superior, meaning that it responds faster or stronger than others (Bebko et al., 2006; Kwakye et al., 2011; Foss-Feig et al., 2017; Balasco et al., 2020). A superior modality has shown to dominate the perception, blocking out information from other sources, leaving the person with a lack of information when trying to grasp the full concept of a situation (Meilleur et al., 2020).

Several studies show ASD children to be superior in visual acuity (Jolliffe and Baron-Cohen, 1997; Joseph et al., 2009; Kaldy et al., 2016). Considering that 80% of included participants in ASD studies from the past 10 years are of male gender and that studies rarely separate between gender (Feldman et al., 2018), we should be cautious accepting results stating that autistic children show certain characteristics. However, the belief of ASD females showing cognitive similarities to a male cognitive style is supported in studies of brain structure and function (Lai et al., 2013) as well as by theories meaning ASD should be seen as an "extreme male brain" (Asperger and Frith, 1991; Baron-Cohen et al., 2011). However, we must bear in mind that all studies including patients already diagnosed with autism will present us with biased data. The screening instrument for autism is based on research mostly made on males; hence, the children passing for a diagnosis will also be matching with the male phenotype of autism whether their biological gender is male or female.

According to the empathizing-systemizing (E-S) theory of psychological sex differences, male brains show a stronger systemizing ability, whereas females show a stronger ability of empathizing. Systemizing is defined as the drive to analyze and predict the behavior of a system, whereas empathizing is defined as the drive to analyze and predict other people's mental states (Baron-Cohen, 2003). The E-S theory differentiates between individual brain types by measuring the dimensions of empathizing and systemizing resulting in five different types. Those having an equal amount of empathizing and systemizing are categorized as *Type B* (E = S). *Type E* show a stronger ability of empathizing than systemizing (E > S) and the reversed situation is represented by *Type S* (E < S). *Extreme Type E* represent those with an extreme ability for empathizing and is more common in females, whereas *Extreme Type S* represent those with an extreme ability for systemizing and is more common in males (Greenberg et al., 2018). When people diagnosed with ASD are categorized in accordance with the E-S brain types, results indicate *Extreme Type E* is highly unusual in both genders (Greenberg et al., 2018) which seems quite logical considering the biased assessment procedure of ASD mentioned above. In another study though, Floris et al. showed that the "male brain syndrome" can only be said to describe a subgroup of the ASD population (Floris et al., 2018) which is supported by DiCriscio and Troiani who published a study showing that an enhanced visual ability is only associated with ASD symptoms in ASD males (DiCriscio and Troiani, 2017).

Rather than relying on old ASD research, perhaps, it is more reasonable to turn our attention toward the normal population for cues as to how we should understand and investigate female ASD.

While TD adult males have shown a visual acuity processing advantage, TD females have shown an auditory acuity processing advantage (McGivern et al., 2019; Siedlecki et al., 2019; Thornton et al., 2019). If the male phenotype of ASD is having an *"extreme male brain"* would it not be reasonable to assume that a female phenotype of autism would involve an *"extreme female brain"?*

An extreme female brain would then be characterized by a superior auditory acuity. Auditory acuity has previously been associated with speech comprehension as well as the development of language and social communication (Lee et al., 2018; Ayasse et al., 2019). In a study from 2017, a better signal-detection ability was seen in people with ASD using camouflaging strategies (Lai et al., 2017; Parish-Morris et al., 2017).

Speech comprehension requires the use of both visual and auditory information processes (King et al., 2019). TD males have shown to be more lateralized in their language processing than TD females, meaning that they favor the left hemisphere where most of the auditory comprehension take place. Females, on the other hand, use bilateral language processes, meaning that they rely on both auditory and visual information to a higher degree than males (Burman et al., 2008; Koles et al., 2010; Ross et al., 2015). As mentioned above, a superior sensory modality will block out information from the other modality; hence, a superior visual ability will be blocking out auditory information whereas a superior auditory ability will be blocking out visual information. Mainly relying on auditory information, the male lateralized language process will be highly vulnerable when faced with a superior visual ability. The bilateral language processing seen in females will be more robust, providing an alternative processing rout when faced with a visual or auditory superior ability. However, in a more complex setting where multisensory integration is required, females will be as vulnerable as males when faced with a superior auditory or visual ability. A superior auditory ability will block out visual information needed to understand the full complexity of a setting.

In a review article from 2020, neurobiological sex differences in language processing are rejected due to the lack of consensus found between results from previous studies (Sato, 2020). However, the studies included in the reviews differ in many ways from each other, some using word generation as a measure, others counting, picture naming, or lip reading, which is not a fair comparison since neural organization of language has shown to be task dependent (Hickok and Poeppel, 2007).

The theory of Social Motivation discriminates between less complex social settings, requiring unisensory information to be processed, and more complex social behavior requiring multisensory integration to be processed (Tamir and Hughes, 2018). In a study from 2021, adult TD women showed an enhanced emotional identification in unisensory processing tasks compared to TD males, whereas in multisensory integration tasks, no gender differences were seen (Lin et al., 2021).

Hypothesizing that female children and youths with ASD have an extreme female brain, it could provide us with an explanation as to why ASD females on a group level, are better social performers in some settings, while still experiencing difficulties in others.

The aim of our study is to look at the auditory and visual processing in boys and girls between seven and 17 years of age. By including measurements representing auditory and visual unisensory and multisensory processing we aimed to look for potential associations with parental ratings of the Social Responsiveness Scale. Since 40%–70% of the ASD population show a comorbidity with Attention Deficit Hyperactivity Disorder (ADHD; Antshel and Russo, 2019), defined by difficulties with inattention and hyperactivity with an onset before the age of 10 [American Psychiatric Association (APA), 2013], we included an ADHD rating scale in order to control for hyperactivity and inattention. As to our knowledge, no previous studies have been looking into this before.

The Integrated Visual and Auditory Continuous Performance Test (IVA CPT; Sandford and Turner, 2000) is a continuous performance task administered using a computerized format. IVA measures various attention-related components in terms of both visual and auditory stimuli. Social Responsiveness Scale (SRS; Constantino and Gruber, 2012) is one of the most used standardized assessments of ASD both internationally and in Sweden (Zander, 2021). It surveys the core symptoms of autistic traits in social communication (Constantino et al., 2003). The Swanson, Nolan, and Pelham scale (SNAP-IV) is a widely used rating scale of ADHD (Hall et al., 2020). It gives scores within the core symptoms of ADHD, i.e., inattentiveness and hyperactivity as well as symptoms of Oppositional Defiance Disorder (ODD; Swanson et al., 2012).

We hypothesized that a female auditory processing advantage would be seen in unisensory processing by associations between a better auditory ability and less rated problems in SRS whereas in the male group no associations between a superior auditory or visual ability and less rated problems in SRS would be seen. In the multisensory IVA measurements, we assumed the females would show associations between an auditory dominance and more rated problems within SRS whereas in the male group a visual dominance would be associated with more rated problems within SRS.

Materials and methods

Participants

To avoid as many assessment biases as possible, all children triaged for an ASD assessment during the year of 2017 were invited to participate in the study whether they later receive an autism diagnose or not. Fifty-seven children between the ages of 7–17 (29 females mean age 12.97 years, SD 3.168 and 28 males, mean age 11.71 years, SD 2.904) were recruited from the child and adolescent psychiatric out-patient clinic in Eslöv, Sweden (Table 1). The children were from the same socioeconomic area, the communities of Eslöv, Höör, and Hörby where the median wage is around 74% of the Swedish median wage and has an unemployment rate of 20% compared to 9.4% for all of Sweden (Statistiska Centralbyrån, 2021).

The children were triaged either through a screening procedure done by clinical psychiatric nurses using the structured Brief Child and Family Phone Interview (BCFPI; Boyle et al., 2009; Cunningham et al., 2009) or by referral from other clinical professionals. Four girls and seven boys already had a diagnosis of ADHD and were included in the study unmedicated. The remaining 46 children had no prior neuropsychiatric diagnosis. To be included in the study a verbal as well as fluid intelligence quotient of 85 and above was required which was measured with the Wechsler Intelligence Scale for Children (WISC-V; Wechsler, 2003). Exclusion criteria were a diagnosis of any hearing disabilities including tinnitus, difficulties communicating in Swedish, and any form of substance abuse. Nine children were excluded due to not passing the IVA validity scales. Four children interrupted and did not want to continue the IVA testing and were therefore excluded. Two children were excluded when screening for outliers within the IVA-results and another two were excluded due to parental assessments not being completed. The remaining participants were 20 females (mean age 13.90 yrs., SD 2.34) and 20 males (mean age 12.15 yrs., SD 2.83). The females had a mean score of 69.8 in the parental ratings of Social Cognition and a mean score of 66.6 in the ratings of Social Communication, whereas the males had a mean score of 64.8 in Social Cognition and 64.3 in Social Communication, indicating females were rated as having higher problems in both Social Cognition and Social Communication than the males. A written informed consent was obtained from all children and their guardians. The study was approved by the regional ethics committee in Lund (Dnr: 2016/964).

TABLE 1 Group statistics.

	Females	Males
Recruited	29	28
Average age (SD)	12.97 (3.17)	11.71 (2.90)
Excluded	8	7
Outliers	1	1
Remained	20	20
Average age[a] (SD)	13.90 (2.34)	12.15 (2.83)
WISC-V Intelligence quotient	>85	>85

SD, Standard deviation.
[a]Participants included in the study.

Tests

IVA-2 CPT

IVA-2 (Sandford and Turner, 2000) is a computerized continuous performance test integrating visual and auditory sensory processes. The visual stimuli are presented on the computer screen, while the auditory stimuli are presented *via* headphones equipped with ear cushions. The output consists of 20 different basic measurements, each providing a combined visual–auditory measure as well as independent measurements of auditory and visual EF. The basic measurements are also used in the construct of different scales. The four primary scales are attention, sustained attention, response control, and symptomatic problems. Eight subscales provide a combined auditory-visual processing score as well as separate processing scores for auditory and visual function. The Validity Scales control for lack of

10.3389/fpsyg.2022.1068001

comprehension, unwillingness to participate, or other misconduct behavior. The unisensory measurements used in this study were chosen to represent aspects in ASD that are either enhanced (Acuity) or dysfunction (Focus, Elasticity). A more complex unisensory measurement in the form of two scales was also used to measure high- and low-demanding tasks. Finally, we also used the auditory–visual difference score from the two extreme measurements of Focus as well as Scale of Agility as a measurement of multisensory processing (Table 2). The IVA-2 profile is summarized quantitatively through standard scores that are familiar to most clinical practitioners. An IVA-testing not passing the validity scales shows no results. Test time: 15 min.

The Swanson, Nolan, and Pelham scale

The Swanson, Nolan, and Pelham scale (SNAP-IV; Swanson et al., 2012) provides measurements of basic ADHD symptoms of inattention, hyperactivity as well as Oppositional Defiant Disorder (ODD). The scale was included since the same symptoms are common in patients with autism. The scale consists of 26 questions divided into three different groups, the first nine being related to inattention, the following nine to impulsivity/hyperactivity, and the remaining eight to ODD. The rating span 0–3 corresponds to the child showing a certain behavior "not at all," "just a little," "quite a bit" and "very much." An average score for each subscale is calculated and used as a measurement, hence ranging from 0.0–3.0. A score above 1.0 indicates deviances. Test time: 10 min.

Social responsiveness scale

The Social Responsiveness Scale (SRS-2; Constantino and Gruber, 2012) measures behavior of a child or adolescent between the ages of 4 and 18, serving as one index of severity of social deficits in ASD. It consists of 65 questions (17 of which are reverse scored) divided into five subscales measuring Social Cognition (ability to interpret social cues once they are picked up), Social Communication (ability to be motoric expressive in social communication), Social Awareness (ability to pick up on social cues), Social Motivation (motivation to engage in social-interpretational behavior), and Social Rigidity (stereotypical behaviors and restricted interests; Constantino and Gruber, 2012). The rating span 0 to 3 represents, in corresponding order: Not true, somewhat true, often true, and always true. The score is compared to a norm curve and the final measurement used is a t-scale score. A t-score above 60 raises suspicions the child/adolescent may be at risk or have signature features consistent with ASD. Test time: 30 min.

TABLE 2 IVA-measurements used.

	Measurements		
Unisensory processing	Elasticity	Acuity	Focus
Auditory	×	×	×
Visual	×	×	×
Complex unisensory processing	Scale of competence (high-demanding processing)	Scale of maintenance (low-demanding processing)	
Auditory	×	×	
Visual	×	×	
Multisensory processing	Scale of focus	Scale of agility	
A/V diff.	×	×	
A/V diff. Inv.	×	×	

Procedure

The IVA-tests were administered by trained staff. Participants were seated on a comfortable chair, adjusted to give the child a comfortable and easy-to-reach position. The participant was presented with the auditory stimuli through tight-fit headphones to reduce ambient noise that might be needless distracting. The test room was empty, and the windows were covered up to shut out possible disturbing visual stimuli outside. The participants were presented with a session of 2 × 1 min of responding to auditory and visual stimuli one at a time. After that, a training session of 1.5 min started where the child got to practice responding to both kinds of stimuli in a random order. The test starts when the computer has registered a proper response pattern in the practice part. The main test consists of either a written number 1 or 2 on the computer screen or a voice reading "one" or "two." The computer voice tells the participants when they are to click on the mouse and when they are not to. The parental rating scales as well as a reply envelope were given to the parents at the first assessment visit to the clinic.

Data analysis

Analyses were done using the Statistical Package for Social Sciences (SPSS; IBM Corp, 2019) using a significance level of 0.05 in all tests. Before further analyzing, the IVA-data were screened for unusual cases above 3 x the interquartile range. The descriptive statistics were used for calculating group mean scores and standard deviations. The Kolmogorov–Smirnov test was used to test for normal distribution. The independent samples *t*-test was used when calculating group mean differences in age. Levene's test of variance was used to explore the homogeneity of variances. An analysis of covariance (ANCOVA) test was used to examine group mean differences within the measurements from the parental scales and the *a priori* chosen IVA measurements, controlling for the covariate of Age. The Bonferroni correction was used to adjust for multiple correlations. The Pearson's correlation test was used when determining relationships between the parental ratings and the selected IVA-measurements using age as a control variable.

As measures for the unisensory processing, we used the independent measures of auditory and visual Focus, Acuity, and Elasticity as well as two more complex unisensory measures in the form of scales, each providing a combined measure of three different aspects from the same modality. The Scale of Competence represented high-demanding tasks whereas the Scale of Maintenance represented low-demanding tasks. As a measure of multisensory processing, we used the difference score between auditory and visual performance in Focus, an individual measure and in the Scale of Agility. A positive difference score indicates an auditory dominance whereas a negative score indicates a visual dominance (Table 2). The IVA-scores were correlated with each of the parental SRS assessment variables. All the correlations were calculated using Pearson rho. The results are presented in r-values between −1 to +1. A positive value indicates a positive correlation, and a negative value indicates an inverse relation. A value around 0 indicates no correlation.

Results

Two patients showed extreme outliers, above the 3 × inter-quarter range (IQR) in several of the IVA-measurements, one male and one female. Both were excluded from the study. Another outlier was detected in the female group within Auditory Acuity showing an extreme low result. The subject was kept in the study but left out from affected analyses, hence the participant was excluded from the analyses including Auditory Acuity and Auditory Scale of Maintenance. The *t*-test used for equality of means in age showed a significant result (Sig. 2-tailed 0.040) with the females having a 1.75 year higher mean age than the males. Levene's test of Equality of Error Variances turned out positive in the cases of Social Rigidity (sig = 0.006), Auditory Acuity (sig = 0.011), and Auditory Scale of Maintenance (sig ≤ 0.001), the females showing a higher variance than the males in the ratings of Social Rigidity and the males showing a higher variance in the measurements of auditory Acuity and auditory Maintenance (Table 3).

The ANCOVA showed significant differences between the group means in the measure of Auditory Maintenance (Table 4).

In the female group, the independent unisensory measurements showed two significant correlations with the parental ratings (Table 5; Figures 1, 2) whereas the scales showed no significant correlation (Table 6). A positive correlation was seen between Auditory Elasticity and Social Motivation (r = 0.519, $p = 0.023$) and a negative correlation was seen between Auditory Acuity and Social Communication (r = −0.535, $p = 0.022$) In the male group, no significant correlations were seen with the Social Responsiveness Scale; however, the unisensory processing showed a negative correlation between the specific measurement of Auditory Acuity and ODD (r = −0.613, $p = 0.005$; Table 4) as well as between the auditory Scale of Maintenance and ODD (r = −0.481, $p = 0.037$; Table 5).

The difference score, representing the multisensory processing showed one significant correlation in the female group. An auditory dominance in Agility was significantly associated with Social Awareness in the female group (r = 0.541, $p = 0.017$; Table 7; Figure 3). In the male group, a visual dominance in Focus was

TABLE 3 Group statistic of the estimated mean score of the IVA-measurements.

Dependent variable	Gender	*N*	Estimated mean	Standard estimated error
Social awareness	Females	20	56.62[a]	3.223
	Males	20	60.23[a]	3.223
Social cognition	Females	20	70.058[a]	3.664
	Males	20	64.492[a]	3.664
Social motivation	Females	20	72.948[a]	3.069
	Males	20	65.952[a]	3.069
Social communication	Females	20	67.258[a]	3.399
	Males	20	63.642[a]	3.399
Social rigidity	Females	20	75.890[a]	3.958
	Males	20	65.710[a]	3.958
ODD	Females	20	1.341[a]	0.172
	Males	20	1.051[a]	0.172
Inattention	Females	20	1.69[a]	0.165
	Males	20	1.700[a]	0.165
Hyperactivity	Females	20	1.052[a]	0.174
	Males	20	1.183[a]	0.174
Auditory acuity	Females	19	95.932[b]	6.361
	Males	20	75.438[b]	6.129
Visual acuity	Females	20	88.265[a]	6.414
	Males	20	80.235[a]	6.414
Auditory elasticity	Females	20	87.797[a]	5.727
	Males	20	81.903[a]	5.727
Visual elasticity	Females	20	79.758[c]	7.314
	Males	19	81.292[c]	7.314
Auditory focus	Females	20	84.210[a]	4.169
	Males	20	78.840[a]	4.169
Visual focus	Females	20	93.658[a]	4.700
	Males	20	86.292[a]	4.700
Auditory maintenance	Females	19	95.932[b]	6.421
	Males	20	71.164[b]	6.250
Visual maintenance	Females	20	81.942[a]	7.545
	Males	20	62.408[a]	7.545
Auditory competence	Females	20	81.757[a]	6.616
	Males	20	77.493[a]	6.616
Visual competence	Females	20	76.706[a]	6.194
	Males	20	75.494[a]	6.194

[a]Covariates appearing in the model are evaluated at the following values: Age = 13.0250.
[b]Covariates appearing in the model are evaluated at the following values: Age = 12.9744.
[c]Covariates appearing in the model are evaluated at the following values: Age = 10.1026.

TABLE 4 Levene's test of equality of variances as well as the ANCOVA for variables showing significant differences between the groups.

Dependent variable	Gender (*N*)	Mean	Std. deviation	Levene's test of equality of error variance: F	Levene's test of equality of error variance: Sig.	Pairwise comparisons: Gender I	Gender J	Estimated mean difference (I-J)	Std. error	Sig.[c]
Social rigidity	Females (20)	74.8500	21.25107	8.550	0.006**	Female	Male	5.566[a]	5.753	0.085
	Males (20)	66.7500	11.96431			Male	Female	−5.566[a]	5.753	0.085
Auditory acuity	Females (19)	94.3684	16.00420	7.198	0.011*	Female	Male	16.416[b]	9.104	0.080
	Males (20)	73.0500	35.34711			Male	Female	−16.416[b]	9.104	0.080
Auditory scale of maintenance	Females (19)	96.8947	13.96382	14.339	<0.001***	Female	Male	24.768[b]	9.190	0.011*
	Males (20)	70.2500	35.17606			Male	Female	−24.768[b]	9.190	0.011*

*The mean difference is significant at the 0.05 level.
**The mean difference is significant at the 0.01 level.
***The mean difference is significant at the 0.001 level.
[a]Covariates appearing in the model are evaluated at the following values: Age = 13.0250.
[b]Covariates appearing in the model are evaluated at the following values: Age = 12.9744.
[c]Adjustments for multiple comparisons: Bonferroni.

significantly associated with Social Rigidity (r = −0.601, *p* = 0.007; Table 7; Figure 4).

Discussion

The results confirm gender differences in unisensory vs. multisensory processing with females showing a superior auditory processing associated with better social communication skills in unisensory processing (Figure 1), whereas the multisensory processing was associated with more problems within social awareness (Figure 3). In the male group, visual processing showed no correlation with social skills in the unisensory processing (Figure 2). In the multisensory processing, a visual dominance was associated with difficulties in social rigidity (Figure 4). The lack of gender differences in the rating of Social Responsiveness indicates both groups show the same number of difficulties.

In the female group, a unisensory processing advantage in Auditory Acuity was associated with less rated problems in Social Communication, the males did not show this correlation (Table 5; Figures 1, 2). This is in line with our hypothesis of ASD females showing the same unisensory processing advantage in social communication as is seen in previous studies of TD women (McGivern et al., 2019; Siedlecki et al., 2019; Thornton et al., 2019). Auditory Acuity has previously been associated with language comprehension (Lee et al., 2018; Ayasse et al., 2019) so, a process such as language, heavily relying on auditory information will naturally be favored by those having a superior auditory processing. However, in the male group, a better performance in Auditory Acuity was associated with less rated problems of ODD (r = −0.613, *p* = 0.005; Figure 2), which is in line with our hypothesis of males having a superior visual processing blocking out auditory information. A higher score of auditory acuity in males will be representing a person with a visual dominance of lesser degree, still limiting the auditory information but perhaps reducing autistic behaviors, resulting in less rated problems within ODD. However, the symptoms being rated in Oppositional defiant disorder [American Psychiatric Association (APA), 2013] differs from other psychiatric symptoms since it is a diagnose based on parental interpretation of a child's intentions and feelings rather than an observation of a specific concrete behavior, hence the measure becomes less specific. Since parental assessments of teen aged children have shown to be influenced by the child's gender due to preconceptions about the underlying cause for the behaviour (Geelhand et al., 2019) we must count that in as a possible explanation for the results. However, the lack of differences in the parental ratings of Social Responsiveness speaks against that theory, in fact, looking at the actual scores, the females were indeed higher rated than the males in both ODD and Social Communication (Table 3).

In the female group, two significant correlations of the opposite direction were also found in the unisensory processing. A higher performance in Auditory and Visual Elasticity was associated with higher ratings of problems within Social Motivation (r = 0.519, *p* = 0.023) and ODD, respectively (r = 0.460, *p* = 0.047). Elasticity has previously been associated with the use of "Camouflaging strategies" (Hull et al., 2021). Since camouflaging strategies are known to cause exhaustion, stress, and anxiety (Rynkiewicz et al., 2016) it seems reasonable to assume that a higher performance in Auditory Elasticity would be associated with higher ratings of problems within Social Motivation. The association between a *higher* performance in Visual Elasticity and ODD seen in the female group stands in contrast to the male on-the-verge of being significant association between a *lower* performance in *Auditory* Elasticity and higher rated problems within ODD

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TABLE 5 Pearson correlation table between the independent unisensory IVA-measurements and the parental rating scales[a].

	Females						Males					
	Elasticity		Acuity		Focus		Elasticity		Acuity		Focus	
Variable (*N*)	Auditory (20)	Visual (20)	Auditory (19)	Visual (20)	Auditory (20)	Visual (20)	Auditory (20)	Visual (19)	Auditory (20)	Visual (20)	Auditory (20)	Visual (20)
Social awareness	0.169	0.228	−0.310	0.218	−0.102	−0.055	0.194	0.228	0.156	−0.050	−0.084	0.142
Social communication	0.394	0.349	**−0.535* (0.022)**	0.270	−0.373	−0.003	0.049	0.151	−0.091	−0.374	−0.232	0.234
Social cognition	0.188	0.271	−300	0.194	−0.226	0.034	0.098	0.192	0.115	−0.209	−0.220	0.288
Social motivation	**0.519* (0.023)**	0.434	−0.170	0.387	0.022	0.330	0.276	0.030	−0.009	−0.040	−0.235	0.133
Social rigidity	0.402	0.367	−0.388	0.265	−0.122	0.086	0.234	0.121	0.090	−0.050	−0.337	0.428
Hyperactivity	0.172	0.270	−0.318	0.276	**−0.464* (0.045)**	−0.111	−0.015	−0.050	0.042	0.136	−0.295	0.311
Inattention	0.161	0.333	−0.347	0.213	−0.321	0.006	0.004	0.354	−0.176	−0.025	0.065	0.279
ODD	0.054	**0.460* (0.047)**	−0.236	0.270	−0.168	0.144	−0.452 (0.052)	0.028	**−0.613** (0.005)**	−0.320	−0.076	−0.289

Pearson r displayed in table. Significant correlations are highlighted and includes (*p*-values).
[a]Using age as a covariable.
*$p < 0.05$.
**$p < 0.005$.

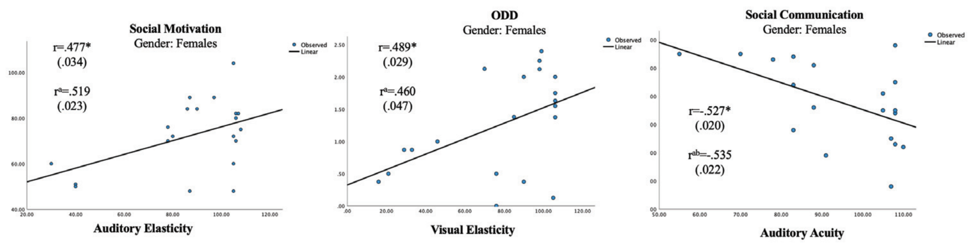

FIGURE 1
Significant correlations in unisensory processing in the female group. [a]Using age as a control variable. [b]Accounted for 19 subjects. *p<0.05.

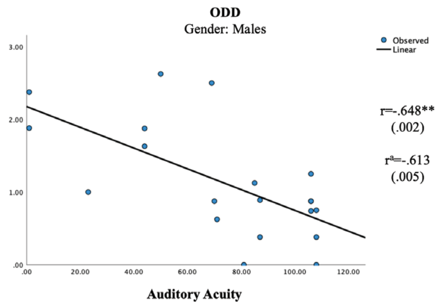

FIGURE 2
Significant correlations in unisensory processing in the male group. [a]Using age as a control variable. **p<0.005.

(r = −0.452, p = 0.052). Again, the lack of gender differences in the parental ratings makes us turn to other explanations than parental preconceptions of their children for interpretations. Difficulties within language and flexibility have previously been identified as risk factors impacting ODD in TD boys, whereas only flexibility was identified as a risk factor in TD girls (Kerekes et al., 2014). As elasticity is a measure of flexibility and auditory acuity is associated with speech comprehension (Lee et al., 2018; Ayasse et al., 2019), our results are in line with previous research as far as the male correlations go. However, in the female group, a higher performance in visual flexibility is associated with ODD rather than a lower performance. How can this be explained? A farfetched but still reasonable interpretation can perhaps be found by applying the "extreme female brain" (Floris et al., 2018) vs. "extreme male brain" theories (Shams et al., 2000; Alais and Burr, 2004). By looking at the two groups' overall performance in Elasticity, the male performance in auditory and visual elasticity are equally good, whereas in the female group, there is an auditory superiority (Figure 3). The female correlation between a higher Visual Elasticity and ODD symptoms could then be a result caused by those females showing more of a male structured brain; hence, the more "male-like" a female autistic child's brain is, the more similar will the outcome of behavior also be.

To get a more complex measure of unisensory processing, we included measures of performance in scales representing low- and high-demanding unisensory processing, respectively. Although no significant correlations were seen in the female group (Table 6) they outperformed the male group in Scale of Maintenance having a 20-point higher average score (Table 3). The female group showed a couple of non-significant correlations with Auditory and Visual Maintenance [Social communication (r = −0.405) and Social Motivation (r = 0.448), respectively] mirroring those seen in the correlations with the specific measurements of Auditory Acuity and Visual Elasticity (Table 6). In the male group, a significant negative correlation was seen between auditory Scale of Maintenance, representing low-demanding tasks and ODD (r = −0.481, p = 0.037; Table 6). Since both groups show correlations that are smaller and less significant than the specific measurements of Acuity and Elasticity, we can assume that the specific IVA measurements are of more value in predicting psychiatric symptoms than the scales built up by several aspects of auditory vs. visual performance. This is noteworthy for future research since it implies it is the superiority of specific auditory vs. visual measurements that are of interest in the association with social responsiveness rather than an overall auditory or visual performance. However, an interesting observation in the female group are the two similar non-significant correlations between Auditory Scale of Maintenance and Social Cognition (r = −0.404, p = 0.096), respectively, and Social Communication (r = −0.405, p = 0.095). In the correlations with the specific measurements, Social Communication showed a significant correlation with Auditory Acuity (r = −0.535, p = 0.22) whereas Social Cognition showed a much smaller non-significant correlation (r = −0.300) which indicates Social Cognition might be better predicted with a more complex measure of auditory performance.

Moving over to the results seen in multisensory processing, we find support for the belief of an extreme female vs. male brain. The multisensory processing represents situations where both

TABLE 6 Correlation table between the complex unisensory IVA Scales and the parental rating scales[a].

	Females				Males			
	Scale of competence		Scale of maintenance		Scale of competence		Scale of maintenance	
Variable (*N*)	Auditory (20)	Visual (20)	Auditory (19)	Visual (20)	Auditory (20)	Visual (20)	Auditory (20)	Visual (20)
Awareness	0.310	0.040	−0.008	0.064	0.135	−0.050	0.238	0.104
Communication	0.097	0.100	−0.405 (0.095)	0.151	−0.005	0.046	0.093	−0.140
Cognition	0.125	0.204	−0.404 (0.096)	0.112	0.114	0.078	0.149	−0.008
Motivation	0.281	0.288	0.117	0.448 (0.055)	−0.022	0.270	0.055	0.170
Rigidity	0.258	0.247	−0.249	0.170	−0.005	0.302	0.194	0.191
Hyperactivity	0.125	−0.011	−0.239	0.039	−0.114	0.345	0.143	0.206
Inattention	−0.026	0.148	−0.374	0.084	0.082	0.275	−0.099	0.081
ODD	0.177	0.298	−0.308	0.209	−0.261	−0.143	**−0.481* (0.037)**	−0.383

Pearson r displayed in table. Significant correlations are highlighted and includes (*p*-values).
[a]Using age as a covariable.
*$p < 0.05$.

TABLE 7 Correlation table between the multisensory IVA-measurements, auditory-visual (A-V) difference score and the parental scales[a].

	Females				Males			
	Focus A-V Difference score		Agility A-V Difference score		Focus A-V Difference score		Agility A-V Difference score	
Variable (*N*)	Biased (20)	Unbiased (20)	Biased (20)	Unbiased (20)	Biased (20)	Unbiased (20)	Biased (20)	Unbiased (20)
Awareness	−0.044	−0.212	**0.541* (0.017)**	0.354	−0.180	−0.052	−0.074	0.022
Communication	−0.392 (0.097)	0.207	0.217	0.016	−0.362	0.073	0.119	0.061
Cognition	−0.263	0.244	0.201	0.000	−0.400	−0.066	−0.039	−0.105
Motivation	−0.323	0.097	0.117	−0.218	−0.277	0.202	−0.448 (0.054)	−0.291
Rigidity	−0.255	0.170	0.162	−0.008	**−0.601** (0.007)**	0.015	−0.349	−0.288
Hyperactivity	−0.358	0.117	0.202	0.142	**−0.471* (0.042)**	0.000	−0.199	−0.165
Inattention	−0.400 (−090)	0.288	−0.256	−0.231	−0.192	0.215	0.017	0.083
ODD	−0.337	0.282	0.023	−0.179	0.193	**0.459* (0.048)**	0.355	0.260

Pearson r displayed in table. Significant correlations are highlighted and includes (*p*-values).
[a]Using age as a covariable.
*$p < 0.05$.
**$p < 0.01$.

auditory and visual information need to be processed. In the female group a superior auditory Agility was associated with more rated problems within Social Awareness, whereas in the male group a superior visual Focus was associated with more rated problems within Social Rigidity (Table 7). This supports our belief that ASD is portrayed through different gender phenotypes. It is also in line with previous research of gender differences in ASD showing males to have more rigid behaviors than females (Werling and Geschwind, 2013; Lockwood Estrin et al., 2021). However, the parental ratings show no significant difference between the groups regarding social rigidity, indicating the females show as many rigid behaviors as males (Table 3). A reasonable explanation can be related to gender differences in the portrayal of rigidity. Previous research of children with ASD has noted gender differences in the portrayal of rigid behaviors where boys are more inclined to show stereotyped behaviors and restricted interests, whereas girls are more compulsive insisting on sameness and having self-injurious behavior (Antezana et al., 2019). Since the phenotypes of female rigidity are not as well represented in rating scales as male rigidity is, it makes sense other scales might be more suitable for rating females. An auditory dominance in the more complex multisensory measure of Agility might then indeed be associated with higher-rated problems within Social Awareness in only ASD females, whereas in males a visual dominance in Focus is related to higher-rated problems in Social Rigidity. The fact that we see gender differences in the correlations between cognitive abilities and social difficulties gives further support to our believe that ASD is differently portrayed in females than in males and that different cognitive profiles produce different kinds of problems.

To be sure our results represent a modality dominance rather than any modality imbalance, we inversed all the negative difference scores to produce an unbalanced measure (Table 7) which were then correlated with the parental ratings.

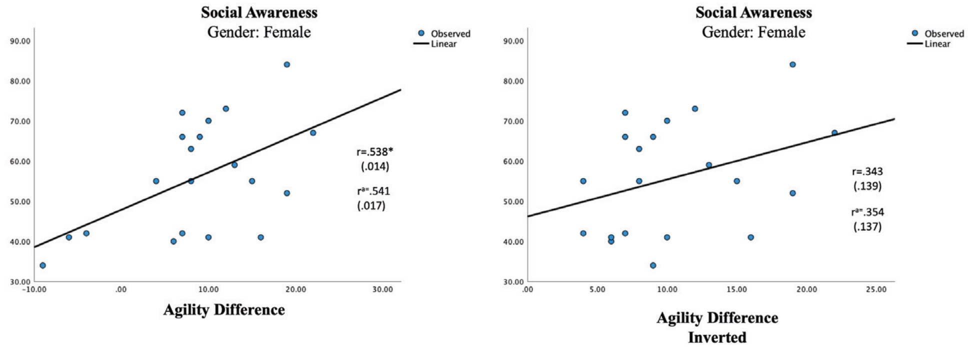

FIGURE 3
Regression analysis for multisensory processing in the female group. Social awareness and agility different vs. social awareness and agility difference inverted. [a]Using age as a control variable. *$p \leq 0.05$.

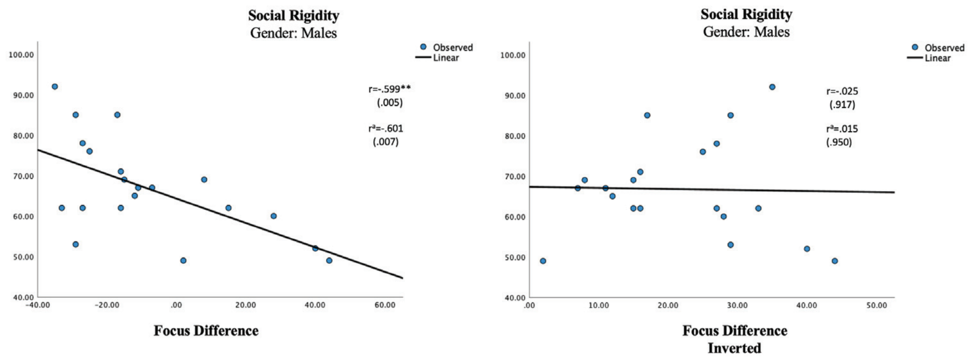

FIGURE 4
Regression analysis for multisensory processing in males. Social rigidity and focus different score vs. social rigidity and focus difference inverted score. [a]Using age as a control variable. **$p \leq 0.01$.

In the female group, the inverted measurement of Agility showed a smaller, non-significant correlation (r = 0.354, $p = 0.137$) with Social Awareness and in the male group, the new measure showed no correlation at all (r = 0.015). The new lower association seen in the female group is in line with research of language processing claiming females use bilateral processing in language processing, relying on both auditory and visual information to a higher degree than males (Burman et al., 2008; Koles et al., 2010; Ross et al., 2015). In our hypothesis, we suggested females need information from both modalities when processing complex settings and if that is true any auditory–visual imbalance in multisensory settings should produce some difficulties which is also what the results show. The lack of correlation between the inverted score and social rigidity in the male group signifies that it is mostly a visual dominance that will affect the language process in males which again is in line with the research mentioned above, claiming males to be more reliant on auditory information in the process of language (Burman et al., 2008; Koles et al., 2010; Ross et al., 2015).

In the female group, a couple of non-significant trends were also seen between a visual dominance in Focus and difficulties with Social Communication and Inattention. Since the correlations are seen in the measurement of Focus, just as in the male group, again one can speculate if those are represented by females being more of the ASD male phenotype.

The result of our study supports the belief of a female phenotype of autism portrayed in form of an extreme female brain making it easier to process unisensory information in case of a sensory disturbance. This could very well be considered as females being biologically protected from ASD as some claim them to be (Baron-Cohen et al., 2011;

Werling and Geschwind, 2013; Werling, 2016); however, one would think that a protection would mean females also have less rated problems within social responsiveness which is not the case. The question we therefor need to ask is whether a unisensory processing advantage is in fact an advantage in a modern complex society of today? As it seems, an auditory–visual processing *advantage* may very well be the downfall in an assessment procedure, allowing female patients to pass at subclinical levels, despite showing an equal or sometimes even higher degree of difficulties than ASD males (Hanley, 2016; Beggiato et al., 2017; Lai and Szatmari, 2020).

Our study showed only one significant gender difference regarding the IVA-performance (Scale of Maintenance) even if the females produced higher scores in all but one measurement (Visual Elasticity). A higher power might have provided more significant differences; however, it is worth noting that most of the IVA-performances in the female group are still well below the average performance of a norm curve (Figure 1). This is important to acknowledge when discussing if females are underrepresented in ASD or not. Females might not be affected in the same way as males, but it does not mean that they are not affected at all.

The thought of females being protected in less complex social settings, still having difficulties in more complex settings raises several questions. For example, what does the concept of "being protected" include and how do you know when that concept is fulfilled? What does it imply to be able to handle a less complex social setting? Does it mean someone is able to handle a social setting in the same way as a TD person? Or does it mean that someone can adapt in a way that from the outside is perceived as a TD behavior but lacking the ability to account for their own feelings and thoughts, leaving them exhausted and vulnerable to develop psychiatric problems? Previous research of Camouflaging behavior in ASD is supportive of the latter definition rather than the first. Camouflaging strategies, the ability to behave in a seemingly flexible way, are said to blur social difficulties and inadvertently contribute to misconstruing important clinical and eligibility decisions (Hull et al., 2017; Young et al., 2018). The lack of flexibility is said to make the individual exhausted and in risk of developing various depression- and anxiety-related disorders (Rynkiewicz et al., 2019).

In the theory of social motivation, they differentiate between social settings requiring unisensory vs. and multisensory processing and refer to less complex social behavior and more complex social behavior, respectively (Tamir and Hughes, 2018). While less complex social behavior is referred to situations that do not require different perspectives, complex social behavior reflects situations where a person needs to take more perspectives into account before action is taken and therefore requires the integration of information from different modalities (Tamir and Hughes, 2018).

A less complex social setting might then be represented by a situation where the individual can understand what is expected here and now and behave in such a way. In the short run, it is not a problem since everybody can handle to set their own emotions aside occasionally, but in the long run, it will create a problem. For several "less complex social settings" to make sense, the individual must see to the overall perspective and be able to account for their own feelings and thoughts. A more complex setting may then be built up by several less complex settings. In order to uphold a psychiatric wellbeing, the individual need to be able to grasp the overall perspective and understand how to adapt to the more complex social setting of which the "less complex setting" is a part.

The ASD assessment procedure of today has been critiqued by those meaning that it is predominantly focused on male ASD symptoms. This has raised the request for more research of how ASD is portrayed in females (Moseley et al., 2018; Young et al., 2018).

Perhaps another important question to be raised is whether the assessment procedure of today can provide such a complex social setting that might be needed for a female ASD patient to be detected? The Autism Diagnostic Observation Schedule (ADOS-2) used in ASD assessment of today includes a certain number of tasks/questions for the patient to adhere to while the assessor assesses whether the patient is showing proof of autistic behavior or not (Lord et al., 2012). Since an ADOS-2 observation only involves the patient and the assessor, takes about 1 h to implement, and the different tasks are in no way connected to each other, it shows every sign of being a representative of "less complex social settings."

By creating an assessment procedure that provides more complex social settings we might be able to detect females at an earlier stage, reducing their risk of them being severely injured. A missed diagnose will not only prolong the course of disease, but it will also put the patient at risk of developing severe psychiatric symptoms (Rynkiewicz et al., 2019; Sveriges Kommuner och Regioner, 2021) putting an extra burden on society since patients with severe psychiatric unhealthy are less likely to uphold a job and more likely to need psychiatric care (Lanctôt et al., 2013; Bailey et al., 2018).

Conclusion

Our result supports a gender-specific understanding of ASD, suggesting a female auditory processing advantage is of importance in the understanding of why females are considered to be "biologically protected" from ASD. However, the results indicate that the social advantages provided by having an auditory processing advantage are limited to social settings of less complexity. More complex social settings seem to be as difficult to handle for ASD females as they are for ASD males.

The lack of significant group differences regarding social responsiveness indicates both groups show an equal level of social functioning despite the superior auditory processing seen in the female group. We suggest the autism assessment procedures of today need to be reworked to include observations of behavior in settings of higher complexity level to be able to detect the difficulties of patients with a feminine ASD profile. As of today, the female "protective" factor might as well be working as a pitfall for those who "passes" the ASD assessment and are left without a diagnosis.

Strength and limitations

To avoid the DSM-5 criteria possibly screening out children we aimed to reach out to, our design included all children coming for an ASD assessment rather than children already diagnosed. We might still have missed several children since the triaging process also is depending on the DSM-5 criteria of ASD. Another strength of this study is the use of the computerized IVA-test. The children have been exposed to the exact same testing procedure which reduces the risk of the assessor affecting the results. The parental scales are used in the same way as they are used in an ASD assessment, hence eventual problems related to parental differences in rating will mirror the reality of using parental assessments as a diagnostic tool.

This study also has limitations, one being the size of the study. With the possible lack of statistical power in this study, it cannot be excluded that statistical correlations, now displaying trends toward a correlation in some cases, may have provided more clearly, significant results in a larger study sample. Also, in a small study, covariables such as age are difficult to control for. Even though we used age as a control variable in all correlations, the possibility of odd cases skewing the results is much higher in a small population than in a larger size population. We tried to secure this by excluding a couple of IVA-measures that were outliers. The high number of subjects (25%) being excluded from the study due to invalid IVA-results or an inability to go through with the IVA-test is also a matter of concern. Hypothetically these subjects can be sharing a specific autistic trait causing difficulties to succeed with an IVA-test; hence, when excluding a group of subjects with similar behavior, we run the risk of getting skewed results. However, there were about the same number of boys and girls that were excluded, indicating that the same difficulties are present in both genders. The lack of a representation of a specific autistic trait will therefore be seen in both groups. Further, the lack of a measure of the child's socioeconomic status could possibly have helped us understand the parental ratings to a better degree perhaps giving us a better understanding of parental abilities to support their child. We tried to reduce the effect of selection bias by using children from the same socioeconomic area, with an IQ of 85 and above, as well as making it easy to participate, no extra travels were needed. A final limitation worth noting is the IQ-level used as an exclusion criterion. The result of the study can only be related to people with an IQ-level within the normal variation or above.

We believe our study has contributed with a different gender perspective of ASD, showing results that are in line with previous research and have the possibility to add a great deal of understanding of female ASD. Future research should focus on ASD gender differences in audio-visual language processing in social settings of different complexity. Also, there is a need for future research to focus on the ASD assessment procedures which is in need for a radical update to be able to pick up those children that today go undetected.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Regional Ethics Committee in Lund. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

SÅ has designed, collected, and analyzed the material and also written the article. AH and EC-K have been supervising the project, as well as proof read the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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.

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Paper IV

Gender Specific Differences in Audio-Visual Processing Related to Auditory Brainstem Response in Children Assessed for an Autism Spectrum Disorder.

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Abstract

Autism Spectrum Disorder (ASD) is a neurodevelopmental sensory processing disorder characterized by difficulties within social interaction and repetitive and stereotyped behavior. It affects 1-3,5% of the population and has a gender distribution of 1:3 favoring males. Some claim females are naturally protected from ASD, others mean the diagnostic process is discriminating toward females. Lately more focus has been given to the audio-visual temporal processing of children with autism, vital for the developing of language and social abilities. In a previous study we found support for a female auditory processing advantage in children being assessed for ASD enabling communication in less complex social settings.

In this study we aim to proceed our investigation of gender differences in audio-visual sensory processing by including auditory brainstem response (ABR). By measuring the ABR from left and right ear in two different time windows (TM) we hope to find gender specific associations with performance on the Integrated Visual and Auditory Continuous Performance Test (IVA-CPT) confirming ASD females have an auditory processing advantage. We hypothesized gender differences would be seen in unisensory processing reflecting a female processing advantage of unisensory processing. In multisensory processing we hypothesized no gender difference would be seen, indicating more complex sounds are as difficult for both genders to process. Thirtysix patients (IQ>85), 19 females (mean age=13.95 years, SD= 2.094) and 17 males (mean age=12.41 years, SD= 2.917) were recruited in the study. Our assumptions were confirmed. Clinical implications are discussed.

Key words: Autism; ASD; ABR; IVA-2; “audio-visual processing”, “Gender differences”, “child- and adolescents”,

Introduction

Autism Spectrum Disorder (ASD) is a set of heterogeneous neurodevelopmental conditions characterized by difficulties in social communication and restricted, repetitive behavior and interests (American Psychiatric Association, 2013 [APA]). ASD affects around 1-3.5 % of the population (Sayal et al., 2018; Chiarotti & Venerosi, 2020; Saito et al., 2020) and has a 1:3 male dominance (Loomes et al., 2017; Chiarotti & Venerosi, 2020; Saito et al., 2020).

Different theories have been suggested to explain the male predominance in ASD, some meaning the double set of x-genes makes females “naturally protected” from ASD (Baron-Cohen et al., 2011; Werling, 2016) others claiming a lack of clinical knowledge about female ASD are causing the skewed numbers (Werling & Geschwind, 2013; Moseley, Hitchiner & Kirkby, 2018; Young, Preve & Speranza, 2018).

From the perspective of social communication, there are clinical support for both theories. It is well established that Typically Developed (TD) females are superior in language development (Krizman, Bonacina & Kraus, 2020; Xu et al., 2020; Ramos-Loyo et al., 2022). In TD adults, females have shown to have an auditory tonal processing advantage, whereas TD males have shown to have a visual spatial and motion processing advantage (McGivern et al., 2019). These gender differences have been seen in as young children as newly born, providing females with a lead in the development of language (Alexopoilos et al., 2022).

In the normal population these differences are often very small and decreases with age whereas in those on the 10th percentile and below the differences are much more prominent, males being more than twice as likely to be diagnosed with a language disorder (Wallentine, 2020). As a contrast, the male predominance is ASD is mainly related to the group of High Functioning (HF), those having an Intelligence Quotient (IQ) of 75 and above whereas in the group of those on the 10th percentile and below the gender differences are not as prominent (Yeargin-Allstopp et al., 2003; Brugha et al., 2016; Baio et al., 2018).

Assuming the male prevalence in ASD is related to a language processing advantage in females we would expect to see the same gender distribution pattern in ASD as in language disorders. However, since that is not the case some argue we are failing in detecting ASD in HF females (Moseley et al., 2018; Young et al., 2018).

The age of receiving an ASD diagnosis has shown to be positively related with a verbal IQ of 70 and above in both genders, but far stronger in girls (Salomone et al., 2016; McDonell et al., 2021), leaving females more vulnerable for a prolonged disease course and in risk of developing more severe psychiatric symptoms (Rynkiewicz et al, 2019). There are also concerns raised around the fact that in subjects with ASD, both genders show an equal number of impairments in social understandings still differing in social behavior, leaving females less likely to meet the diagnostic criteria of ASD (Hiller, Young & Weber, 2014; Rynkiewicz et al. 2016; Dean et al., 2017; Parish-Morris et al., 2017; Ratto et al. 2018; Cola et al., 2020).

Camouflaging

"Camouflaging" describes the ability to imitate social behavior and meet social demands despite having social communication deficiencies. It is predominantly seen in ASD females and is said to make the behavior almost indistinctive from normal behavior, leaving many females undetected in clinical assessments (Hull et al, 2017; Young et al. 2018; Hull et al., 2021). The use of camouflaging strategies requires some knowledge of social communication, however, the individuals' inability to be fully flexible leaves the person exhausted and in risk of developing various depression- and anxiety related disorders (Rynkiewicz et al., 2019).

Sensory processing in ASD

The view of ASD as a sensory processing disorder has gained more interest over the years (Robertson and Baron-Cohen, 2017; Posar and Visconti, 2018; Zhou et al., 2021). Sensory processing refers to the ability to detect, interpret, regulate, and respond to sensory information (Little, 2018). Sensory processing difficulties are defined as hyper- and hypo-sensitive responses to sensory information (Marco et al., 2011; Robertson and Baron-Cohen, 2017). Sensory processing difficulties are reported in more than 96% of children with ASD (Marco et al., 2011; Robertson and Baron-Cohen, 2017) and has shown to affect the individuals' ability to adapt in various situations (Neufeld et al., 2021).

Temporal-processing is the term used when describing the integration of two contemporary sensory inputs into an adequate global representation (Wallace and Stevenson, 2014) whereas Temporal Binding Window (TBW) describes the period of time allowed to pass between two exposed stimuli in order for them to be perceived as connected.

The Sensory Integration Theory (SIT; Ayres, 1979) declares the importance of sensory integration for the human development. It separates between Unisensory and Multisensory integration, the first referring to the integration process of one or more stimulus from one sensory modality such as auditory *or* visual stimuli whereas the second refers to the integration and process of stimuli from different modalities, such as auditory *and* visual stimuli.

Research of unisensory temporal processing in ASD has showed varied results, some indicating that a larger TBW is seen in ASD others that it is smaller (Zhou et al., 2018; Meilleur et al., 2020). The studies are hard to compare since they refer to different kind of stimuli and different age groups but there seem to be a factor of age involved interpreted as children with ASD are delayed in the developing of temporal processing (Kwakye et al., 2011). Children and youths with ASD have showed a reduced audio-visual temporal acuity, mostly affecting the audio-visual speech stimuli (Bebko et al., 2006; Foss-Feig et al., 2010; Kwakye et al., 2011; Zhou et al., 2021).

In regard to research in multisensory processing in children with ASD focus has mostly been directed towards audio-visual temporal processing and its effect on language development (Ocak et al., 2018; Tanigawa et al., 2018; Jain et al., 2020; Meilleur et al., 2020). However, social abilities (Wallace and Stevenson, 2014) and global perspectives (De Niear et al., 2018) have also gained some attention.

Sensory integration difficulties are often caused by one sensory modality responding quicker or stronger than the other causing a blockage of other sensory information resulting in a lack of information when trying to understand the global perspective (Shams, Kamitani & Shimojo, 2000; Alais & Burr, 2004).

Children with ASD often show an enhanced sensory perception (Marco et al., 2011; Robertson and Baron-Cohen, 2017) and there is evidence for specifically *visual acuity* standing out as enhanced (Jolliffe and Baron-Cohen, 1997; Joseph et al., 2009; Kaldy et al., 2016). Since a superior visual acuity is also seen in the TD adult male population (McGivern et al., 2019; Siedlecki et al., 2019; Thornton et al., 2019) some have chosen to see ASD as a form of "extreme male brain syndrome" (Asperger and Frith, 1991; Baron-Cohen et al., 2011). This theory is supported by a recent study from 2021, showing a larger brain size can be related to ASD in both genders which in turn has shown to be a direct effect of typical male behavior (Van Eijk & Zietsch, 2021). Having in mind that 80% of included subjects in ASD studies from the past 10 years are of male gender (Feldman et al., 2018) we must interpret such results with care. Also, using already diagnosed children provides biased data since included children must fulfill the criteria for an ASD diagnosis which have shown to be biased towards the male phenotype of ASD (Werling & Geschwind, 2013; Moseley, Hitchiner & Kirkby, 2018; Young, Preve & Speranza, 2018, Rynkiewicz, Janas-Kozik & Slopień, 2019).

The theory of Social Motivation defines a complex social setting as a situation where multiple sensory modalities need to be integrated for the individual to grasp an adequate understanding. Less complex social settings are defined as situations where only one source of sensory information needed to be processed (Tamir and Hughes, 2018). In a previous study our research team investigated ASD gender differences in audio-visual processing related to Social Responsiveness. In the female group an auditory advantage was associated with less rated problems in Socal Communication in unisensory processing whereas in multisensory processing a superior Auditory Agility was associated with a higher number of rated problems within Social Awareness (Åkerlund, Håkansson, Clasdotter-Knutsson, 2023).

The Integrated Visual and Auditory Continuous Performance Test (IVA CPT; Sandford and Turner, 2000) is a continuous performance task in form of a computerized test. Using both auditory and visual stimuli, IVA measures attention in various ways and provides both unisensory and multisensory audio-visual processing measures.

Extreme male brain versus extreme female brain.

According to the empathizing-systemizing (E-S) theory of psychological sex differences male brains are oriented towards analyzing and predicting a behavior of a system whereas female brains are oriented towards analyzing and predicting people's mental states (Baron-Cohen, 2003). They categorize people into five groups by measuring the dimensions of empathizing and systemizing. An extreme Type E represent those with an extreme ability for empathizing and is more common in females, whereas Extreme Type S represent those with an extreme ability for systemizing and is more common in males (Greenberg et al., 2018). In studies of ASD the Extreme Type S is common in both genders whereas the Extreme Type E is highly unusual in both genders (Wang et al., 2019). In 2018, Floris et al. presented an alternative approach to the "extreme male brain theory", suggesting that the "extreme male brain syndrome" can only be said to describe a subgroup of the ASD population, proposing different parts of the brain can be related to different aspects of male and female behavior, hence ASD can also be portrayed as an "extreme female syndrom" affecting both males and females. Supporting evidence for this theory is found in a study from 2017 (DiCriscio and Troiani, 2017) showing an enhanced visual ability is only associated with ASD symptoms in males. Considering adult females in the normal population have shown to be superior in auditory acuity (McGivern et al., 2019; Siedlecki et al., 2019; Thornton et al., 2019) one could assume that an extreme female brain would show the same characteristics.

Language processing

According to the dual stream theory (Hickok and Poeppel, 2007; Rauschecker and Scott, 2009; King, Hammond-Kenny & Nodal, 2019) the process of speech is depending on auditory and visual information being processed in two streams called the Ventral- and Dorsal Stream (VS/DS). As the VS is sorting out relevant auditory and visual information for further processing while blocking nformation considered to be irrelevant (Zeki, 2016; Hickok & Poepple, 2004; Mostert-Kerckhoffs, 2015) the DS prioritizes all incoming stimulus rather than making assessment of what to pay attention to (Sininger & Bhatara, 2012).The streams are interdependent, passing on and blocking information between each other (Zeki, 2016; Hickok & Poepple, 2004; Mostert-Kerckhoffs, 2015; Fu et al. 2020). The VS has a left ear advantage and is more connected to the right hemisphere (Sininger & Bhatara, 2012) and the

DS has a stronger connection to the left hemisphere and has a right ear advantage (Sun, Cai & Lu, 2015). Auditory stimuli presented to the right ear is therefore primarily processed in the left hemisphere and vice versa.

The two hemispheres differ in specialization. The left hemisphere dominates in the language processing (Vingerhoets, 2019; Rasmussen and Milner, 1975) it is analytical and uses the past and future for critical thinking (Corballis, 2012). The right hemisphere processes present non-verbal information and is concrete in thinking (Corballis, 2012). While the left hemisphere is important for a global understanding the right hemisphere has shown to be important for the process of prosody (Buchanan et al., 2000; George et al. 1996). A right ear advantage is therefore seen in speech perception and a left ear advantage for tonal stimuli (Kimura, 1961, 1963, 1964, 1973).

When it comes to language processing, specific gender differences have been noted. Males have a more lateralized language process than females, favoring auditory information in the left hemisphere (DS) whereas females uses bilateral processing and bimodal information to a much higher degree than males (Koles et al. 2010).

A lesion in the VS causes auditory comprehension deficits (Kümmerer et al., 2013) whereas lesions in the DS are associated with repetition deficits and stereotyped speech (Kümmerer et al., 2013). Several impairments in the VS has been noted in people with ASD (Greenway & Plaisted, 2005; Chan & Naumer, 2014), making it difficult to understand the overall meaning of a text or social interaction as well as making them being overloaded with stimuli (Robertson & Baron-Cohen, 2017; Gomot & Wicker, 2012). In some cases where the DS is impaired, the VS has showed to work as a compensatory function with suboptimal performance as a result (López-Barroso et al., 2011).

The brainstem

The brain stem is the first receiver of acoustic information and can be divided into five different parts. In the Auditory Nerve (AN) information is received and passed on to the Cochlear Nucleus (CN) where the first stage of processing takes place. In the CN information is sorted out and passed on to the Ventral (VS) and Dorsal (DS) Stream which in turn transports the information to the Superior Olivary Complex (SOC). The SOC converges binaural inputs and then passes it on to the Lateral Lemniscus (LL). The LL is innervated by the contralateral DS and have the ability to choose what information will be passed on to the Inferior Colliculus (IC) by inhibitory and excitatory inputs. Besides acoustic information being integrated in the IC multisensory integration also takes place (Peterson, Reddy & Hamel, 2020; Pickles 2015; Eggermont, 2019a).

Auditory Brainstem Response (ABR) is a method used for measuring aberrant auditory activity in the brainstem (Eggermont, 2019b). The most commonly used measures in ABR is “speed of transmission” as a transmissional delay signifies a slower processing speed, however amplitude are sometimes also used as a low or lack of amplitude signifies difficulties in hearing. A high amplitude on the other hand signifies an auditory sensitivity in the earlier part of the brainstem and further into the brainstem it represents a high activation in the integration of sensory stimuli (Pickles, 2015; Peterson, Reddy & Hamel, 2020).

Findings on pathological brainstem activity in children with ASD are highly inconclusive but two main trends seem to be consistent, deviances occur mainly at higher levels of auditory processing further into the brainstem and are more common in younger than older children (Pillion, Boatman-Reich & Gordon, 2018). More specific findings are seen in the associations between a delayed ABR transmission and language developmental deficiencies as well as ability to adjust behavior (Banai et al., 2009; Miron, Beam & Kohane, 2018; Ramezani et al., 2019).

More specific findings have shown a higher amplitude in the area of the AN in children with ASD, indicating a higher sensibility to sound (Santos et al. 2017; Vlaskamp et al. 2017). In the area of SOC as well as in IC a lower amplitude has been seen indicating processing difficulties (Smith et al. 2009; Baldwin et al., 2016). The area of LL has also shown a lower amplitude than in TD indicating a desynchrony in the converging of multiple sensory information (El Moazen et al., 2020).

Aim and hypothesis

The aim of this study is to investigate whether possible specific gender differences in sensory processing can be related to brainstem activity in children and youth assessed for ASD. Our hope is to gain a better global understanding of the gender differences associated with ASD diagnoses and see whether there might be relevant to also include an extreme female brain syndrome as part of ASD. We hope to contribute with an understanding as to why females go undetected in the ASD assessment of today. We also believe gender differences in sensory processing is an important area to highlight especially since there are, as far as we have been able to see, very few studies within the field of ASD touching this area with gender differences in mind.

By using auditory and visual unisensory versus multisensory measurements we aim to look for associations with ABR at different levels of sensory processing in the brainstem. We made the following assumptions: ASD is portrayed as either an extreme male-brain syndrome or an extreme female-brain syndrome. A superior sensory modality will block out other kind of sensory information. Hence, ASD males, having a lateralized language process mostly relying on auditory information will be showing language processing difficulties in both unisenory and multisensory processing. Females, using auditory and visual information to a higher degree in language processing will not be as affected in unisensory processing. However, in multisensory processing where information from both sources is needed ASD females will be as affected as ASD males.

We hypothesized that in the male group a negative association would be seen between ABR and the measure of visual unisensory processing as well as audio-visual multisensory processing in both areas of the brainstem indicating the male visual enhancement causes them processing difficulties in all levels of processing. In the female group we hypothesized ABR would be positively correlated with auditory unisensory processing in both parts of the brain, indicating an enhanced auditory sensory will cause no processing difficulties in unisensory processing. In multisensory processing we hypothesized that an auditory dominance in the female group would show no associations with the ABR in the CN/SOC area indicating they use compensatory strategies when faced with a lack of visual information. In the LL/IC area of the brainstem we assumed an auditory dominance would be negatively associated with ABR in the female group indicating a lack of information due to impairments in temporal acuity affecting the integration of multiple stimuli.

Method

Subjects

Parts of the method has previously been described in another article (Åkerlund, Clasdotter-Knutsson & Hakansson, 2023) since the same material gave rise to two articles. To avoid assessment biases in the recruiting of subjects all patients being referred to the clinic for an autism assessment were invited to participate in the study. The patients were triaged either through a screening procedure done by clinical psychiatric nurses using the structured Brief Child and Family Phone Interview (BCFPI) (Boyle et al. 2008; Cunningham et al. 2008) or by referral from other clinical professionals. Fifty-seven patients between the ages of 7-17 (29 females, mean age 12.97 years, SD 3.168 and 28 males, mean age 11.71 years, SD 2.904) were recruited from the child and youth psychiatric out-patient clinic in Eslöv. The patients were from the same socioeconomic area, the communities of Eslöv, Höör and Hörby where the median wage is around 74% of the Swedish median wage and the unemployment rate is around 20%, compared to 9.4% for all of Sweden (Statistiska Centralbyrån, 2021).

To be included in the study a verbal as well as fluid intelligence quotient of 85 and above was required which was measured with the Wechsler Intelligence Scale for Children (WISC-V; Wechsler, 2003). Exclusion criteria were a diagnosis of any hearing disabilities including tinnitus, difficulties communicating in Swedish, and any form of substance abuse. Four girls and seven boys already had a diagnose of

ADHD and were included in the study unmedicated. The remaining 46 children had no prior neuropsychiatric diagnosis. Nine patients (6 females/ 3 males) were excluded due to getting an invalid IVA result. Four male participants interrupted their IVA testing due to frustration created by the test. One female participant interrupted the ABR testing due to having difficulties handling the sound stimuli. Six outliers were identified amongst the ABR (2 females/ four males) and one outlier was identified in the IVA test (female). The remaining subjects were 19 females (mean age=13.95 years, SD= 2.094) and 17 males (mean age=12.41 years, SD= 2.917) (Table 1).

A written informed consent was obtained from all patients and their parents. The study was approved by the regional ethics committee in Lund (Dnr: 2016/964).

Table 1. Group statistics

	Females	Males
Recruited	29	28
Average age (SD)	12.97 (3.168)	11.71 (2.904)
Excluded	7	7
Outliers	3	4
Remained	19	17
Average age[a] (SD)	13.95 (2.094)	12.41 (2.917)
WISC-V intelligence quotient	>85	>85

Tests

Auditory Brainstem Response. The ABR -test and its procedure has been described by our team in two previous articles (Claesdotter-Hybinette et al. 2016; Claesdotter-Knutsson et. al. 2019). ABR was measured using SensoDetect BERA (Brainstem Evoked Response Audiometry) A1000. The sound stimuli are presented via TDH-50P headphones with Model 51 cushions (Telephonics, Farmingdale, New York, USA). Presentations are made binaurally with the stimuli in phase over headphones. Four different sound stimuli (Figure 2) are presented during a 30 min period. The first sound stimuli consist of square-shaped click pulses (0.136 milli second (ms) duration, including 0.023 ms rise and fall; 192 ms interstimulus interval. The second sound stimuli have a filter, allowing only pulses over 3000hz to pass. The third and fourth stimulus are forward respectively backward masked sounds, having a 12.3 ms gap from masker to click pulse. A 1500-Hz Butterworth low- pass filtered white noise, with 15 ms duration (including 0.4 Ms rise and fall times) is used as masker for both forward and backward masking stimuli. All stimuli were constructed using MATLAB Signal Processing Toolbox (The MathWorks, Inc., Natick, Massachusetts, USA) and stored in a flash memory in the SensoDetect® BERA system. The click pulses are repeated until a total of 1024 accepted evoked potentials has been collected for each sound stimulus. Transistor-transistor logic (TTL) trigger pulses coordinate the sweeps with the auditory stimuli. With a correctly timed TTL pulse, all ABR representations will be synchronized. Sound levels were calibrated using a Bruel & Kjaer 2203 sound level meter and Type 4152 artificial ear (Bruel & Kjaer S&VMeasurement, Naerum, Denmark). The acoustic output from the earphones corresponded to SPL: 80 dB HL or 109 peSPL (peak equivalence). The collected evoked potentials for each sound stimulus from each ear of each individual was imported to Microsoft Excel (Microsoft Corp, Redmond, WA, USA) and analyzed using SensoDetect® BAS. The output is generated by a wave pattern over the time of 10 milliseconds (ms). Seven waves appear, of which the first five are of importance for the brainstem (Figure 1). Placing the electrodes on the mastoid as is done in this study, gives a CAP amplitude around 0.1-0.3µV (Eggermont, 2019b). Test time: 30-40 minutes.

Integrated Visual and Auditive Performance Test (IVA-2 CPT). The IVA-2 test is a computerized continuous performance test integrating visual and auditory sensory processes (Appendix 1). The test has been described by our team in a previous study (Åkerlund et al. 2023). The visual stimuli are presented on a computer screen while the auditive stimuli are presented via headphones equipped with ear cushions. The output consists of 20 different basic measurements, each providing a combined visual-auditive measure as well as independent measurements of auditive- and visual EF. The basic measurements are then used in the construct of different scales. The four primary scales are attention, sustained attention, response control and symptomatic problems. Eight sub scales provide, beside a combined score also separate scores for visual and auditory function, enabling explorations of the balance between the modalities. The test is made to produce errors such as omissions (i.e. inattentiveness), errors of commission (i.e. impulsiveness) and idiopathic errors enabling a better understanding of the deviant result. The Validity Scales control for lack of comprehension, unwillingness to participate or other misconduct behavior. "The IVA-2 profile is summarized quantitatively through standard scores that are familiar to most clinical practitioners" An IVA-testing not passing the validity scales shows no results. The test starts when the computer has registered a proper response pattern in the practice part. The main test consists of either a written number 1 or 2 on the computer screen or a voice reading "one" or "two". The computer voice tells the participants when they are to click on the mouse and when they are not to. Test time: 15 minutes.

Procedure

The ABR tests were performed and administered by trained staff. The participants, seated in a comfortable chair were given a neck brace to ensure the neck was fixed and relaxed during testing. Two reference electrodes were placed on the mastoid bone behind the left and right ear, respectively, with two active electrodes and one ground electrode placed on the forehead. The transmission sites were washed with disinfectant. Abrasive paste was used to fasten the electrodes. Absolute impedances and inter-electrode impedances were measured before and after the experiments to verify that electrode contact was maintained (below 5000 Ω). Earphones were fitted to cover both ears and the subjects were instructed to turn off their mobile phones and relax with their eyes closed. The test required no active participation.

Wave amplitude was measured from the lowest point of the wave to the top; hence the average amplitude of a certain period equals the standard deviation (SD). The SD of left and right ABR were measured in two predefined time windows (TW I: 2.5-4.0 ms and TW II 4.5-6.5 ms) representing the CN/SOC as well as LL/IC area of the brainstem respectively. All registered ABR-potentials for each ear and for each of the four sounds in each of the two TW were then copied and pasted into a SPSS-data sheet for each subject. The standard deviation (SD) of wave amplitude within each of the four sounds was used when calculating the average SD for each ear in respective TW for each patient resulting in four different measurements. Left and right ear SD in time window I and left and right ear SD in time window II (Table 2).

Table 2. Output of ABR measures.

		TW I 2.5 – 4.0 ms	TW II 4.5 - 6.0 ms
Area		CN/SOC	LL/IC
Output	LE	SD LE	SD LE
	RE	SD RE	SD RE

Note. LE=Left ear. RE=Right ear. SD=standard deviation (amplitude).

The IVA-tests were administered by trained staff. Participants were seated on a comfortable chair, adjusted to give the patient a comfortable and easy-to-reach position. The participant was presented the auditive stimuli through tight fit headphones to reduce ambient noise that might be needless distracting. The test room was empty, and the windows were covered up to shut out possible disturbing visual stimuli outside. The participants were presented with a session of 2 x 1 minute of responding to auditive and visual stimuli one at a time. After that a training session of 1.5 minutes started where the patient got to practice responding to both kinds of stimuli in a random order. The test starts when the computer has registered a correct answering pattern and then continues for another 13 minutes. Elasticity, Acuity, Focus and Agility was uses as unisensory measures. The Scale of Compentence and the Scale of Maintainability was uses as measures of a more complex unisensory measure. Each scale is built upon different aspects of the same sensory modality (Table 3).

Table 3.

Scale of Competence (High demanding tasks)		Scale of Maintainability (Low demanding tasks)	
Auditory	Visual	Auditory	Visual
Prudence		Reliability	
Steadiness		Acuity	
Stability		Dependability	
Quickness		Swiftness	

As multisensory measures the difference score between audio-visual processing was used in the measures of Elasticity, Acuity, Focus and Agility.

Data analysis

Analyses were done using the Statistical Package for the Social Sciences (SPSS) (IBM Corp. 2019). A significance level of 0.05 was used in all tests. Before further analyzing, the data was screened for unusual cases above 3 x the interquartile range. The descriptive statistics were used for calculating group means, and standard deviations. The Kolmogorov-Smirnov test was used to test for normal distribution whereas the independent samples t-test was used to calculate group mean differences in age. Levene's test of Variance was used to explore homogeneity of variances (Table 4).

An analysis of covariance (ANCOVA) with a Bonferroni adjustment for multiple comparisons using *Age* as a covariant, was made to examine group differences within the a priori chosen IVA measurements of Elasticity, Acuity, Focus, Agility, Scale of Competence and Scale of Maintainability. The Pearson correlation test was used when determining relationships between the selected IVA-measurements and ABR performance. The results are presented in r-values between -1 to +1. A positive value indicating a positive correlation, and a negative value indicating a reverse relation. A value around 0 indicates no correlation

The audio-visual difference score, used in the analysis of multisensory processing were calculated by subtracting the visual performance score from the auditory performance score leaving a positive score when having an auditory dominance and a negative score when having a visual dominance. The difference scores used were taken from the same measurements used in the unisensory processing, hence the difference score of Elasticity, Acuity, Focus and Scale of Agility were analyzed.

Table 4. Estimated mean scores.

Variable	Sex	Mean[a]	Std Error
Left Ear SD TW I	Females	.070	.006
	Males	.080	.006
Right Ear SD TW I	Females	.072	.007
	Males	.074	.008
Left Ear SD T W II	Females	.080	.006
	Males	.082	.007
Right Ear SD TW II	Females	.081	.007
	Males	.086	.007
Auditory Agility	Females	103.025	3.566
	Males	107.325	3.780
Visual Agility	Females	94.908	3.073
	Males	99.279	3.257
Auditory Elasticity	Females	90.703	5.815
	Males	82.567	6.163
Visual Elasticity	Females	83.505	6.953
	Males	83.671	7.370
Auditory Acuity	Females	87.169	7.365
	Males	78.870	7.806
Visual Acuity	Females	89.723	6.962
	Males	78.663	7.379
Auditory Focus	Females	82.581	4.534
	Males	79.939	4.805
Visual Focus	Females	92.916	4.704
	Males	92.505	5.024
Auditory Competence	Females	84.073	6.237
	Males	78.448	6.610
Visual Competence	Females	79.226	6.412
	Males	78.806	6.796
Auditory Maintainability	Females	90.826	7.438
	Males	75.254	7.884
Visual Maintainability	Females	83.413	7.003
	Males	61.833	7.423

Note. a. Covariates appearing in the model are evaluated at the following values: Age= 13.22.

Results

Two females and four male outliers were identified in the ABR another female outlier was identified in the IVA, which were all excluded from the study. T-test did not come out significant regarding the variable of age although a trend towards a significancy was seen (sig. 2-tailed= .076) with the female group showing a mean difference of 1.536 more years than the males (Table 5). For this reason, we used age as a covariable in all correlations made.

Table 5. Independent Samples Test

Levene's Test for Equality of Variances				t-test for Equality of Means		
		F	Sig	t	df	Sig. (2-tailed)
Age	Equal variances assumed	2.231	.137	1.829	34	.076
	Equal variances not assumed			1.796	28.731	.083

Table 6. ANCOVA

Levene's Test of Equality of Error Variances					Pairwise Comparisons		
	Sex	Mean[a]	F	Sig.	Mean difference (F-M)	Std. Error	Sig.[b]
Auditory Maintainability	Female	90.826	6.885	.013	15.572	11.089	.170
	Male	75.254			-15.572	11.089	.170
Visual Maintainability	Female	83.413	1.554	.221	21.580	10.440	.047
	Male	61.833			-21.580	10.440	.047

Note. a. Covariates appearing in the model are evaluated at the following values: Age= 13.22.
b. Ajustments for multiple comparisons: Bonferroni.

Levene's test of Equality of Error Variances showed a positive outcome in the case of Scale of *Auditory Maintainability* (sig=.013) and trended toward being positive in the case of *Auditory Acuity* (sig.=.079) (Table 6). The ANCOVA showed one significant difference between the groups, in the case *Visual Maintainability* (.047) where the female group had a 21 point higher average score than the male group (Table 6).

In unisensory processing the male group showed a negative association between *Visual Acuity* and ABR activity in left ear (r=-.602, p=.014) and in right ear (r=-.555, p=.026) in TW I. In TM II *Visual Acuity* showed a negative association with right ear ABR activity (r=-.527, p=.036) (Table 7). The complex unisensory measures showed no association at all in the male group (Table 8) and neither did the multisensory measurements (Table 9).

In the female group a negative association was found between *Auditory Acuity* and left ear ABR in TW I (r= -.478, p=.045). Two positive associations were seen between Auditory (r= .513*, p=.030) versus Visual Agility (r= .565, p=.015) and ABR activity in right ear ABR in TW I. The female group showed no associations between unisensory processing and TW II (Table 7). The complex unisensory measures showed no significant associations with ABR. In multisensory processing a Visual Dominance in Agility was associated with lower ABR activity in the left ear of TW II.

Table 7. Correlation table for unisensory measures and ABR activity in TW I and II.

	FEMALES				MALES			
Area of brainstem	TW I CN/SOC		TW II LL/IC		TW I CN/SOC		TW II LL/IC	
Ear	LE	RE	LE	RE	LE	RE	LE	RE
Auditory Elasticity	-.377	.176	-.215	-.186	.019	.264	.017	.228
Visual Elasticity	-.295	.341	-.077	-.013	-.073	.502* (.048)	.003	.282
Auditory Acuity	-.478* (.045)	.216	-.334	-.386	-.162	-.197	-.214	-.192
Visual Acuity	-.292	.073	-.351	-.229	-.602* (.014)	-.555* (.026)	-.442 (.087)	-.527* (.036)
Auditory Focus	-.061	-.047	.261	.206	-.183	.295	-.103	-.181
Visual Focus	-.135	.088	.092	.021	-.490 (.054)	.200	-.275	-.014
Auditory Agility	-.228	.513* (.030)	-.295	-.211	.503* (.047)	.030	.237	.052
Visual Agility	-.100	.565 (.015)	-.046	-.063	.257	-.199	.095	-.134

Table 8. Correlation table for complex unisensory measures and ABR activity in TW I and II.

	FEMALES				MALES			
Variable	TW I CN/SOC		TW II LL/IC		TW I		TW II	
Ear	LE	RE	LE	RE	LE	RE	LE	RE
Auditory Scale of Competence	-.391	.267	-.215	-.258	-.259	.061	-.321	-.095
Visual Scale of Competence	-.216	.278	.086	-.051	-.440 (.088)	.159	-.158	.032
Auditory Scale of Maintainability	-.449 (.062)	.320	-.369	-.348	-.268	-.156	-.298	-.151
Visual Scale of Maintainability	-.333	.106	-.195	-.116	-.414	-.076	-.316	-.143

Table 9. Correlation table for multisensory processing and ABR activity in TW I and II.

	FEMALES				MALES			
Variable	TW I CN/SOC		TW II LL/IC		TW I		TW II	
Ear	LE	RE	LE	RE	LE	RE	LE	RE
Elasticity Difference Score	.020	-.235	-.089	-.136	.115	-.322	.016	-.086
Focus Difference Score	.121	-.128	.174	.196	.334	.052	.188	.168
Acuity Difference Score	-.095	.105	.044	-.094	.274	.206	.100	.205
Agility Difference Score	-.341	.162	-.590 (.010)	-.368	.148	.155	.091	.123

Table 10. Correlation table for unbiased multisensory processing meausres and ABR activity in TW I and II.

	FEMALES				MALES			
Variable	TW I CN/SOC		TW II LL/IC		TW I		TW II	
Ear	LE	RE	LE	RE	LE	RE	LE	RE
Elasticity Difference Score	.194	-.044	-.002	-.026	-.208	-.181	-.223	-.239
Focus Difference Score	.079	.249	.143	-.113	.056	.123	.185	.113
Acuity Difference Score	.345	-.148	.286	.200	.232	.404	.174	.460 (.073)
Agility Difference Score	-.206	-.099	-.476 (.046)	-.293	.027	.145	-.022	.089

Discussion

To gain a better understanding of gender differences in ASD we explored auditory and visual unisensory versus multisensory processing and its relation to brainstem activity in areas representing different levels of sensory processing. We hypothesized a female auditory enhancement would be associated with a higher ABR activity in both TW I and TW II in unisensory processing confirming a unisensory processing advantage in female ASD. The measures of multisensory processing we hypothesized would show association with lower ABR activity in TW II only indicating ASD females are having processing difficulties in multisensory processing. In the male group we hypothesized an enhanced visual ability would show association with a lower ABR activity in both unisensory as well as multisensory processing in both TW I and TW II as an indication of them being affected in all levels of sensory processing.

Our hypothesis of gender specific audio-visual processing was confirmed although not always portrayed in the way we predicted. In the female ASD group, a better performance in *Auditory Acuity* was associated with lower activity in left ear ABR in the CN/SOC area of the brainstem. We hypothesized an “extreme female brain” would have the same, but more pronounced processing characteristics as TD females. Considering TD females have shown to be superior in processing of tonal stimuli in the VS (McGivern et al., 2019; Siedlecki et al., 2019; Thornton et al., 2019) our results are in line with our hypothesis. Since no control group is used in this study, we cannot say their ability is more pronounced compared to TD females, however, the fact that it is associated with a lower ABR activity indicates it causes some form of processing difficulty (Mansour & Kulesza, 2020). As a better *Auditory Acuity* is highly associated with speech comprehension (Ayessa, Penn & Wingfield, 2019) it is possible that is providing ASD females with some advantage compared to ASD males. However, one might ask why *Auditory* Acuity then is associated with a lower activity in the brainstem?

As sensory processing difficulties are often caused by one sensory modality reacting faster or stronger than others, causing a blockage of information from other sensory modalities (Shams, Kamitani & Shimojo, 2000; Alais & Burr, 2004) it is possible that the lower ABR activity is caused by a lack of other kinds of sensory information.

We hypothesized a unisensory processing advantage in females would be associated with higher ABR activity, but in hindsight it seems reasonable that it is associated with a lower activity. However, we cannot say what kind of information is blocked out considering ABR is only responding to auditory information. Considering the more complex unisensory measures: the *Scale of Maintainability* and *Scale of Competence*, consisting of several aspects of auditory functioning, did not show any significant associations to ABR it indicates that specific auditory abilities have different impact on sensory processing. *Auditory Acuity* on its own is a better predictor of ABR activity in the left ear of TW I in female ASD, compared to a wider measure of auditory functioning. Theoretically, that means there is a possibility that an enhanced *Auditory Acuity* might also be blocking out other kinds of auditory information perhaps information that will be needed in more complex language processing.

In the female group two positive significant associations were also seen in TW I. ABR in the right ear of TW I showed positive associations to both *Auditory* and *Visual Agility*. Considering females use bimodal information in language processing to a higher degree than males (DiCriscio & Troiani, 2017) the association to both *Auditory* and *Visual* aspects seem logical.

Agility is a measure of rapid processing (Sandford and Turner, 2000). In a study from 2017 deficits in rapid auditory processing are associated with clinical assessments of receptive language impairments in ASD children (Foss-Feig et al., 2017). As ABR activity gets higher the better the *Agility* it indicates this might be seen as a language processing advantage in unisensory processing.

In TW II no associations were seen with measures of unisensory processing, indicating that in females a loss of information in TW I of unisensory processing can be compensated for. It is known that as sensory information is passed on for processing further up in the brainstem the streams interact with each other and exchange information (Zeki, 2016; Hickok & Poepple, 2004; Mostert-Kerckhoffs, 2015; Fu et al. 2020).

In the measures of multisensory processing an interesting find was seen. In the female group a *Visual* dominance *in Agility* was associated with lower ABR activity in left ear of TM II. No associations were seen with any of the multisensory measures in TW I. The lack of correlation in TW I was predicted since the earlier parts of the brainstem only processes auditory information and therefore will have limited association with a multisensory measure.

As said before deficits in *Auditory Agility* are associated with receptive language impairments in ASD children (Foss-Feig et al., 2017). A *Visual* dominance in *Agility* in the left ear means *Auditory Agility* is blocked which logically would be causing comprehension difficulties. Since previous studies have shown TD males to be superior in visual-spatial information processing in the DS (DiCriscio & Troiani, 2017), one might consider whether this dominant *Visual Agility* seen in the female group should be considered supporting evidence for an *"extrema male brain"* being adequate in ASD females as well. However, the total lack of associations between multisensory measures and ABR activity in the male ASD group, speaks against it.

The multisensory measures in the male group did not come out as we had predicted. We assumed a multisensory measure would be associated with lower ABR activity in both TW I and TW II as a proof of males being affected by a dominant *Visual* ability. An explanation to these results might be found looking at the language processing in males. In the male group, unisensory processing showed a better performance in *Visual Acuity* to be associated with lower activity in both left and right ear of TW I and in left ear of TM II, implies *Auditory* information is being blocked out from both streams. Given male language processing has shown to be more lateral than females, relying mostly on auditory information from the DS (Koles et al., 2010) a blocking of auditory information in both streams must leave males with very little information left to work with. As multisensory measures do not show association with ABR it must mean that a multisensory measure is not relatable with male language processing, most likely because *Auditory* information is blocked out at an early processing stage, leaving males more handicapped than females.

In females only left ear ABR showed a lower activity in relation to an enhanced Auditory Acuity, meaning the DS is left open for receiving information that otherwise would have been blocked out, information that can be picked up by the VS if needed in later processing. This would mean that the Visual dominance in multisensory processing being related to lower ABR activity in the right ear should be specific for ASD females. However, it is difficult to say in why it becomes an obstacle in multisensory processing since the unisensory measures of *Agility* both showed positive associations with ABR, indicating no one is superior to another.

However, considering the ABR sounds are made to resemble language we might consider the *Visual* dominance in Agility to be related to a language processing difficulty. The results are in that case in line with a previous study of sex differences in rapid detection of emotional Facial Expression where females showed to be much faster than males. The reaction time was positively associated with physical response created by the image that was being identified (Sawada et al., 2014). It is impossible to say what causes the other but given that girls have shown a greater need to adapt their behaviour outside of family than have boys (Chapline & Aldao, 2013; Lindbom, 2020) a reasonable guess could be that they use their *Visual Agility* to detect things needing to adapt for, leading to a better developed *Visual Agility*. This is supported by a study of camouflaging behaviours in ASD females, where some ASD females describes their empathy skills as being built up by memorising specific details from each situation almost like building a jigsaw puzzle (Tierney, Burns & Kilbey, 2016).

To make sure our findings were in fact related to a *Visual* or *Auditory* dominance rather than just any audio-visual difference we created an unbalanced difference score by inverting all the negative IVA measurements after the audio-visual subtraction.

In the male group a trend towards a significant association was seen in *Acuity* difference score (r=.460, p=.073) indicating that the higher the difference between auditory and visual Acuity the lower the activity in right ear ABR in TM II. An association is also seen in TM I (r=.404) although not trending toward being significant. These results confirm our previous arguments that an enhanced *Visual Acuity* will block out sound no matter what, an even better *Visual Acuity* will not be blocking off more auditory information as it seems.

In the female group a significant correlation was seen between right ear ABR and Agility, although it was of less significancy compared to the balanced measurement indicating a *Visual* dominance have a better value of explanation.

Summary

To sum it up. Our findings suggest there are specific gender differences in audio-visual processing affecting language processing in both genders. The female more dynamic language processing allows for compensating strategies to be used when a dominating sensory modality is blocking out sensory information in unisensory processing. However, when faced with multisensory processing a Visual dominance in Agility is associated with lower ABR activity in TW II indicating compensating strategies are not as easy to applicate as settings gets more complicated.

Males, having a more rigid language processing will be facing more severe difficulties when an enhanced sensory modality is blocking out information, leaving less possibilities to compensate in both unisensory and multisensory processing.

Theories of social motivation discriminates between “basic social building blocks” and “complex social behavior”. The first refers to reactions regarding “proximal” causes - the immediate response to something close in time, for example an understanding that a smile creates a more socially accepted behavior here and now. The later refers to the person’s ability to evaluate the efforts put into the situation vs the gain received which requires a higher form of cognition (Tamir & Hughes, 2018). Hypothetically, an ASD female would be showing a processing advantage in “proximal” responses, by using compensatory resources. As social contexts get more complex, a higher order of brainstem processing is necessary making it difficult to compensate, leaving females with the same social difficulties as males.

Clinical implications

Our results are in line with previous research showing an Auditory Acuity to be positively related with Camouflaging strategies in girls.

As an enhanced *Auditory Acuity* works as an aiding factor in less complex social settings, it facilitates communication which might be seen as a positive aspect arguing against an ASD diagnosis (Lai et al.,2017).

At that point it is important to remember that an enhanced *Auditory Acuity* it is highly associated with the use of camouflaging strategies in female ASD, strategies that are known to blur communication difficulties, making clinical assessments more difficult (Hull et al., 2017; Young, Oreve & Speranza, 2018).

From a clinical perspective it is therefore important to acknowledge the importance of taking a more global perspective when assessing female ASD. Clinicians need to remember that ratings of ASD behaviors in a clinical setting might not be an adequate measure of female ASD as the setting might not be relating to complex sensory processing. The same goes for parental ratings of child behavior, questions relating to less complex social settings might not be able to pick up female ASD.

We suggest there is a need for assessment tools to include complex social settings for females to be properly understood.

Strengths and limitations.

Strengths. We believe the relatively even number of female and males participating in the study is one of the strengths in this study. Many studies of gender differences in ASD have a much lower percentage of female subjects compared to male subjects. We believe the even number might be related to another strength in our study, the inclusion of all subjects being assessed rather than using those already assessed. We hoped to be able to include some of those female patients that otherwise might pass without a diagnose and therefore not be included. The screening procedure that all patients go through before being sent for an autism assessment will of course prevent us from reaching out to all females that go undetected, in the same time it provides us with an assurance that there are markers for autism present in all subjects participating in this study.

In our study we did not include any autism symptom rating scales which might be seen as a limitation although it was done to be seen as a strength. Since it is the current diagnostic system we are questioning, asking whether it can pick up female ASD or not, it seems unreasonable to use scales and tests based on that same system in order to justify someone participating in the study.

Like many other studies this study has limitations. Since ABR is a measurement of activity in response to auditory stimuli it cannot be expected to show direct associations with Visual Acuity. The negative associations seen between ABR and visual Acuity must rather be interpreted as a relationship with unknown mediators.

Another limitation is related to the low power due to the limited number of subjects participating in the study. The testing procedures in this study were difficult for many of the children to endure. Some found the sound stimuli in ABR to be very annoying others were frustrated by having to do boring tasks on the computer related to the IVA-testing. For that reason, several of the children were excluded from the study.

The use of ABR measurements in children is also a question that needs to be raised. Some studies have shown that ABR amplitudes are delayed at a lower age due to less maturity of the brainstem. The major maturation of the brainstem takes place before the age of six, and then slows down and reaches full maturity in adulty (Sharma, Bist et Kumar, 2016). After the age of six, only a small delay of wave V is seen. Even if the Time Widows used in our study are designed to include a small delayal the maturity level might be affecting our results in some unknown way. A correlation with age was also done in all four ABR measures which did not show any associations in any of the groups. Still, we decided to use age as a control variable due to the "on the edge of being significant" difference of age seen between the groups and to make sure to adjust the results in the IVA tests.

Another limitation is the lack of some sort of language test which could have contributed to an evaluation of what the gender differences seen in our study are related to. Adding a control group would also have provided a better understanding of the results and how they relate to the normal population.

Future directions

There is a need for future research to replicate these findings as there are no other similar studies out there as far as we have been able to see. There is also a need for more gender perspective in temporal sensory processing in relation to complexity of social settings. We need to answer the question as to what differentiates a less complex social setting from a complex social setting? Is a complex social setting defined by a setting where the child's own feelings cannot be set apart in order to adapt? Or is it rather any setting triggering the child's emotions, or is it directed by child intelligence or previous experiences? These are all questions that need answers.

Detecting female ASD at an earlier stage will not only provide the individual with better prospects in regard to future mental health it will also reduce the number of undetected females developing anxiety-related disorder often hard to treat.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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