A sensory processing perspective on behavioral difficulties in preterm children

Tinka Bröring

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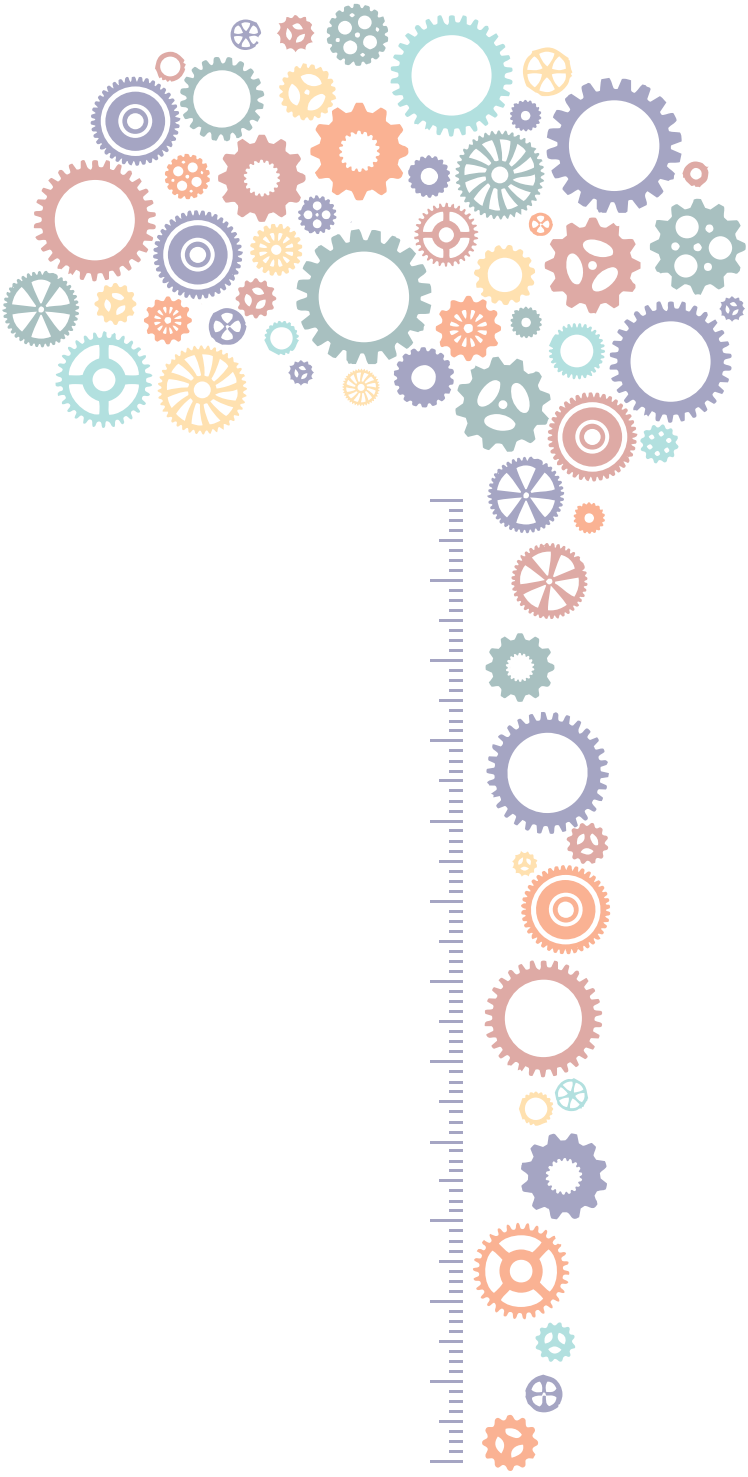

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General introduction

ABOUT SVEN

After a pregnancy of only 29 weeks Sven is born unexpectedly. Sven is the first child of a 30-year-old mother, who is working as a school teacher and a 33-year-old father, employed as a physiotherapist. After Sven's birth, his parents are in distress, unsure if he will survive. Sven is in the incubator and needs assistance breathing. His parents are proud to have a son, but also afraid of what comes next. After two weeks, Sven is fighting off an infection and he still needs mechanical ventilation. His parents take it day by day. It is a marathon of worries. The nurses are busy taking care of him and although Sven's parents are allowed to change his diaper and hold him every day, they often feel powerless. Breastfeeding is not an option and although they enjoy the kangaroo care, they cannot, for instance, rock him to sleep. After four weeks at the neonatal intensive care unit (NICU) and four more weeks at the high care baby unit, Sven is strong enough to leave the hospital. At home, Sven turns out to be a fussy baby, that likes to be held and has trouble falling asleep. His parents are struggling to find a soothing rhythm in feeding, playing and putting Sven to bed. Although they are happy to have him home, they worry a lot about his health as well. After a few months, when friends and family all have come to see Sven, both parents start working again and things seem to get back to normal. However, Sven's parents often think back on what they went through at the hospital.

By now, Sven is a blossoming 2-year-old. He started walking at 17 months and talking around the same time. He is a shy and happy little boy, who had some trouble adjusting to daycare and the weekly play group. Sven seemed almost afraid of other children and preferred to play by himself as if the other children were too much for him. Sven is also highly focused on the whereabouts of his parents, he can be very stubborn and he is fussy about clothes. He also has car sickness and he sometimes even gets nauseous riding on the backseat of a bike. At the corrected age of two years, Sven returns to the hospital for a comprehensive check-up. Although his parents are pretty confident about his development, the developmental test he will undergo is tense. During the test Sven is shy and a bit overwhelmed by the unknown environment and unfamiliar psychologist interacting with him. His parents notice he does not speak as much during the test as he does at home, that he is easily scared by new materials and that it takes longer to complete jigsaw puzzles and a pegboard than at home: they worry he does not show his full potential. Luckily, a week later, the psychologist calls to tell that Sven performs at an average level of both cognitive and motor development. A questionnaire on behavioral problems is also reassuring; Sven does not show any serious internalizing or externalizing behavioral problems. Sven's parents are happy with the good results and they try to close this chapter of being born too soon, at least until the next follow-up visit at age 5. Yet, they sometimes wonder how their shy and sensitive boy will manage in preschool and later on.

Each year around 15 million babies (11%) worldwide are born prematurely[1] and in most high and middle income countries preterm birth is the leading cause of neonatal death.[2] Preterm birth is defined by the World Health Organization (WHO) as birth before 37 weeks of gestation and is subdivided in moderate to late preterm birth (32–37 weeks of gestation), very preterm birth (28–32 weeks of gestation), and extremely preterm birth (< 28 weeks of gestation).[3] This thesis focuses on very preterm born children (≤ 32 weeks of gestation). Preterm birth may either be medically indicated, mainly because of (pre-)eclampsia, fetal distress and intrauterine growth restriction or may occur spontaneously and is in that case associated with multiple risk factors, including maternal infection, vascular disease, and uterine and cervical abnormalities, as well as with previous preterm birth, ethnicity and unfavorable social environmental factors.[4] Immediate consequences of preterm birth include respiratory distress syndrome, intracranial hemorrhage, necrotizing enterocolitis, inflammation and retinopathy.[5]

The premature brain at the Neonatal Intensive Care Unit

Preterm birth may lead to cerebral hypoxia-ischemia, especially in white matter, because of cerebrovascular immaturity and deficient autoregulation of cerebral blood flow.[6–9] Furthermore, inflammation is hypothesized to lead to raised levels of pro-inflammatory blood cytokines, which destroy oligodendrocyte progenitors.[6] Hypoxia-ischemia and inflammation are considered potentiating pathogenetic mechanisms that disrupt maturation of myelin forming oligodendrocytes and ultimately lead to diffuse white matter damage and periventricular leucomalacia (PVL).[6,10,11] In addition, harmful environmental factors of the Neonatal Intensive Care Unit (NICU) further compromise normal brain development,[12–14] through early exposure of the rapidly developing immature preterm brain to extra-uterine sensory experience.[15–17] The NICU is a high-tech environment where sensory stimuli are very different from the natural intra-uterine environment. Both sensory overstimulation and understimulation are common in the NICU.[16,18,19] Sensory overstimulation comprises bright lights, noise, nursery handling and repetitive pain due to NICU care procedures such as heel lancing, venipunctures and nasal suctioning.[18,20] Sensory overstimulation as well as repetitive pain are hypothesized to result in excitotoxic neural damage.[12,13] Sensory understimulation comprises tactile, vestibular and kinesthetic deprivation due to parental separation during unavoidable stay in the incubator.[19,21,22] Apoptotic damage may be a result of sensory understimulation.[12,13] As a consequence children born very preterm show reduced white and grey brain volumes,[22,23] abnormal white matter integrity and disrupted structural and functional brain connectivity.[24,25]

Long-term consequences of preterm birth

In recent years survival rates of premature infants have increased thanks to advances in perinatal and neonatal care and nowadays around 72% of extremely preterm infants, 96% of very preterm infants and 99% of moderate to late preterm infants survive in Western countries.[5,26] Unfortunately, this reduced mortality is still accompanied by high levels of long-term morbidity and neurodevelopmental sequelae.[5] Unsurprisingly, preterm birth morbidity exerts a heavy burden on families, health services, social services and education.[1,27]

In the Netherlands, 7.7% of all births are preterm and 1.5% are very preterm.[28] Almost 25% of very preterm children worldwide show major neurodevelopmental sequelae and almost 33% of very preterm children show minor sequelae,[5] including sensory, motor, cognitive and behavioral problems.[29–32] Major impairments following preterm birth are for instance primary neurosensory impairments (visual/auditory), cerebral palsy, and intellectual disabilities,[5] whereas sensory processing problems,[33] motor coordination problems,[31] cognitive deficits (e.g. intelligence impairments, low processing speed and poor executive functioning),[30,34] adverse behavioral outcomes (e.g. internalizing and externalizing behavioral problems)[30,35] and mental health problems (e.g. attention deficit hyperactivity disorder, autism spectrum disorders, anxiety, depression)[29,36,37] are deemed minor impairments. Yet, there is increased awareness that the impact of these minor impairments on both adaptive functioning and quality of life of preterm born infants may be substantial,[38] since they interfere with family functioning and adaptive social and school functioning.[39,40] For instance, parents of very preterm born children show higher levels of parenting stress, anxiety and depression symptoms, and poorer family functioning compared with parents of full-term born children.[39,41] Also, very preterm children frequently manifest school difficulties such as grade repetition, lower academic achievement levels and extensive use of special educational services.[40,42,43]

Understanding long-term behavioral consequences of preterm birth from a sensory processing perspective

Although extensive research has been undertaken to grasp mechanisms underlying neurodevelopmental impairments in very preterm children, our current understanding is still incomplete. In this thesis we explore an underlying mechanism for behavioral difficulties in very preterm children within the domain of sensory processing. A growing body of evidence suggests that white matter abnormalities are associated with behavioral problems in very preterm children.[44–47] Cerebral white matter integrity and connectivity is also crucial for information processing, in particular sensory processing, and reduced white matter integrity is strongly associated with sensory processing difficulties.[17,48] Adequate sensory processing is pivotal for normal child

development, as sensory processing difficulties hamper normal development by interfering with social activities, play and leisure.[49,50] Due to the observed abnormal white matter integrity and disrupted structural and functional brain connectivity,[24,25] very preterm born children may be at risk for sensory processing difficulties. Yet, sensory processing difficulties have scarcely been studied in very preterm children.

Sensory processing difficulties concern impaired processing of sensory information and/or ineffective responses to sensory information that may crucially affect daily life.[51,52] Sensory processing includes *registration*, *integration* and *modulation* of sensory stimuli.[51,52] Sensory registration difficulties comprise disturbances in identification, discrimination and interpretation of sensory stimuli.[53] Sensory integration difficulties include disturbances in the integration of information from multiple sensory modalities.[53,54] The integration of multisensory information is crucial for the reconstruction of a full representation of the multisensory environment and efficient interaction with this environment.[54] Sensory *modulation* difficulties pertain to an impaired regulation of the intensity of responses to sensory stimuli, resulting in behavioral underresponsivity and/or overresponsivity with subsequent maladaptive emotional, attentional, and motor responses to sensory stimuli.[52,53,55] According to Dunn, four sensory modulation quadrants may be distinguished (see Figure 1.1), relating to different sensory modulation types, including *Low Registration* (i.e. high sensory threshold in combination with passive self-regulation strategies), *Sensation Seeking* (i.e. high sensory threshold in combination with active self-regulation strategies), *Sensory Sensitivity* (i.e. low sensory threshold in combination with passive self-regulation strategies), and *Sensory Avoiding* (i.e. low sensory threshold in combination with active self-regulation strategies).[52,56]

Adequate sensory processing is strongly related to behavioral functioning.[57] In fact, sensory processing difficulties are frequently associated with autism spectrum disorder (ASD) and

	Self-regulation strategies/behavioral response	
Neurological threshold	Passive	Active
High threshold	Low Registration	Sensation Seeking
Low threshold	Sensory Sensitivity	Sensation Avoiding

Figure 1.1. Sensory modulation matrix, according to Dunn.[56]

attention deficit hyperactivity disorder (ADHD).[54,58–61] In ASD, abnormalities in registration, integration and modulation have been thoroughly established.[62,63] ASD is a psychiatric disorder that manifests in early childhood and causes significant impairment in social, occupational and daily functioning.[64] ASD is defined by the Diagnostic and Statistical Manual of mental disorders, 5th edition (DSM-V)[64] as a disorder with persistent deficits in social communication and social interaction across multiple contexts in combination with restricted, repetitive patterns of behavior, interests of activities. The global prevalence of autism has been estimated at 0.6%.[65] In ADHD, research on sensory processing is less extensive. ADHD is a neurodevelopmental disorder with a worldwide prevalence of around 5%,[66] which emerges during childhood and is characterized by impairing and developmentally inappropriate symptoms of inattention and/or hyperactivity and impulsivity.[64] According to the DSM-V, ADHD symptoms must be present in at least two settings and impact directly on daily life functioning.[64] ADHD may lead to significant functional impairment.[64,67] At the behavioral level, characteristics of ADHD and ASD show striking similarities with both overresponsive and underresponsive reactions of children with sensory modulation difficulties. For instance, underresponsive children react less readily and more slowly to sensory stimuli. They may seem oblivious and disengaged to their environment, tend to miss things and show little effort to capture additional input.[55,57] A comparison with attention problems as seen in ADHD and with aloof, withdrawn behavior in ASD, is easily made. Likewise, overresponsive children, readily triggered by sensory input, tend to be hyperactive, redirecting their attention from one stimulus to the next as seen in ADHD, or display repetitive play as seen in ASD.[57] Our studies on sensory processing in children with ADHD showed us that the domains of both sensory registration and modulation were affected (**Chapter 6&7**). School-aged children with ADHD not only displayed less accurate somatosensory registration but also higher levels of tactile overresponsiveness. These findings underpin our hypothesis to evaluate symptoms of ADHD (and given the frequent sensory processing abnormalities, also ASD) in very preterm children from a sensory processing perspective.

In very preterm children, symptoms of ADHD and ASD are often observed.[29,68,69] In fact, very preterm children have a two to three-fold risk of developing ADHD at school-age[35,36,70] as well as higher rates of ASD diagnoses (5–9%)[71,72] in comparison to the general population (0.6%).[73] Moreover, symptoms of ADHD and ASD frequently co-occur in both the full-term born population[74,75] as well as in the very preterm born population,[36] with attention problems as the suggested linking factor to both disorders.[75] However, few studies have included both ADHD and ASD measures to study symptoms of ADHD and ASD in very preterm children. What is more, no studies have investigated the impact of sensory processing difficulties on ADHD and ASD symptoms in very preterm children thus far. Yet, it is possible that disengaged (underresponsive) or overly sensitive (overresponsive) behavior in very preterm children is

(mis)labeled as symptoms of ADHD and/or ASD. Unraveling the impact of sensory processing difficulties on symptoms of ADHD and ASD might enhance our understanding of the behavioral problems occurring in very preterm children and benefit interventions in this large group of children.

Follow-up care in the Netherlands

In the Netherlands, all children admitted to a NICU are considered at risk for problems in growth and development. However, given the large numbers of admitted children, eligible for follow-up care in nine Dutch university hospitals are only those children born very preterm (< 30 weeks) and/or with a very low birth weight (< 1000g).[76] Additionally included in follow-up care are children 1) born small for gestational age (birth weight < 1500g and < P10); 2) with major perinatal cerebral pathology; 3) with asphyxia and treated with hypothermia; 4) with major white matter abnormalities; 5) with parenchymal abnormalities, and 6) with post-hemorrhagic ventricular dilatation. Children with neonatal epilepsy, congenital hydrocephalus/brain malformations/muscular disease and cerebral damage due to chromosomal/syndromal/metabolic disorders are excluded from the follow-up care (but are included in tailored clinical care). A national multidisciplinary group (Werkgroep Landelijke Neonatale Follow-up [LNF]) of neonatologists, child psychologists and physiotherapists agreed on national guidelines to which standard follow-up care should comply.[76] These guidelines contain fixed ages at which follow-up should take place as well as fixed measures to screen for growth and developmental problems. Follow-up should take place at 6, 12 and 24 months corrected age, and 5 and 8 years (see guidelines for complete overview of measures at each time interval).[76] Briefly, follow-up care includes a general pediatric/neurological check-up, update of medical history, assessment of motor skills (age > 12 months), assessment of neurocognitive development (> 24 months) and screening of behavioral problems with a parent-reported questionnaire (> 24 months). At age 8, academic achievement is assessed using a series of standardized tests that are part of the Dutch National Pupil Monitoring System (CITO) collected from primary schools.[77] If needed, referral takes place to specialized care, including other medical specialists, physiotherapists and child psychologists. Unfortunately, not all university hospitals providing follow-up care fully adhere to these guidelines due to financial constraints, excluding some of the follow-up visits.

AIMS OF THIS THESIS

This thesis aims to provide a detailed picture of sensory processing difficulties and behavioral problems, in particular symptoms of ADHD and ASD in very preterm children and to unravel the impact of sensory processing difficulties on symptom levels of ADHD and ASD. Specifically, this thesis aims to:

1. systematically review the existing literature on sensory modulation difficulties in preterm children (< 37 weeks of gestation)
2. investigate the effects of preterm birth (≤ 32 weeks of gestation) on sensory processing, in terms of registration, integration and modulation
3. investigate symptoms of ADHD and ASD in very preterm children by both parent and teacher report
4. study whether sensory processing impacts on symptom levels of ADHD and ASD in very preterm children

The above aims were partly derived from our earlier studies into sensory processing difficulties of children diagnosed with ADHD, investigating somatosensory functioning, pain experience and tactile overresponsiveness.

OUTLINE OF THIS THESIS

This thesis is divided in two different parts. *Part one* covers studies on sensory processing difficulties and behavioral problems in very preterm born children. A comprehensive systematic review integrating available evidence on sensory modulation difficulties in preterm born (< 37 weeks) children is presented in **Chapter 2**. In addition, we explore the relation between sensory modulation difficulties and neurocognitive and behavioral problems in these children. Next, **Chapter 3** explores the nature of sensory processing difficulties in very preterm children in comparison to full-term born children. Registration, integration and modulation are studied in a sample of 57, 9-year-old very preterm born children (≤ 32 weeks of gestation) using a multimodal assessment battery including behavioral somatosensory registration tasks, a computerized multisensory integration task and a parent-reported sensory modulation questionnaire. **Chapter 4** describes a study investigating symptom levels of ADHD and ASD, and their co-occurrence, from both parent and teacher reported questionnaires and a diagnostic interview in very preterm born school-aged children in comparison to full-term born children. Additionally, associations are investigated between both ADHD and ASD symptoms, and gestational age (GA), neonatal infections, PVL, socio-economic status (SES) and sex in very

preterm children. Finally, **Chapter 5** elucidates whether aggregated symptoms of ADHD and ASD in very preterm born children are mediated by sensory processing difficulties, as measured by sensory registration and sensory modulation.

Part Two describes the context and basis of our hypothesis on the relation between sensory processing and behavioral difficulties by addressing sensory processing and pain experience in children diagnosed with ADHD in comparison to non-affected siblings and control children. Firstly, **Chapter 6** describes a study investigating somatosensory functioning (tactile perception and kinesthesia) and subjective intensity and emotionality of pain experience in children with ADHD, their non-affected siblings and normal controls. **Chapter 7** describes tactile overresponsiveness in children with ADHD, their non-affected siblings and normal controls, differentiating between boys and girls.

Finally, at the end of this thesis, a summary and discussion of the presented findings is provided, as well as our thoughts on clinical implications and avenues for future research. Insights from the different studies are combined to progress towards a better understanding of the multifaceted problems occurring in the developmental trajectory of very preterm children. Moreover, these insights may target new domains for follow-up care and benefit interventions in very preterm born children.

SAMPLE AND STUDY DESIGN

Two different samples were examined in the studies described in this thesis. The sample of primary interest (*Part One*) consists of very preterm children who participated in a randomized controlled trial (RCT) called "Study Towards the Effects of Postdischarge nutrition on growth and body composition of infants born ≤ 32 weeks of gestation and/or ≤ 1500 gram birth weight (STEP)".[78] Eligible for inclusion in STEP were all very preterm children admitted between August 2003 and July 2006 to the neonatal intensive care unit (NICU) of the VU University Medical Center, Amsterdam, The Netherlands. At birth, 152 infants were included in STEP. Inclusion criteria were a gestational age less than or equal to 32 weeks or a birth weight less than or equal to 1500 gram and at least one main caretaker with a good command of Dutch or English. Exclusion criteria were: infants with congenital malformations or conditions known to affect growth and/or body composition (i.e. severe bronchopulmonary dysplasia, inborn errors of metabolism, cardiac or renal disease, necrotizing enterocolitis with substantial gut loss, grade IV intraventricular hemorrhage). Baseline characteristics of the sample have previously been reported.[78] At term age, subjects were randomized to receive either a protein- and mineral-enriched postdischarge formula (PDF) or a standard term formula (TF) until 6 months

corrected age. A control group of infants fed human milk was also included. Of the 152 infants included in the original RCT, 139 completed the study at six months corrected age and 122 were eligible for inclusion in the current study in 2010–2015 at 8–10 years of age. Very preterm children with severe physical disabilities were excluded (n = 10). All other 112 children were contacted and invited to participate, to which 57 (51%) agreed (**Chapter 3**, **Chapter 4**, **Chapter 5**). No differences were found between the group of participants and the total group of non-participants (n = 95) on sex, parental education, gestational age (GA), birth weight, PVL, and the presence of perinatal infections (all $p \geq .14$). A gender and age matched full-term control group was recruited from primary schools located in the same provinces as schools attended by the very preterm children, and included children without histories of preterm birth (GA > 37 weeks), perinatal complications, neurological disorders, and diagnoses of ADHD and/or ASD as reported by parents.

The ADHD sample (*Part Two*) was included in the Amsterdam part of the International Multicenter ADHD Genes (IMAGE) study, a prospective longitudinal follow-up study of participants with ADHD, affected and unaffected siblings, and control participants.[79,80] Families with at least one child with ADHD and at least one additional sibling were recruited from 12 specialist clinics in eight European countries. At the Amsterdam site, 190 families agreed to participate of which 178 families fulfilled all the criteria. During a 6-month period in 2004–2005 of the ongoing recruitment/testing, families were asked to participate in this part of the study as well, which was aimed at examining somatosensory functioning and recent pain experience (50 children with ADHD and 38 non-affected siblings, **Chapter 6**) and tactile overresponsiveness (47 children with ADHD and 36 non-affected siblings, **Chapter 7**). Only children aged between 5 and 12 years were included in this part of the study. Exclusion criteria were an IQ < 70, a diagnosis of autism, epilepsy, general learning difficulties, brain disorders or known genetic disorders, such as Down syndrome or Fragile-X-syndrome. Within an affected family, both the children already clinically diagnosed with ADHD as well as their siblings were similarly screened on a diagnosis of ADHD using the standard procedures of the IMAGE project.[79,80] An additional 35 control children were recruited from primary schools in the same geographical region as the participating families of the children with ADHD. Control children were required to have no formal or suspected ADHD diagnosis.

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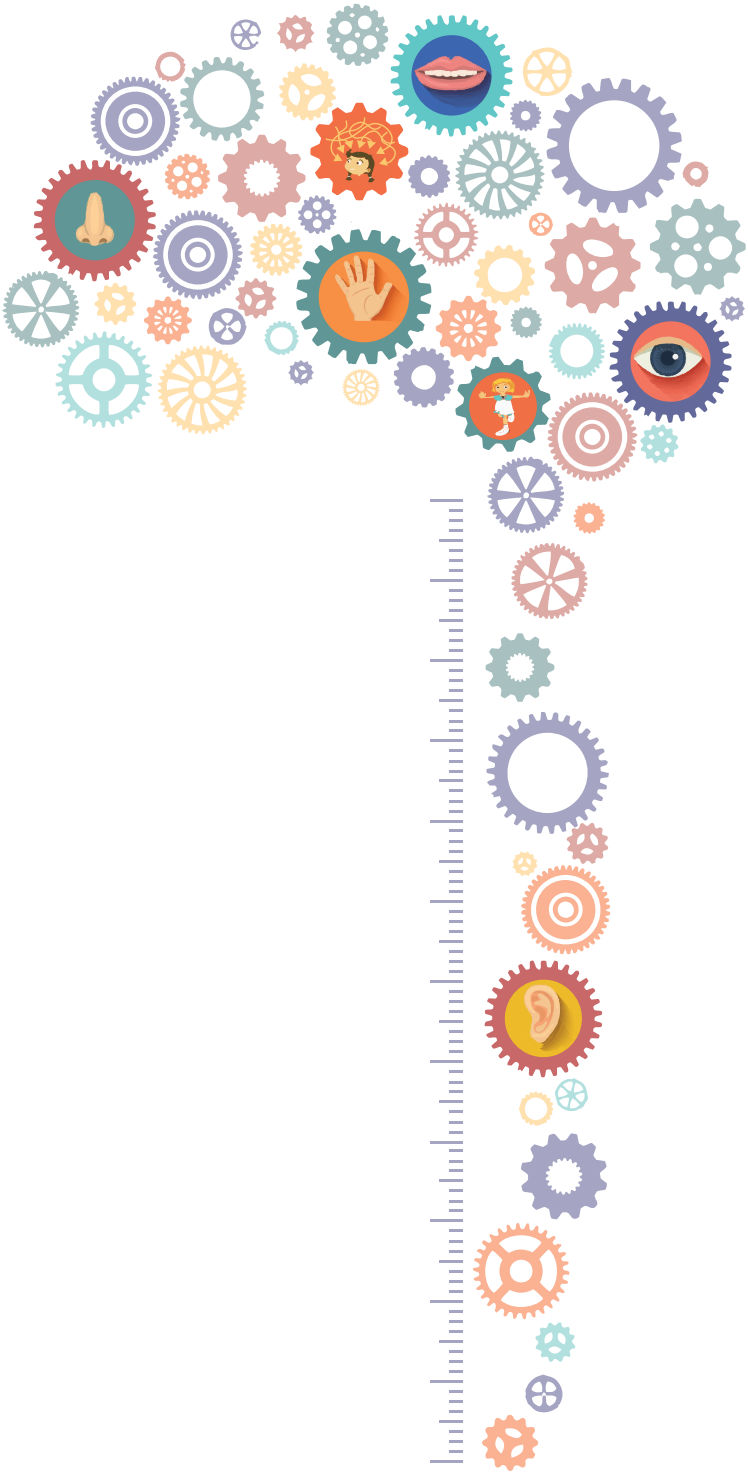
PART ONE



2

Sensory modulation in preterm children: theoretical perspective and systematic review

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ABSTRACT

Background Neurodevelopmental sequelae in preterm born children are generally considered to result from cerebral white matter damage and noxious effects of environmental factors in the neonatal intensive care unit (NICU). Cerebral white matter damage is associated with sensory processing problems in terms of registration, integration and modulation. However, research into sensory processing problems and, in particular, sensory modulation problems, is scarce in preterm children.

Aim This review aims to integrate available evidence on sensory modulation problems in preterm infants and children (< 37 weeks of gestation) and their association with neurocognitive and behavioral problems.

Method Relevant studies were extracted from PubMed, EMBASE.com and PsycINFO following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Selection criteria included assessment of sensory modulation in preterm born children (< 37 weeks of gestation) or with prematurity as a risk factor.

Results Eighteen studies were included. Results of this review support the presence of sensory modulation problems in preterm children. Although prematurity may distort various aspects of sensory modulation, the nature and severity of sensory modulation problems differ widely between studies.

Conclusions Sensory modulation problems may play a key role in understanding neurocognitive and behavioral sequelae in preterm children. Some support is found for a dose-response relationship between both white matter brain injury and length of NICU stay and sensory modulation problems.

INTRODUCTION

Advances in perinatal and neonatal intensive care have led to markedly increased survival rates in premature infants. Unfortunately, this reduced mortality is accompanied by an increased morbidity and high prevalence of neurodevelopmental problems, including neurocognitive and motor sequelae.[1–5] In addition, behavioral impairments in terms of increased incidence of both attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) are found in preterm children.[6–9] At school age, preterm born children have a two to threefold risk to develop ADHD and ASD.[10,11] Moreover, all these sequelae may translate in school difficulties, such as grade repetition, lower academic achievement levels and extensive use of special educational services.[12–14] Our current understanding of the mechanisms underlying the neurodevelopmental impairments in preterm children is still incomplete. This review aims to elucidate these impairments in terms of sensory processing problems and, specifically, sensory modulation problems.

Neurodevelopmental sequelae in preterm children are generally considered to result from early brain damage due to hypoxia-ischemia and inflammation,[15] typically caused by concomitant medical conditions, such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) and sepsis.[16–19] Premature infants tend to develop cerebral hypoxia-ischemia, especially in white matter, because of anatomical and physiological vulnerabilities of the vascular system. Furthermore, inflammation is common in preterms due to maternal intra-uterine infection and postnatal sepsis because of the immature immune system and is hypothesized to lead to inflammatory responses with subsequently raised levels of blood cytokines.[15] Some of the cytokines are toxic to oligodendrocyte progenitors (pre-OLs), disrupting the maturation of myelin-forming oligodendrocytes.[15,20] In addition to this cytokine injury, both hypoxia-ischemia and inflammation can lead to further damage to pre-OLs by the mechanisms of excitotoxicity and enhanced apoptosis caused by free radical attack, in turn exacerbating diffuse white matter damage and leading to periventricular leucomalacia (PVL).[15,21] Volpe described hypoxia-ischemia and inflammation as two mutually potentiating pathogenetic mechanisms for developing 'encephalopathy of prematurity', which is a constellation of PVL and associated neuronal/axonal disease.[15,21,22] This neuronal/axonal disease is delineated by decreased volumes of the cerebral white matter, thalamus, basal ganglia, cerebral cortex, brainstem, and cerebellum.[15,23–25]

In addition to the mechanisms of hypoxia-ischemia and inflammation causing PVL and axonal/neuronal disease, environmental factors of the neonatal intensive care unit (NICU) further compromise normal brain development.[20,26–29] The NICU is a stressful environment to which the preterm infant's rapidly developing but immature brain is particularly vulnerable. Animal models demonstrate that the brain has critical periods in development which require optimal

environmental exposure to enhance brain development.[27,30] Moreover, structural organization of the brain is altered by longer extra-uterine exposure as a consequence of the preterm birth, even without concomitant brain injuries.[31–33] In preterm infants, brain development may be further compromised by sensory overstimulation by bright lights, noise, nursery handling and repetitive pain in terms of inflammatory pain and NICU care procedures such as heel lancing, venipunctures and nasal suctioning.[31,34,35] In fact, preterms show structurally elevated stress markers such as increased heart rate and decreased oxygen saturation.[36] It is hypothesized that sensory overstimulation and repetitive pain propel excessive activation of central afferent pain pathways with subsequent excessive N-methyl-D-aspartate (NMDA) receptor activation resulting in, again, excitotoxic damage.[26] Indeed, NICU stressors are associated with decreased brain size in frontal and parietal regions and altered brain microstructure and functional connectivity within the temporal lobes.[37] In addition, normal brain lateralization may even be compromised by unstructured extra-uterine auditory stimulation before 30 weeks of gestation.[35] Together with the detrimental effects of sensory overstimulation and repetitive pain, also parental separation and sensory understimulation in terms of tactile, vestibular and kinesthetic deprivation are hypothesized to further compromise normal brain development, as afferent activity is reduced with a subsequent lack of NMDA activity which in turn induces apoptosis.[26]

All of these destructive processes occur in the context of already insufficient self-regulatory abilities of the preterm and at a time where the sensory system is shaped by the amount and type of sensory experiences.[31,38] To counteract these challenges 'Developmental Care' interventions have been developed. For example, effective analgesia, kangaroo care, fine-tuned sensory stimulation and the Newborn Individualized Developmental Care and Assessment Program (NIDCAP)[30,39] to support the infant's active self-regulation are believed to mitigate the adverse environmental effects of NICU care on the brain.[1,27,40–42] Thus, preterm birth as well as NICU environment can compromise brain development, especially cerebral white matter integrity. Cerebral white matter integrity is crucial for information processing, in particular sensory processing, and reduced white matter integrity is associated with sensory processing dysfunctions.[31,43] In fact, Owen and colleagues[43] recently showed a biological substrate of reduced white matter microstructure in children with sensory processing dysfunctions. Both primary sensory cerebral tracts and connective pathways to multimodal sensory regions were found to be affected. Therefore, the widespread white (and grey) matter abnormalities in preterms and altered structural brain organization in combination with the sensory over- and understimulation in the NICU strongly suggest that preterms are at risk for sensory processing dysfunctions.

Sensory processing can be defined as a three-stage construct including registration, integration and modulation of sensory stimuli. Dysfunctions in sensory processing are identified as sensory processing disorder (SPD) and pertain to the different stages in the sensory process.[44–47]

Sensory registration dysfunctions range from basal sensory deficits (impaired sense of hearing, vision, taste, touch and/or, smell) to sensory discrimination disorder (SDD), in which children have difficulty discriminating or interpreting qualities of sensory stimuli in one or more sensory modalities.[44] Sensory integration dysfunctions include sensory-based motor disorder (SBMD), in which children show disturbances in integration of vestibular, proprioceptive, and visual information, resulting in poor postural control (postural disorder) or poor coordination (dyspraxia).[44] Sensory modulation dysfunctions are defined as Sensory Modulation Disorder (SMD), in which children show an impaired regulation of the intensity of responses to sensory stimuli, resulting in hyporesponsiveness and/or hyperresponsiveness with subsequent maladaptive emotional, attentional, and motor responses to sensory stimuli.[44,46,48]

A recent review found that SPD frequently occurs in preterm children, with some evidence for SDD (auditory, visual and tactile system) and SBMD.[49] Mitchell and colleagues[49] concluded that SMD was most frequently found in preterms up to age three years, with sensory overresponsivity being the most prevalent category. Indeed, registration and integration of sensory information are known to be compromised in preterm infants. Evoked potential (EP) studies show anomalous results in preterm infants on registration of all sensory modalities,[31] ranging from lower activation of somatosensory cortical neurons and decreased thermal sensitivity[50,51] to frequent occurrence of cerebral visual impairment,[52,53] abnormal auditory brain stem conduction[54,55] or smaller auditory event-related potentials[56] and abnormal vestibular EPs.[57] Integration dysfunctions in terms of dyspraxia (SBMD) and visual-motor integration problems are also known to be highly frequent in preterms.[4,49,58] Remarkably, modulation of sensory information has only been scarcely studied in preterm children. However, there are several reasons to suspect sensory modulation problems in preterm children. First, the pattern of diffuse white matter damage and axonal/neuronal disease in basal ganglia, cerebral cortex, brainstem and cerebellum[15,23,24] shows striking parallels with the so-called excitation-inhibition-modulation loop of sensory processing described by Koziol et al.[59] This loop is thought to be crucial for effective sensory modulation, where the cortex, basal ganglia and cerebellum select, gate and regulate sensory stimuli, respectively. Secondly, sensory modulation is part of the already vulnerable self-regulatory abilities of the preterm, further compromised by both sensory overstimulation and understimulation in the NICU.[60] Third, common behavioral dysfunctions in preterm children, i.e. ADHD and ASD in particular, are strongly associated with problems in sensory modulation[61–63] Both over- and underresponsivity are found in multiple sensory areas in ADHD and ASD.[62,64–66] Sensory modulation problems may form at least a partial link between prematurity and ADHD/ASD symptoms.

The current systematic review examines all available studies on the prevalence and nature of sensory modulation problems in preterm infants and children. Furthermore, we aim to integrate available evidence on risk factors of prematurity in association with sensory modulation

problems and to elucidate associations between sensory modulation and neurocognitive and behavioral problems in preterms.

METHOD

Literature search and selection criteria

Relevant studies were retrieved using a comprehensive systematic search employing the bibliographic databases PubMed, EMBASE.com and PsycINFO (via EBSCO). Search terms included controlled terms from MeSH in PubMed and EMtree in EMBASE, thesaurus terms in PsycINFO as well as free-text terms. Search terms expressing 'preterm children' were used in combination with search terms comprising 'sensory processing'/'sensory modulation' and 'questionnaire/rating scale/test' (see online material; Search terms and strategy). Reference lists of the included studies were hand-searched for additional relevant publications. This review included all empirical studies that met the following inclusion criteria: the study had to 1) report on preterm children born < 37 weeks of gestation, and 2) assess the construct of sensory processing (disorder) in terms of sensory modulation, and 3) use a measurement (test, questionnaire, rating scale) to evaluate sensory processing/sensory modulation, and/or 4) evaluate a diagnosis of sensory processing disorder/sensory modulation disorder, and 5) be published in an English language peer-reviewed journal. Full-text articles were excluded if 1) the study did not report on preterm children born < 37 weeks of gestation or did not describe prematurity as a risk factor, or 2) no measurement (test, questionnaire, rating scale) was used to evaluate the construct of sensory processing (disorder) in terms of sensory modulation, or 3) the study was not published in an English language peer-reviewed journal, or 4) the study was not an empirical study. No limits were set on the age of the participants. All relevant studies published up to 5 December 2016 were included (see online material; PRISMA checklist).

Assessment of study quality

Two authors (TB and KJO) independently assessed the quality of the included studies using the Newcastle–Ottawa Scale.[67] This scale rates the quality of observational studies in terms of the selection of subjects (four criteria, four points), comparability of study groups (one criterion, two points) and outcome assessment (three criteria, three points). Total rating scores may range from zero to nine points, where higher scores indicate higher study quality (see Table 2.1). Differences in assessment between authors were solved by consensus. Since five studies did not use a control group, but did use a norm-referenced group, the selection criterion

'Definition of Controls', option 'no history of disease' was scored positive if norm-referenced data were used in the statistical analyses. All 13 cross-sectional/cohort studies (and two RCT/intervention studies) were evaluated with the Newcastle-Ottawa Scale, but this scale does not allow the assessment of the three included population-based studies because of lack of comparability on assessment criteria.

Definitions of prematurity

The World Health Organization (WHO) defines prematurity as birth before 37 weeks of gestation and subdivides prematurity in: moderate to late preterm birth (32–37 weeks), very preterm birth (28–32 weeks), and extremely preterm birth (< 28 weeks).[68]

Operationalization of sensory modulation

The construct of sensory modulation is operationalized and measured differently between the studies. In this review, we use the framework developed by Dunn to organize the construct of sensory modulation.[46–48,69] The framework of Dunn can be conceptualized as a quadrant scheme with either high or low neurological perception thresholds on the rows, and either active or passive self-regulation on the columns. Using this quadrant scheme, four types of individuals can be distinguished: 1) individuals with high neurological perception thresholds and passive self-regulation strategies ('Low registration'); 2) individuals with high neurological perception thresholds and active self-regulation strategies ('Sensation seeking'); 3) individuals with low neurological perception thresholds and passive self-regulation strategies ('Sensory sensitivity'), and 4) individuals with low neurological perception thresholds and active self-regulation strategies ('Sensory avoiding'). Dunn used this framework to develop the widely used Sensory Profile, a rating scale that can be completed by caregivers.[46,69–72]

Measures

Across the 18 included studies two caregiver questionnaires (Sensory Profile [SP];[71] Sensory Rating Scale [SRS][73]) and one infant test battery (Test of Sensory Functions in Infants [TSFI])[74] were used and described below (see also Table 2.1). A recent review on sensory processing measures shows that these three measures are reliable and valid measures of sensory processing (see for details a review by Eeles and colleagues[75]).

Sensory Profile

The Sensory Profile (SP) is a caregiver-completed five-point scale questionnaire measuring sensory modulation abilities and problems in daily life.[71] Three versions exist: the 48-item Infant/Toddler Sensory Profile (ITSP) for ages birth-3 years,[69] the 125-item standard SP for ages 3–10 years,[71] and the Short Sensory Profile (SSP) for ages 3–10 years comprising 38-items. Both the ITSP and SP provide section and quadrant scores. The two rating scales comprise sections that pertain to five sensory systems, i.e. Auditory, Visual, Vestibular, Tactile and Oral systems, and a Multisensory section. Only the SP has eight additional sections, i.e. five modulation sections and three behavioral sections. The five modulation sections measure combinations of sensory input, concerning Endurance/tonus, Body position and movement, Movement in relation to activity level, Emotional responses and Visual input. The three behavioral sections describe Emotional/social reactions, Behavior and Perception thresholds for a response. Principal component analysis on the SP items has revealed nine factors. These factors pertain to the four quadrants of Dunn's scheme,[46] including Sensation seeking, Sensation avoiding/emotionally reactive, Sensory sensitivity and Low registration, and to five other factors, i.e. Low stamina/tonus, Oral-sensory sensitivity, Inattention/distractibility, Preference for sedentary activities and Fine motor/perceptual skills. Principal component analysis on items of the ITSP have only revealed the four quadrants. In the SSP seven factors are identified: Tactile sensitivity, Taste/smell sensitivity, Movement sensitivity, Auditory filtering, Low energy/weak, Underreactive/seeks stimulation and Visual/ auditory sensitivity.

Low scores on sections, factors and quadrants indicate sensory modulation problems and can be described as atypical (< -1 SD), as reflecting a probable difference (between -1 SD and -2 SD) and definite difference (< -2 SD). For the SP adequate reliability has been found for sections, quadrants and factors with Cronbach's alpha scores of 0.63–0.91.[69,71] In the ITSP adequate reliability has been found, with Cronbach's alpha scores of 0.70–0.86 for the quadrants, and 0.63–0.71 for the sections, with three exceptions for the Visual, Vestibular and Oral-sensory sections ($0.44 < \alpha < 0.55$). Moreover, adequate test-retest reliability of ITSP has been found for sections ($r = 0.86$) and quadrants ($r = 0.74$). The SSP Total score has high reliability ($\alpha = 0.96$) and discriminative validity, correctly identifying > 95% children with and without sensory modulation dysfunction.[70] Internal consistency of SSP factors ranged from 0.70 to 0.90. Content and construct validity have been established for all versions.[69,71]

Sensory Rating Scale

The Sensory Rating Scale (SRS)[73] is a caregiver-completed 136-item questionnaire to evaluate sensory modulation, referred to as sensory responsiveness, sensory defensiveness and temperament in infants aged 9–36 months. The SRS comprises six sections; Touch section,

Movement/gravity section, Hearing section, Vision section, Taste/smell section, Temperament/general sensitivity section and a Total score. Adequate psychometric properties have been obtained: high to adequate reliability was found for the total scale, form a (α = 0.90) Total score (α = 0.83) and sections (0.65 < α < 0.82), with two exceptions for the Vision (α = 0.56) and Taste/Smell section (α = 0.46).[73] Intra-rater reliability was high for mothers (r = 0.89) and fathers (r = 0.95), whereas inter-rater reliability was only moderate (r = 0.43). Content validity has been established. No research was conducted on construct and criterion-related validity.[73]

Test of Sensory Functions in Infants

The Test of Sensory Functions in Infants (TSFI)[74] is a 24-item test to assess sensory modulation (referred to as sensory processing and reactivity) in infants aged 4–18 months by presenting visual, tactile and vestibular stimuli to assess the intensity of the infant's response. Scores can be calculated for five subscales, i.e. Response to tactile deep pressure, Visual-tactile integration, Adaptive motor, Ocular motor, and Reactivity to vestibular stimulation. The five subscales sum up to a Total scale. Scores can be categorized as normal, at risk, or deficient, using normative data derived from normal, delayed and regulatory disorder groups of infants or children. Adequate psychometric properties have been obtained for the TSFI: the test-retest reliability for the Total scale score was r = 0.81 and ranged from r = 0.64–0.96 for the subtests scores, with a single exception for Reactivity to vestibular stimulation (r = 0.26). Inter-observer reliability is high with convergence between the raters of 81–96% for all scales.[74] Content and construct validity have been established.

RESULTS

Study selection

The literature search generated a total of 581 references. After removing duplicates of references that were selected from more than one database, 545 references remained. Title and abstracts were screened for relevance, by two authors (T.B. and K.O) independently, and 49 studies were further assessed for eligibility using the full text of the study report and the data extraction form (see online material; Data extraction form). A total of 18 studies (published between 1996 and 2016) met the inclusion criteria and were included in the present review (Figure 2.1).[76]

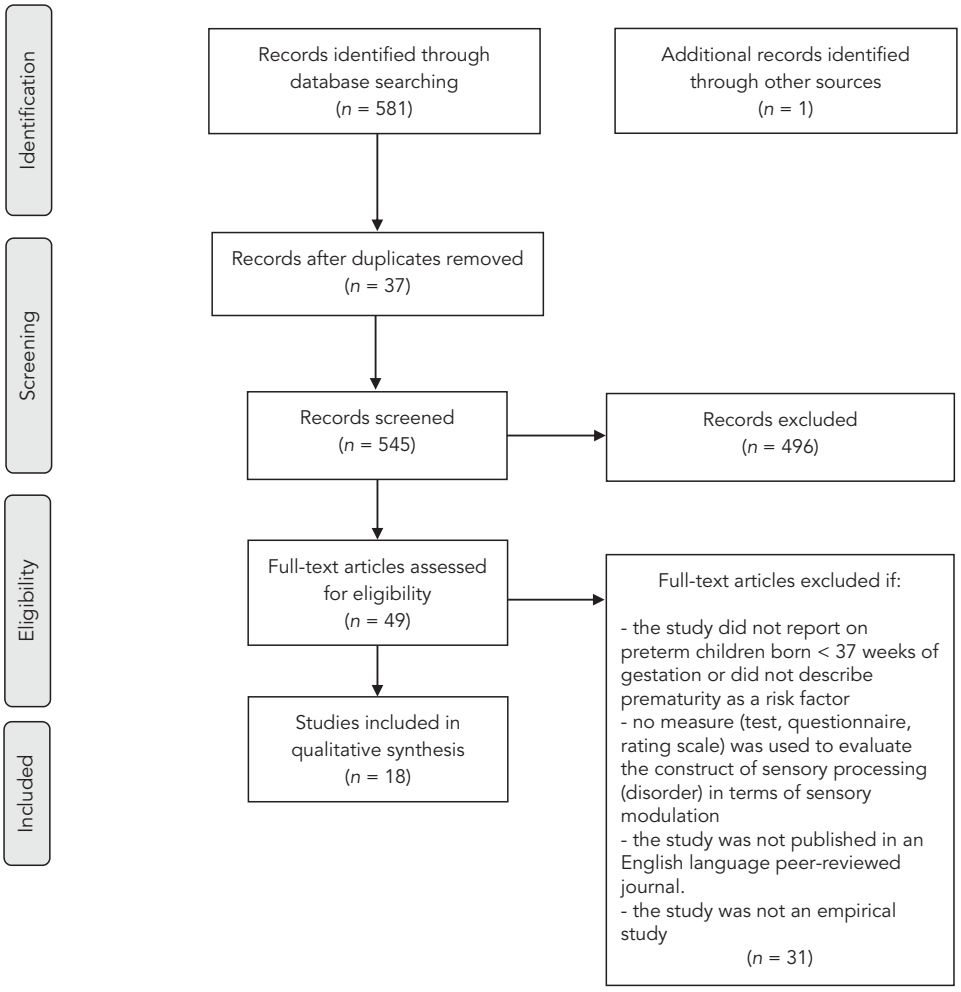

Figure 2.1. Flow chart of literature search and study selection.
From: Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6: e1000097.

Study characteristics

The systematic literature search yielded 18 eligible studies of which 15 reported on sensory modulation in a preterm sample[77–91] and three reported on sensory modulation in general population samples,[92–94] analyzing GA as a risk factor for sensory modulation problems (Table 2.1). Of the included studies, one study specifically reports on late preterm children.[78] Five studies report on the full spectrum of prematurity (22–37 weeks).[77,79,80,90,91] Seven studies report on very

preterm/very low birth weight (< 1500g) children[81–84,86,87,89] and one study reports on extremely preterm children.[85] In the 15 studies in preterms, 22 groups of children were evaluated, including 1259 preterm and 542 controls. Nine studies were case-controlled.[77–80,82,86,87,90,91] Sample sizes of the preterms ranged from 15 to 253 and of the controls ranged from 15 to 228. Control populations in all the studies were matched with the preterms on one or more demographic feature (gender, age, number of siblings/multiple birth, socioeconomic status [SES]). Twelve studies[77–80,82–85,89–92] evaluated sensory modulation before or at two years corrected age (CA). Of the 15 studies reporting in a preterm sample; 33% are 1-year-olds or younger (CA), 30% are 2-year-olds (CA), 29% are 3–5 year olds and one sample, 8%, is cross-sectional (1–8 year olds). The TSFI was used in five of our included studies.[77,78,89–91] In 11 of our included studies a version of the SP was used; the ITSP and SP were combined in one study,[81] the ITSP was used in six other studies;[78,80,82–85] the SP was used in one other studies,[87] and the SSP was used in three studies.[86,88,93] The SRS was used in one of our included studies.[79] Eight studies contained data from the United States,[77,79,81,86,89,92–94] five studies were conducted in Europe,[80,84,85,87,91] two in Australia,[82,83] one in Israel,[78] one in Brazil[90] and another one in Canada.[88]

Sensory modulation

Evidence in support of sensory modulation problems in preterms[77–86,88–91] was reported in 14 preterm studies and two population-based studies reported significant associations between GA and sensory modulation problems.[92,93] The other two studies[87,94] did not find evidence for the idea that preterm birth is associated with sensory modulation problems.

Sensory Profile

The ITSP/SP/SSP was used in 11 studies[78,80–88,93] of which ten[78,80–86,88,93] found that preterm born infants showed significantly more problems in sensory modulation compared to term-born controls or reference groups. Six studies reported explicitly on the SP/ITSP/SSP in preterms.[78,81,82,85,86,88] Problematic Auditory modulation was the most robust finding; all six studies found this section to be affected in preterms. All other sections (Visual, Vestibular, Tactile, Oral) were found in four out of the six studies. The Low registration quadrant was found to be (most) affected in five studies.[81,82,85,86,88] Three studies (also) found the other quadrants to be affected in preterms.[81,82,85] However, in all ten studies that found significantly more sensory modulation problems using the same measure, no clear pattern of problems emerged for the quadrants and/or sections, with the exception that three studies found Low registration (underresponsivity) to be the most affected quadrant with 23–46% of preterm children scoring < 1 SD.[81,85,88] One cross-sectional study[81] found that the incidence of atypical score(s) on the

Table 2.1. Study characteristics and key results of included studies

	Group characteristics		Study characteristics				Key results							
			Design	Measures	Aim	QS	Sensory modulation			Perinatal risk factors			Behavioral/neurocognitive measures		
	n/GA/age							*p*		Stat	*p*		Stat	*p*
Standardized test														
Wiener et al., 1996	*n* PT/NC	56/228	Cross sectional	TSFI BSID	Sensory modulation and neurodevelopment in late preterm infants	6	Sensory modulation PT<NC:			-			No significant associations:		
	GA (wks)	< 36					TSFI Total scale	< .01					TSFI-BSID		
	GA M(SD)	31(-)					All TSFI subscales	< .05							
	Age (mo)	7–18													
Chorna et al., 2014	*n* PT/NC	72/-	Cross sectional	TSFI BSID-III	Sensory reactivity and neurodevelopment in preterms	4	Sensory modulation PT < norm-referenced group:			One week ↓GA ↑odds of lower tactile deep pressure score	1.68[e]	< .001	No significant associations:		
	BW (g)	< 1500					Abnormal score ≥ 1 TSFI subscale = 82%:			Ocular-motor control-severe WMI	16.7[e]	< .001	Total number of deficient TSFI subscales-BSID-III		
	GA median (IQR)	28 (27–30)					Adaptive motor function = 40%								
	Age (mo)	4–12					Reactivity to tactile deep pressure = 49%								
							Visual-tactile integration = 21%								
							Ocular–motor control = 12%								

Table 2.1. *Continued*

	Group characteristics		Study characteristics				Key results							
			Design	Measures	Aim	QS	Sensory modulation		Perinatal risk factors			Behavioral/neurocognitive measures		
	n/GA/age							*p*		Stat	*p*		Stat	*p*
							Reactivity to vestibular stimulation = 21%							
Cabral et al., 2016	*n* PT/NC	15/15	Cross sectional	TSFI	Sensory processing in preterms	6	Sensory modulation PT < NC:		-			-		
	GA (wks)	< 37					TSFI Total scale	.01						
	GA M(SD)	31.3 (1.8)					Reactivity to tactile deep pressure	< .001						
	Age (mo)	4–6 CA												
Pekçetin et al., 2016	*n* PT/NC	34/34	Interven-tion study	TSFI	Efficiency of sensory integration interventions in preterms	6	Sensory modulation PT<NC (before intervention):		-			-		
	GA (wks)	< 37					TSFI Total scale	< .001						
	GA M(SD)	-/-					all TSFI subscales	< .02						
	BW M(SD)	1503(482)												
	Age (mo)	7 CA												
Standardized test and Caregiver Questionnaire														
Bart et al., 2011	*n* PT/NC	124/33	Cross sectional	TSFI ITSP	Sensory modula-tion and participation in preterms	7	Sensory modulation PT<NC:		Explained variance:			-		
	GA (wks)	34–37					ITSP Oral	.04	SP+TSFI-GA	0.08[a]	< .001			

Table 2.1 continues on next page.

Table 2.1. *Continued*

	Group characteristics		Study characteristics				Key results						
			Design	Measures	Aim	QS	Sensory modulation		Perinatal risk factors		Behavioral/neurocognitive measures		
	n/GA/age							*p*	Stat	*p*		Stat	*p*
	GA M(SD)	34.9 (0.6)					ITSP Auditory	.03					
	Age (mo)	12					TSFI Total scale	.001					
							all TSFI subscales	< .01					
Caregiver Questionnaire													
Case-smith et al., 1998	*n* PT/NC	45/22	Cross sectional	SRS BSID-II	Sensory responsiveness and temperament in preterms	6	Sensory responsiveness PT<NC:		-		No significant associations:		
	GA (wks)	24–36					Total	.001			SRS-BSID-II		
	GA M(SD)	29.7(3.1)					Touch	.001					
	Age (mo)	12 CA									Positive associations within SRS:		
											Touch-difficult temperament	.63[b]	< .01
											Hearing-difficult temperament	.41[b]	< .01
											Vision-difficult temperament	.31[b]	< .05
Janssen et al., 2009	*n* PT/NC	69/30	Cohort	ITSP BSID-II	Prevalence of psychopathology in preterms	6	Prevalence of psychopathology:		-		-		
	GA (wks)	25–36					PT(54%) > NC(30%):	< .05					

Table 2.1. *Continued*

	Group characteristics		Study characteristics				Key results						
			Design	Measures	Aim	QS	Sensory modulation		Perinatal risk factors		Behavioral/neurocognitive measures		
	n/GA/age							*p*	Stat	*p*	Stat		*p*
	GA M(SD)	2.7(2.4)					Multisystem develop-mental disorder: PT(6/69) > NC (0/30)						
	Age (mo)	12 CA					Regulatory disorder: PT (3/69) > NC(0/30)						
Verkerk et al., 2011	*n* PT/NC	151/42	RCT	SP	Intervention study of sensory processing in preterms	6	Sensory modulation PT = NC, except: PT + intervention > NC		-		-		
	GA (wks)	< 32					Oral	.03					
	GA M(SD)	29.8(2.2)					PT+ care as usual < NC:						
	Age (mo)	44 CA					Endurance/Tone	< .001					
Wickrema-singhe et al., 2013	*n* PT/NC	107/-	Cross sectional	ITSP/SP BSID-III WPPSI WISC	Sensory modula-tion in preterms	4	Sensory modulation PT < norm-referenced group:		No significant associations with perinatal factors		No significant associations:		
	GA (wks)	< 32					Auditory	< .01			ITSP-BSID/ WPPSI/WISC		
	GA M(SD)	28.3(2.3)					Tactile	< .02					
	Age (yrs)	1–8					Vestibular	< .01					
							All four quadrants	< .03					
							87% < -1 SD any section/quadrant						

Table 2.1 continues on next page.

Table 2.1. *Continued*

	Group characteristics		Study characteristics				Key results							
			Design	Measures	Aim	QS	Sensory modulation		Perinatal risk factors			Behavioral/neurocognitive measures		
	n/GA/age							*p*		Stat	*p*		Stat	*p*
							58% < -1 SD (> 1section/ quadrant) 39% < -2 SD any section/quadrant Low registration: 23% < -1 SD Other quadrants: 10/11% < -1 SD							
Eeles et al., 2013(a)	*n* PT/NC	253/65	Cohort	ITSP	Sensory modulation in relation to environmental and biological risk factors in preterms	7	Sensory modulation PT < NC:		Negative associations:			-		
	GA (wks)	< 30					All sections	< .007	Auditory-WMA	-0.54[c]	.03			
	GA M(SD)	27.3(-)					All quadrants	< .002	Visual-WMA	-0.55[c]	.03			
	Age (yrs)	2 CA							Sensation avoiding-WMA	-0.58[c]	.003			
									Oral-NICU stay	-0.05[c]	.03			
									Vestibular-NICU stay	-0.07[c]	.02			
									Sensation seeking-NICU stay	-0.05[c]	.04			

Table 2.1. *Continued*

	Group characteristics		Study characteristics				Key results						
			Design	Measures	Aim	QS	Sensory modulation		Perinatal risk factors		Behavioral/neurocognitive measures		
	n/GA/age							*p*	Stat	*p*		Stat	*p*
Eeles et al., 2013(b)	*n* PT/NC	241/-	Cohort	ITSP	Sensory modulation and neurodevelopment in preterms	4	See Eeles et al., 2013(a)		-		Positive associations:		
	GA (wks)	< 30									Low registration-MDI	4.24[c]	.001
	GA M(SD)	27.3(-)									Auditory-MDI	4.33[c]	.001
	Age (yrs)	2 CA									Visual-MDI	3.81[c]	.01
											Touch-MDI	2.94[c]	.03
Dudova et al., 2014	*n* PT/NC	75/-	Cross sectional	ITSP MCHAT CSBS-DP-ITC	Screening for autism spectrum disorders in preterms	4	Sensory modulation PT<norm-referenced group		No significant associations with perinatal factors		-		
	birth weight	< 1500g					15% < -2 SD (ITSP/MCHAT/CSBS-DP-ITC)						
	GA M(SD)	28.4(2.8)					42% < -2 SD (≥ 1 questionnaires)						
	Age (yrs)	2 CA					12% ASD diagnosis confirmed by clinical assessment						

Table 2.1 continues on next page.

Table 2.1. *Continued*

	Group characteristics		Study characteristics				Key results							
			Design	Measures	Aim	QS	Sensory modulation		Perinatal risk factors			Behavioral/neurocognitive measures		
	n/GA/age							*p*		Stat	*p*		Stat	*p*
Rahkonen et al., 2015	*n* PT/NC	44/-	Cross sectional	ITSP BSID	Sensory modulation neonatal risk factors and neuro-development in extreme preterms	4	Sensory modulation PT < norm-referenced group		Sensation seeking PT < NC if:			-		
	GA (wks)	< 28					52% < -1 SD (≥ 1 quadrant/section):							
	GA M(SD)	26.3(1.2)					Low registration: 23%		Grey + WMA	-	< .01			
	Age (yrs)	2 CA					Sensory avoiding: 18%		Surgical PDA	-	.01			
							Sensation seeking: 14%		Oral PT < NC if:					
							Sensory sensitivity: 7%		Surgical PDA	-	< .01			
							Vestibular: 18%							
							Oral: 18%							
							Visual: 16%							
							Tactile: 9%							
							Auditory: 7%							
Adams et al., 2015	*n* PT/NC	54/73	Cross sectional	SSP BRIEF-P EF tasks Vineland	Sensory modulation and executive/adaptive functioning	7	Sensory modulation PT (37%) < NC (12%):	.001	Explained variance in sensory modulation:			Negative associations Total SSP with BRIEF-P:		
	GA (wks)	< 34					SSP Total	< .001	SSP Total -GA	0.16[a]	< .001	Total score	-.59[d]	< .01
	GA M(SD)	29.5 (2.5)					Underresponsive/ seeks sensation	< .001	No other significant associations			Working memory	-.63[d]	< .01

Table 2.1. *Continued*

	Group characteristics		Study characteristics				Key results						
			Design	Measures	Aim	QS	Sensory modulation		Perinatal risk factors			Behavioral/neurocognitive measures		
	n/GA/age							*p*		Stat	*p*		Stat	*p*
	Age (yrs)	3–5					Movement	< .002				Inhibition	-.55[d]	< .01
							Auditory	< .001				PT+(elevated SSP) vs PT-(no elevated SSP):		
							Visual/auditory	< .001				EF battery-Gift wrap		.02
							Low energy/weak	.003				No significant association SSP-Vineland		
Crozier et al., 2016	*n* PT/NC	160/-	Cohort	SSP	Prevalence and type of sensory processing differences	4	Sensory modulation problems in PT (< -1 SD)		PT + (SSP < -1 SD) vs PT - (SSP > -1 SD): negative association:			-		
	GA (wks)	< 32					All domains: 46%		Apgar score	0.81[e]	.03			
	GA median (IQR)	26 (25–28)					Underresponsive/seeks sensation: 46%		Positive association					
	Age (yrs)	4.5					Movement: 33%		NICU days	1.01[e]	.02			
							Auditory: 44%							
							Visual/auditory: 46%							
							Tactile: 45%							
							Taste/smell: 31%							
							Low energy/weak: 40%							
							Underresponsive/seeks sensation: 46%							

Table 2.1 continues on next page.

Table 2.1. *Continued*

	Group characteristics		Study characteristics				Key results							
			Design	Measures	Aim	QS	Sensory modulation		Perinatal risk factors			Behavioral/neurocognitive measures		
	n/GA/age							*p*		Stat	*p*		Stat	*p*
May-Benson et al., 2009	*n* SPD/ SPD+ ASD	1000/465	Population based	Clinical exam	Incidence perinatal/developmental problems in children with SPD (and ASD)		No significant difference between SPD and SPD + ASD group on GA					-		
	% < 37 wks SPD/ SPD+ ASD	12.4/16					Prevalence of prematurity higher than national average in SPD + ASD group							
	Age (yrs)	3–17												
Franci Crepeau-Hobson 2009	*n* NC	152	Population based	SSP	Perinatal risk factors and sensory modulation		GA predicted SSP Total and subscales		Negative associations:			-		
	Age (yrs)	3–7							Total SSP-GA	-.16[b]	< .05			
									Tactile-GA	-.24[b]	< .05			
									Movemen-GA	-.20[b]	< .05			
									Underrespon-sive/seeks sensation-GA	-.14[b]	< .05			
									Explained variance:					
									Tactile-GA	.051[a]	.004			

Table 2.1. *Continued*

	Group characteristics		Study characteristics				Key results						
			Design	Measures	Aim	QS	Sensory modulation		Perinatal risk factors			Behavioral/neurocognitive measures		
	n/GA/age							*p*		Stat	*p*		Stat	*p*
Van Hulle et al., 2012	*n* NC twins	978	Population based cohort	TBAQ	Sensory over-responsivity in typically developing twins		GA was associated with stability of sensory modulation problems		One week ↑GA ↓odds modulation problems both 2 and 7 years	.087[e]	.05	Stability of Tactile over-responsivity (2 and 7 years): positive association:		
	Age (yrs)	2 and 7							Stability of Tactile over-responsivity (2 and 7 years) negative association:			Object fear	4.1[f]	< .001
									GA	3.2[f]	.002	Social fear	2.8[f]	.006
												Soothability	2.1[f]	.04
												Stability of Auditory over-responsivity (2 and 7 years): positive association:		
												Social fear	2.2[f]	.03
												Soothability	2.1[f]	.04

Note. A dash (-) means that associations were not investigated.
[a] = R^2; [b] = Pearson correlation; [c] = Regression coefficient; [d] = Spearman correlation; [e] = odds ratio; [f] = *t*-value.
Abbreviations: QS = quality score; PT = preterms; NC = normal controls; TSFI = Test of Sensory Functions in Infants; BSID (II/III) = Bailey Scales of Infant Development (II/III); ITSP = Infant/Toddler Sensory Profile; GA = gestational age; CA = corrected age; SRS = Sensory Responsiveness Scale; SP = Sensory Profile; RCT = randomized controlled trial; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; WISC = Wechsler Intelligence Scales for Children; WMA = white matter abnormalities; NICU = neonatal intensive care unit; MDI = mental development index M-CHAT = Modified Checklist for Autism in Toddlers; CSBS-DP-ITC = Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist; ASD = autism spectrum disorder; SSP = Short Sensory Profile; BRIEF-P = Behavior Rating Inventory of Executive Function- Preschool Version; EF = executive functioning; IRQ = inter quartile range; SPD = sensory processing disorder; TBAQ = Toddler Behavioral Assessment Questionnaire (Sensory overresponsivity scale; similar to SSP).

ITSP/SP was similar across two different age groups with 37% of the 1–4 year olds (*n* = 70) and 43% of the 4–8 year olds (*n* = 37) obtaining at least one atypical score.

Sensory Rating Scale

One study used the SRS, showing that preterm born infants had more sensory modulation problems than term born children as assessed with the SRS Total score and most pronounced for Touch sensitivity.[79]

Test of Sensory Functions in Infants

Five studies used the TSFI.[77,78,89–91] Three studies found that preterm infants performed worse than term-born controls on the Total scale and all subscales, tapping into different aspects of sensory modulation (i.e. Response to tactile deep pressure, Visual-tactile integration, Adaptive motor, Ocular motor and Reactivity to vestibular stimulation).[77,78,91] Cabral and colleagues[90] found that preterm infants performed worse on the Total scale and on their Response to tactile deep pressure in comparison to term-born controls. One study, with norm-referenced comparison, found that 82% of preterms had at least one at-risk/deficit range subscale score, with Response to tactile deep pressure and Reactivity to vestibular stimulation most frequently affected.[89] Also, Wiener et al.[77] found that with increasing age, preterms more frequently reached scores in the at-risk and deficit range. On Reactivity to vestibular stimulation, all preterms scored in the at-risk or deficit range, independent of their age.

Sensory modulation and perinatal risk factors

Eight of the included studies investigated relations between prenatal, perinatal and neonatal factors, and sensory modulation problems.[78,82,85,86,88,89,92,93] Five studies found that GA was negatively associated with sensory modulation problems.[78,86,89,92,93] Three studies found that white (and grey) matter brain abnormalities were positively associated with sensory modulation problems (poor ocular motor control, auditory modulation, sensation seeking and sensation avoiding),[82,85,89] and two studies found that length of NICU stay was positively associated with sensory modulation problems (oral modulation and sensation seeking).[82,88] In addition, Rahkonen et al.[85] found that surgical closure of patent ductus arteriosus (PDA) was positively associated with the Sensation Seeking quadrant and Oral modulation and Crozier et al.[88] reported that Apgar scores were associated with sensory modulation problems in very preterm children.

The population-based study of Franci Crepeau-Hobson[93] found that GA was negatively associated with the Total SSP score, Tactile sensitivity, Movement sensitivity and the

Underresponsive/Seeks Sensation factor scores. Another population-based study, by Van Hulle et al.,[92] showed that an increase of one week in gestational age decreased the odds of having sensory overresponsive symptoms at both 2 and 7 years of age, as measured with the Sensory Overresponsivity subscale (item content highly similar to SSP) of the Toddler Behavioral Assessment Questionnaire (TBAQ).[95] In addition, an interaction was found between GA and stability of tactile overresponsivity, such that the earlier a child was born, the more strongly early tactile symptoms were found to predict later tactile symptoms. Thus, symptoms of tactile overresponsivity were more stable across time among children born prematurely than among term-born children.

Sensory modulation and neurocognitive functioning

The relationship between sensory modulation problems and cognitive development was examined in seven studies of which five found that sensory modulation problems were not significantly related to cognitive development.[77,79,81,85,89] However, two studies did find associations between sensory modulation problems and cognitive functioning.[83,86] Eeles et al.[83] found that lower scores in the Low registration quadrant and the Auditory, Visual and Touch sections were related to lower mental scores on the BSID (BSID II-III).[96] Adams et al.[86] found that elevated numbers of sensory modulation symptoms (SSP Total score, Taste/smell sensitivity, Underresponsive/seeks sensation, Auditory filtering, Low energy/weak, Visual/auditory sensitivity) showed more executive impairment on the Behavior Rating Inventory of Executive Function- Preschool Version (BRIEF-P) Total score.[97] SSP total score had the highest correlation with the subscales Working memory and Inhibition. Also, the SSP total score was positively associated with inhibition/delayed gratification (Gift wrap) on a performance-based EF battery[86] when preterms were split in two groups (elevated SSP scores vs no elevated SSP scores).

Sensory modulation and behavioral functioning

The relationship between sensory modulation and behavior was examined in five studies.[79,80,84,92,94] Both Dudova et al.[84] and May-Benson et al.[94] found evidence that sensory modulation problems and ASD coincide, by showing a higher prevalence of ASD and sensory modulation problems in preterm born infants than in term controls. Case-Smith[79] found moderate positive associations between both Hearing sensitivity and Vision sensitivity (SRS) and difficult temperament. Strong positive associations were found for Touch sensitivity, explaining 40% of the variance in temperament.[79] Janssens et al.[80] classified infants according to the Diagnostic Classification Zero to Three (DC:0-3)[98] with structured interviews, clinical observations, ITSP, BSID-II and a language inventory. The ITSP was used to diagnose Regulatory

Disorders (RD) and Multisystem Developmental Disorder (MSDD). It was found that significantly more preterms (54%) than controls (30%) suffered from psychopathology. The most common diagnosed disorders in preterms were MSDD and RD, whereas none of the controls had MSDD or RD. Van Hulle et al.[92] found that sensory overresponsivity was associated with temperament dimensions of fear and soothability and that stability of sensory overresponsive symptoms over time was partly determined by fearful and less soothable temperaments. However, this was true for the complete sample of typically developing twins, and not specific for preterm born children.

Risk of bias

Some selection bias is present in the 15 studies in preterm children due to both recruitment procedures and differences in terms of inclusion and exclusion criteria for preterms and controls. In only two out of 15 studies, a consecutive sample was included.[84,85] In all other studies, a fixed timeframe of inclusion was used or children shared a uniform selection method at one hospital or clinic, mitigating this effect of bias. Selection bias in the control groups mainly comprises the (absence of reports on) non-response rates due to convenience sampling.[77–80,82,83,86,88,90,91] However, all control groups were community controls and there were no preterm born children included in control groups. Exclusion criteria were not reported in five out of 15 studies.[78,81,85,87,88] Exclusion criteria (e.g. congenital/metabolic disease, major neurosensory disabilities, CP, language) were sufficiently described and equal in the remaining ten studies.[77,79,80,82–84,86,89–91]

Preterms participating in the included studies differed in terms of baseline characteristics, including GA, birth weight, neonatal complications and social background characteristics. Of the 1259 included preterm infants, 10% were late preterm, 17% were born between 23–37 weeks, 70% were born very preterm and 3% were born extremely preterm. Yet, comparability between the preterm groups and the control groups is relatively high as almost all case-controlled studies matched on age, and four studies also matched on social economic status and/or gender.[80,83,86,87]

Some performance bias advances as administration of the TSFI and cognitive tasks was not blinded.[77–80,83,86,87,89–91] However, most studies used the SP/ITSP which are based on parental reports and therefore not susceptible to performance bias.[78,80–87] Detection bias is present due to differences between the studies in terms of the measures used to assess sensory modulation, however, 11 out of 18 studies shared the same measurement (ITSP/SP/SSP). Attrition bias is common in observational studies with preterm children, but in almost half of the studies reasons for attrition were fully reported (death, refusal, language, emigration) and unlikely to confound results.[78,80,84,85,87] Reporting bias is low in all the included studies. Publication bias is a possible

risk. This line of research in preterm children is relatively new and the topic is scarcely studied. It is possible that studies with non-significant results between preterm and term born children may not have been published. No conflicts of interest are reported in any of the studies.

DISCUSSION

The present study reviewed the empirical literature on sensory modulation problems in preterms. Evidence was found in support of sensory modulation problems in preterms.[77–86,88–91] It was found that prematurity may distort various aspects of sensory modulation, including problems across sensory modalities (auditory, visual, vestibular, tactile and taste)[81–83,85,86,88] and sensory modulation functions (Response to tactile deep pressure, Visual-tactile integration, Adaptive motor, Ocular motor and Reactivity to vestibular stimulation)[77,78,89–91] resulting in behavioral patterns of various nature (Low registration, Sensation seeking, Sensation avoiding/ emotionally reactive, Sensory sensitivity).[81–83,85,86,88] Consequently, the nature and severity of the sensory modulation problems differed widely between the studies. The observed heterogeneity in the distortions might be explained by differences between the studies in terms of the measures used to assess sensory modulation. Although even in the studies where the same measure (ITSP) was used, no clear pattern of problems emerged for either one of the quadrants and/or sections, with the exception that Low registration (underresponsivity) was the most affected quadrant.[81,85,88] A second explanation for the heterogeneity in the findings of the present review might be differences in the factors leading to sensory modulation problems in preterms, including altered cortical organization due to too early extra-uterine exposure.[31] hypoxia-ischemia and inflammation leading to disturbances in cerebral white matter integrity, as well as under- and overstimulation during NICU stay due to parental separation and lights, noises, nursery handling and pain, respectively. Some preterms could have suffered more from overstimulation with excitotoxic damage and possible downregulation of the sensory system, while other preterms might have suffered more from understimulation with apoptosis and upregulation of the sensory system. Consequently, the atypical sensory modulation scores across the ITSP/SP quadrants are suggested to be an offshoot of originally adaptive responses to this down- and upregulation.[82] However, after the NICU stay, these regulatory responses may have become maladaptive, resulting in sensory modulation problems later in life.[82] The relatively high incidence of regulatory disorders among preterms would also fit this hypothesis.[80]

The included studies that did not find sensory modulation problems[87,94] differed from the other studies in terms of their study design. Rather than using a comparative group design, Verkerk et al.[87] performed an intervention study within a sample of preterm born infants. Nevertheless, no significant differences in sensory modulation were found in this study in comparison with

term born controls, except for Endurance/tone. May-Benson et al.[94] conducted an explorative descriptive study in children with ASD and SPD, in which prematurity was used as a dichotomous within-subject factor, whereas in the other population-based studies GA was used as a continuous variable, offering a statistically more powerful design to assess the effects of GA.

Our findings are in accordance with a recent review demonstrating greater risk of SPD in preterm born preschoolers.[49] Our review adds to that finding by showing that problems are not limited to preterm infants, but that sensory modulation problems are also evident in preterm children (1 to 8 years of age). Moreover, associations were described between sensory modulation and perinatal risk factors, neurocognitive and behavioral measures.

The mechanisms of brain development in preterms and the detrimental effects of NICU stay are highly suggestive for sensory modulation problems.[7,43,51,59] However, research on the etiological mechanisms causing sensory modulation problems in preterms is scarce. The current review has found relevant predictors for developing sensory modulation problems, including GA, birth weight, white (and grey) matter abnormalities, length of NICU stay and PDA.[78,82,85,86,88,89,92,93] These studies await replication, but the results suggest a dose-response relationship between both white matter brain injury and NICU stay and sensory modulation problems. However, given the correlational design of these studies, a causal relationship between sensory modulation problems and NICU environment and white brain matter abnormalities is not established.

The relationship between sensory modulation problems and cognitive development is still unclear. In the reviewed literature some study results suggest that sensory modulation problems are a separate and independent part of child development,[77,79,81,85,89] whereas other studies found significant associations between sensory modulation and neurocognitive outcomes, including executive functioning problems.[83,86] These results suggest that children with low registration, described by high perception thresholds and passive self-regulation, are hampered in their learning opportunities due to little exploration and engagement. In addition, Adams et al.[86] found that sensory modulation problems coincided with problems in executive functioning, especially working memory and inhibition. These findings suggest that the vulnerable self-regulatory abilities of preterm infants in the NICU may grow into disrupted higher-order cognitive control in terms of executive functioning problems and sensory modulation problems later in life.[99] To increase our understanding of the possible relations between sensory modulation and cognitive development, more research is needed.

In addition, sensory modulation and behavior may be related.[79,80,84,92,94] Two included studies showed that sensory modulation problems and ASD coincide[84,94] and associations were found between sensory modulation problems and regulatory disorder and difficult, fearful and less soothable temperament.[79,80,92] These results are in accordance with studies in both ADHD and

ASD, showing that problems in sensory modulation are strongly associated with ADHD and ASD symptoms.[61–63] Given the fact that ADHD and ASD symptoms are known to be elevated in preterms,[6–9] a possible developmental trajectory emerges in which preterms with sensory modulation problem are at enhanced risk to develop symptoms of ADHD and ASD. In fact, sensory modulation problems may be one of the explanations for the high prevalence of ADHD and ASD symptoms found in preterms. This possible association between ADHD, ASD and sensory modulation also requires additional research.

Although the present review supports the idea that sensory modulation in preterm born infants is at stake, caution is required in interpreting the results due to risk of bias and limited quality of some studies. First, some selection bias is present in the studies due to recruitment procedures, different exclusion criteria and lack of comparability between groups of preterms. In addition, characteristics of the samples, if reported, vary in terms of neonatal complications, race and SES, hampering generalizability of findings. Second, common short-comings in research in preterm children, such as convenience sampling of control participants, high attrition rates, and sole use of norm-referenced data, are also present in some of the included studies. However, comparability between the preterm groups and the control groups is relatively high as almost all studies matched on age and social economic status and/or gender. Thirdly, the available studies on sensory modulation pertain to a restricted age group. Although three studies with different age ranges[81,86,88] show persistent sensory modulation problems in preterm children aged > 2 years and more apparent impaired sensory modulation with increasing age, this important finding awaits replication. Lastly, publication bias is a possible risk, as sensory modulation is a scarcely studied area in preterm children and studies with non-significant results may fail to be published.

Future research on sensory modulation in preterm children is clearly needed to replicate and extend the available results. Such studies need to be term-born controlled longitudinal studies combining sensory modulation measures with neurocognitive measures and behavioral measures tapping into ADHD and ASD.

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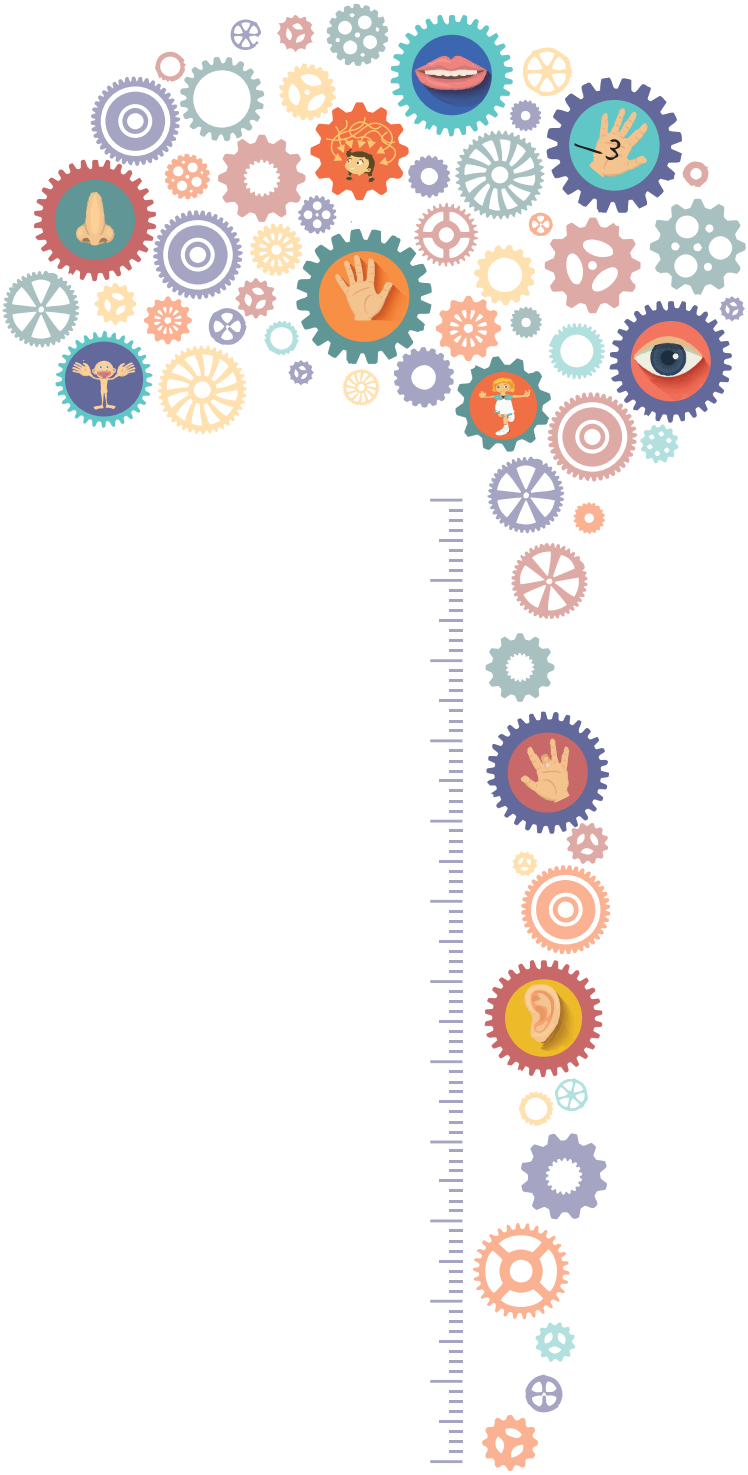

3

Sensory processing difficulties in school-age children born very preterm: an exploratory study

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ABSTRACT

Background Very preterm birth has a detrimental impact on the developing brain, including widespread white matter brain abnormalities that threaten efficient sensory processing. Yet, sensory processing difficulties in very preterm children are scarcely studied, especially at school age.

Aims To investigate somatosensory registration, multisensory integration and sensory modulation.

Participants 57 very preterm school-age children (mean age = 9.2 years) were compared to 56 gender and age matched full-term children.

Methods Group differences on somatosensory registration tasks (Registration of Light Touch, Sensory Discrimination of Touch, Position Sense, Graphestesia), a computerized multisensory integration task, and the parent-reported Sensory Profile were investigated using *t*-tests and Mann-Whitney *U* tests.

Results In comparison to full-term children, very preterm children are less accurate on somatosensory registration tasks, including Registration of Light Touch (d = 0.34), Position Sense (d = 0.31) and Graphestesia (d = 0.42) and show more sensory modulation difficulties (d = 0.41), including both behavioral hyporesponsivity (d = 0.52) and hyperresponsitivity (d = 0.56) to sensory stimuli. Tactile discrimination and multisensory integration efficiency were not affected in very preterm children. Aspects of sensory processing were only modestly related.

Conclusion Very preterm children show sensory processing difficulties regarding somatosensory registration and sensory modulation, and preserved multisensory (audio-visual) integration. Follow-up care for very preterm children should involve screening of sensory processing difficulties at least up to school age.

INTRODUCTION

Worldwide, around 1.6 million children are born very preterm (< 32 weeks of gestation) each year.[1] An estimated 24% of very preterm children show neurodevelopmental impairments,[1] including motor, cognitive and behavioral problems.[2–5] These functional impairments arise from the detrimental impact of very preterm birth on the developing brain, with widespread white matter abnormalities[6–8] that threaten the efficient processing of sensory information as a consequence.[9] The current study aims to elucidate the effects of very preterm birth on sensory processing at school age.

The neuropathology of very preterm birth is thought to be caused by a complex constellation of primary pathological mechanisms[10] and secondary harmful environmental influences related to treatment and stay at the neonatal intensive care unit (NICU).[8] Very preterm infants tend to develop hypoxia-ischemia and inflammation, leading to damage to oligodendrocyte progenitors resulting in disrupted maturation of myelin forming oligodendrocytes and ultimately diffuse white matter damage and periventricular leucomalacia (PVL).[10–12] In addition, environmental factors of the NICU further compromise normal brain development,[8,13,14] through early exposure of the rapidly developing immature preterm brain to extra-uterine sensory experience.[15–17] More specifically, sensory overstimulation (e.g. bright lights, noise, nursery handling, repetitive pain)[18,19] may cause excitotoxic neural damage, while sensory understimulation (e.g. tactile, vestibular and kinesthetic deprivation due to parental separation during unavoidable stay in the incubator) is suggested to cause apoptotic damage.[8,13,20,21]

Consistent with these findings, children born very preterm show deviant brain development as compared to their term born peers.[17,22] The available body of research has shown reduced brain volume,[23,24] abnormal white matter integrity and disrupted structural and functional brain connectivity in children born preterm.[25,26] Since very preterm birth threatens the connectivity of brain networks that facilitate efficient integration of sensory information throughout the brain,[9,27] children born very preterm are at risk of sensory processing difficulties.

Sensory processing difficulties concern impaired processing of sensory information and/or ineffective responses to sensory information that affect participation in daily life activities.[28,29] Sensory processing includes *registration*, *integration* and *modulation* of sensory stimuli.[28,29] Sensory *registration* difficulties comprise disturbances in identification, discrimination and interpretation of sensory stimuli.[30] The burden on the tactile sense (i.e. somatosensory processing) in particular is significant for very preterm children, because of early exposure to frequent and painful somatosensory stimuli (e.g. nursery handling, heel lancing, venipunctures, nasal suctioning, inflammatory pain) and early deprivation of parental stimulation.[15,16,18] Sensory *integration* difficulties include disturbances in the integration of information from

multiple sensory modalities.[30,31] The integration of multisensory information is crucial for the reconstruction of a full representation of the multisensory environment and efficient interaction with this environment.[31] Sensory *modulation* difficulties pertain to an impaired regulation of the intensity of responses to sensory stimuli, resulting in behavioral hyporesponsivity and/or hyperresponsivity with subsequent maladaptive emotional, attentional, and motor responses to sensory stimuli.[29,30,32] Sensory processing abilities relate to neurocognitive and academic functioning[33–35] in school-age children. For example, efficient sensory processing in one year old infants has even been found to predict intelligence at age six.[36] In addition, sensory processing difficulties hamper normal development by interfering with social activities, play and leisure[35,37] and have been found implicated in neurodevelopmental disorders, including attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD).[31,38–40] These findings indicate that adequate sensory processing is pivotal for normal child development.

Sensory processing difficulties have scarcely been studied in very preterm children. In the domain of somatosensory registration, thermal sensitivity was found to be affected in extremely preterm children[41] and in very preterm children less effective manual form perception, kinesthesia, finger identification, graphestesia and localization of tactile stimuli were found.[42] However, this last study was an uncontrolled study that compared very preterm children to norm referenced scores. In the integration domain, visual-motor integration problems have been observed in preterm children,[43,44] and have been shown to persist up to adult age.[45] However, multisensory integration involving other modalities has not received much attention, with only one study showing poor visual-proprioceptive integration in very low birth weight adolescents[46] and one study showing no difference between very preterm and full-term children in visual-tactual integration.[36] Yet, early multisensory interventions during NICU stay have been studied more extensively in the past decades[47–52] and have recently been reviewed by Pineda and colleagues.[53] These authors concluded that multisensory interventions resulted in better infant development and lower maternal stress, but also warned that results were inconsistent and that interventions were implemented for only short periods of time. In the modulation domain, our recent systematic review reported evidence in 14 out of 16 studies for sensory modulation difficulties in preterm children across all sensory modalities and both behavioral hyporesponsivity and hyperresponsivity to sensory stimuli.[54] Moreover, it was found that sensory modulation difficulties were related to lower social participation in one-year-old late preterm infants,[55] neurodevelopmental delay in two-year-old very preterm children,[56] executive functioning in 3–5-year-old extreme preterm children[57] and symptoms of ASD in two year old very preterm children.[54,58] Yet, only one study has included children at school age, using an uncontrolled design.[59] All other studies in this review included children below age five and mostly around one or two years of age.[54] Taken together, the available studies on sensory

processing difficulties after preterm birth are scarce, frequently use uncontrolled designs or focus on children at infant or preschool age.

This study aims to explore the effects of prematurity on somatosensory registration, multisensory integration and sensory modulation in very preterm school-age children in comparison to full-term children, using a multimodal assessment battery including behavioral somatosensory registration tasks,[60] a computerized multisensory integration task[61] and the parent-reported Sensory Profile[62] to assess sensory processing difficulties. The results of this exploratory study may contribute to a better understanding of the multifaceted problems occurring in the developmental trajectory of very preterm children and may additionally target sensory processing as an important domain for follow up care in this large group of children.

METHODS

Participants

A sample of 57 very preterm children and 56 gender and age matched full-term children participated in the current study. The very preterm children had participated in a randomized controlled trial (RCT) evaluating the effects of postdischarge formula on growth and body composition between term age and six months corrected age.[63] Eligible for inclusion in the current study were all very preterm children admitted between August 2003 and July 2006 to the neonatal intensive care unit (NICU) of the VU University Medical Center, Amsterdam, The Netherlands. Inclusion criteria were a gestational age less than or equal to 32 weeks or a birth weight less than or equal to 1500g and at least one main caretaker understanding the Dutch or English language. Exclusion criteria were: infants with congenital malformations or conditions known to affect growth and/or body composition (i.e. severe bronchopulmonary dysplasia, inborn errors of metabolism, cardiac or renal disease, necrotizing enterocolitis with substantial gut loss, grade IV intraventricular hemorrhage). Baseline characteristics of the sample have previously been reported.[63] Of the 152 infants included in the original RCT, 139 completed the study at six months corrected age. For the current study at 8–9 years of age, 17 children were lost to follow up and 10 children were additionally excluded because they could not meet the test situation demands due to severe physical/neurosensory disabilities. All other 112 children were contacted and invited to participate, to which 57 (51%) agreed. No differences were found between the group of participants and the total group of non-participants (n = 95) on sex, parental education, gestational age (GA), birth weight, PVL, and the presence of perinatal infections (all $p \geq .14$).

The gender and age matched full-term control group was recruited from primary schools located in the same provinces as schools attended by the very preterm children, and included children without histories of prematurity (GA > 37 weeks), perinatal complications, neurological disorders, and diagnoses of ADHD and/or ASD as reported by parents.

Socio-economic status (SES) was determined by classifying the highest level of parental education in a household on a four-point scale (low, low intermediate, high intermediate, and high) with higher scores indicating higher levels of education and corresponding higher SES.[64] Medical characteristics of the very preterm group were obtained from medical files and included GA (weeks of gestation), birth weight (grams), small for GA (SGA, defined as either birth length or weight < 2 SD), length of stay in a hospital (defined by the total number of days between admission to the VU University Medical Center and discharge from any hospital after potential transfers, including stay on the (neonatal) intensive/high care unit), presence of PVL (defined by flaring on ultrasound and/or PVL grade I/II[65]), presence of blood-culture-proven infection, subependymal hemorrhage (graded I–V[66]), and the Neonatal Medical Index (graded I–V[67]). In both the very preterm and the full-term group the full Scale Intelligence Quotient (FSIQ) was estimated using a four-subtest short form of the currently available Dutch version of the Wechsler Intelligence Scales for Children - third version (WISC-III),[68] including the subtests Similarities, Vocabulary, Picture Arrangement, and Block Design. FSIQ as measured by this short form has high reliability (r = .93) and correlates strongly with Full Scale IQ (r = .92).[69]

Measures

Sensory processing assessment included a fixed battery of experimental and validated tasks for somatosensory registration (tactile perception, kinesthesia, and graphestesia), multisensory integration (MultiSensory Integration Test; MSIT), and sensory modulation (Sensory Profile).

Somatosensory registration

Tactile perception

Two aspects of tactile perception were measured: registration of light touch and sensory-discriminative aspects of touch.[70] *Registration of Light Touch* was assessed by touching the child in a sequence of five and eight times, respectively, with a cotton wool on the skin of the right forearm, which had been placed under a screen. The child was asked to count the number of times the cotton wool touched the skin. Dependent measure was the number of errors (maximum of 2). *Sensory Discrimination of Touch* was assessed by applying a pencil with a blunt (three times) and a sharp side (pinprick; four times) to the right forearm, which had

been placed under a screen. The child was asked to indicate whether the blunt or the sharp side was applied. Number of errors (maximum of 7) was used as the dependent measure.

Kinesthesia

Kinesthesia was assessed by testing *Position Sense* of finger joints.[70] The examiner slowly stretched (six times) or bent (four times) one finger of the participant into a final joint position under a screen. The child had to indicate the final position of the finger (five repetitions for each hand). Dependent measure was the number of errors (maximum of 10). To exclude the possibility that impaired finger gnosis caused an elevated number of kinesthesia errors, finger gnosis was checked by lightly touching (but not bending or stretching) one of the fingers of the child using the index finger of the examiner, upon which the child had to indicate the finger. The number of errors (maximum of 10) was the dependent variable.

Graphestesia

Graphestesia for symbols was assessed by the subtest *Graphestesia* of the Sensory Integration and Praxis Test.[60] The examiner drew 14 symbols with the index finger tip on the back of each of the child's hands under a screen, alternating the left and right hand. The child had to duplicate the symbol on the same hand with the index finger of the opposite hand. Dependent measure was the number of errors (maximum of 14 per hand, 28 in total). Content and construct validity of the SIPT have been demonstrated, and inter-rater reliability (r = .94–.99) and test–retest reliability were found to be satisfactory (r = .48–.93, Graphestesia = .74).[60,71]

Multisensory integration

The Multisensory Integration Test (MSIT)[61] is a computerized test to measure the ability to flexibly shift between conditions (i.e. set-shifting) and the efficiency of multisensory integration (see Figure 3.1). The MSIT involves three experimental conditions (*Set, Visual Shift* and *Audiovisual Shift*), pertaining to three different trial types that were presented in semi-randomized order. In the Set condition, trials initiated with the presentation of the target (i.e. a penguin presented in the center of the screen) for a random duration between 500–1500 ms, after which the target tilted to either the left or the right side of the screen. The participant was expected to deliver a motor response that was compatible with the tilt direction of the target, by pressing one of two buttons located on each side of the laptop. However, there was a 28% probability that a *shifting cue* was presented at the moment that the target tilted, indicating that now an incompatible button response was required. In the *Visual Shift* condition (14% of all trials), the shifting cue was visual (i.e. a question mark presented just above the target, not requiring any eye movement). In the *Audiovisual Shift* condition (14% of all trials), the shifting cue was

auditory (i.e. a 500 Hz monophonic tone presented through earphones). Correct responses in the *Visual Shift* condition required (1) identification of the visual set-shifting cue, and (2) identification of the direction of the visual target, measuring set-shifting based on integration within the visual modality (i.e. monosensory set-shifting). By contrast, correct responses in the *Audiovisual Shift* condition required (1) identification of the auditory set-shifting cue, and (2) identification of the direction of the visual target, therefore requiring integration across the auditory and visual modalities (i.e. multisensory set-shifting). Speed and accuracy of simple visual and auditory processing were measured in a separate testing block, using simple button responses to the appearances of a centrally presented visual target (the penguin) and auditory targets (1000 Hz monophonic tone), respectively.

Dependent variables were calculated for the three conditions separately and included mean reaction time (MRT) for correct responses and accuracy (proportion correct responses). Trials with very short RTs suspected of anticipatory behavior (RT < 250 ms) and trials with very long RTs suspected of inattentive behavior ($z > 3.29$ at the individual level) were discarded in each task condition separately. The MSIT allowed measurement of the speed and accuracy of: (1) set-shifting; and (2) multisensory integration. Set-shifting was measured by the difference in performance between the *Set* condition and the *Visual Shift* condition, whereas multisensory integration was measured by the difference in performance between the *Visual Shift* condition and the *Audiovisual Shift* condition.[61] The MSIT has proven to be sensitive to the impact of traumatic brain injury on multisensory integration.[61] Reliability of MRT and accuracy as measured by internal consistency in the relevant task conditions ranged from excellent (*Set* condition: Spearman-Brown = .97 and .96, respectively) to good (*Visual Shift* condition: Spearman-Brown = .89 and .85, respectively) and from excellent to good in the *Audiovisual Shift* condition (Spearman-Brown = .91 and .81, respectively).[61]

Sensory modulation

Sensory Profile

Sensory modulation difficulties were investigated by the Sensory Profile (SP), which is a caregiver-completed questionnaire measuring sensory modulation abilities and the effect of sensory modulation on functional performance in daily life.[62] Sensory modulation is rated on 125 items using a 5-point scale, with lower scores indicating worse sensory modulation. To compare overall sensory modulation between the very preterm and full-term group a *Total Score* of the 125 items was computed and used as a dependent measure. The rating scale is further grouped into three main sections, which are also used as dependent measures: *Sensory Processing* section, *Sensory Modulation* section, and *Behavioral and Emotional*

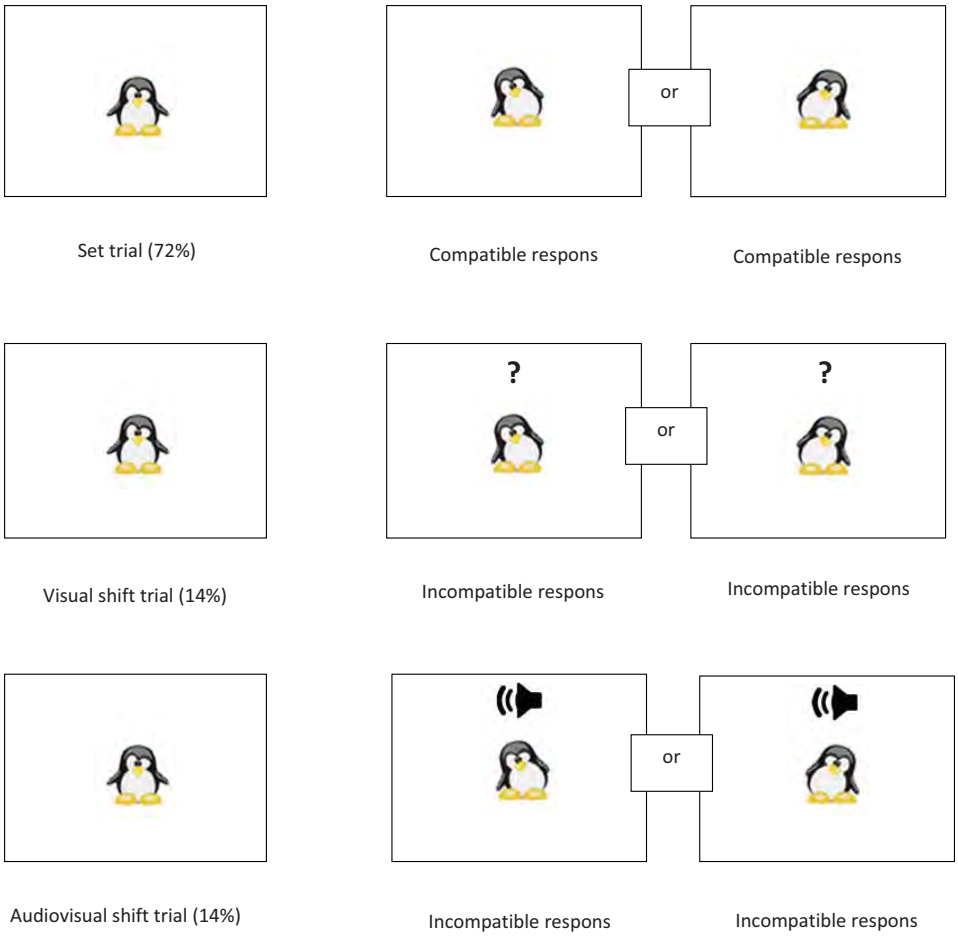

Figure 3.1. Procedure of the multisensory integration test (MSIT).
The MSIT involves three experimental conditions (*Set*, *Visual Shift* and *Audiovisual Shift*), pertaining to three different trial types that were presented in semi-randomized order. In the *Set Condition*, trials initiated with the presentation of the target (i.e. a penguin presented in the center of the screen) for a random duration between 500–1500 ms, after which the target tilted to either the left or the right side of the screen. The participant was expected to deliver a motor response that was compatible with the tilt direction of the target, by pressing one of two buttons located on each side of the laptop. However, there was a 28% probability that a *Shifting Cue* was presented at the moment that the target tilted, indicating that now an incompatible button response was required. In the *Visual Shift* condition (14% of all trials), the shifting cue was visual (i.e. a question mark presented just above the target, not requiring any eye movement). In the *Auditory Shift* condition (14% of all trials), the shifting cue was auditory (i.e. a 500 Hz monophonic tone presented trough earphones). Set-shifting was measured by the difference in performance between the set condition and the visual shift condition, whereas multisensory integration was measured by the difference in performance between the visual shift condition and the audiovisual shift condition. Speed and accuracy of simple visual and auditory stimuli detection processing were measured in a separate testing block using simple button responses to the appearances of a centrally presented visual target (the penguin) and auditory targets (not displayed).

Responses section.[62] Items in the *Sensory Processing* section pertain to the child's responses to information received through individual sensory systems. The *Sensory Modulation* section refers to the child's ability to manage competing sensory inputs and the impact of this ability on activity engagement.[62] The *Behavioral and Emotional Responses* section describes the child's emotional and behavioral responses to sensory processing. In addition, items can be categorized according to Dunn's quadrant scheme, differentiating between sensory perception thresholds (high vs. low) and self-regulation (active vs. passive).[29,62] Accordingly, four quadrants are distinguished and used as dependent measures, relating to different sensory modulation types: *Low Registration* (i.e. high sensory threshold in combination with passive self-regulation strategies), *Sensation Seeking* (i.e. high sensory threshold in combination with active self-regulation strategies), *Sensory Sensitivity* (i.e. low sensory threshold in combination with passive self-regulation strategies), and *Sensory Avoiding* (i.e. low sensory threshold in combination with active self-regulation strategies).[29,62] Content and construct validity have been established, and adequate reliability was found for the Sensory profile.[62]

Procedure

Very preterm children were assessed by a child psychologist (TB) and a trained research assistant (AB) at the pediatric outpatient clinic of the VU University Medical Center, where parents completed the SP. Children were tested in a friendly, quiet environment. Assessment of full-term children was performed likewise at their own school.

The present study was carried out between 2010 and 2015. Parents of all participating children provided written informed consent. The medical ethic committee of the VU University Medical Center approved the study protocol (# NTR2972).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, NY, USA). Dependent variables were screened for outliers ($-3.29 > z\text{-score} > 3.29$) which were rescaled according to Tabachnik and Fidell[72] by replacing outliers with the next highest or lowest score that is not an outlier.[73] This method reduces the disproportionate influence of outliers on the statistical analysis, while retaining extreme forms of variability that may be a natural aspect of the study sample. If necessary, data were normalized using Van der Waerden transformation. There were no missing data, except for three SP questionnaires in the control group that were missing due to a lack of parental compliance. Group characteristics (i.e. gender and age of the child, IQ, SES, GA, and birth weight) were compared between preterm and

full-term children using chi-square and *t*-tests. Except for *Graphestesia*, group differences on sensory registration measures (*Registration of Light Touch*, *Sensory Discrimination of Touch*, and *Position Sense*) were tested using non-parametric, Mann-Whitney *U* tests, since these measures did not meet the assumptions of normality and were immune to transformation. Group differences in multisensory integration task performance (MSIT MRT and accuracy) were assessed using repeated measures ANOVAs with group as between subjects variable (very preterm, term control) and task condition as within-subject variable. Two separate analyses were performed in which task condition had two levels (1) the task conditions *Set* and *Visual Shift* were entered to assess set-shifting, and (2) the task conditions *Visual Shift* and *Audiovisual Shift* conditions were entered to assess multisensory integration. Group differences in sensory modulation (SP questionnaire) were tested stepwise, by first comparing very preterm and full-term children on the *Total Score* using a *t*-test. If a significant difference was found on the Total Score, then group comparisons were also performed for the *Sensory Processing* section, *Sensory Modulation* section, *Behavioral and Emotional Responses* section, and the SP quadrants (*Low Registration*, *Sensation Seeking*, *Sensory Sensitivity*, and *Sensation Avoiding*). Given the relatively large number (16) of dependent variables; four in the somatosensory registration domain, four in the multisensory integration domain and eight in the sensory modulation domain, we explored the probability that our findings are random: if each individual measure would have a 50% chance of showing a difference between very preterm and full-term children (i.e. a positive result), the total number of positive results follows a binomial distribution.[74] This makes it possible to analyze formally, using a binomial distribution, whether or not the number of positive results could have been due to purely random fluctuations. To evaluate the interdependency of somatosensory registration, multisensory integration, and sensory modulation, Pearson product-moment correlation analyses were performed on all dependent variables. In case of non-normality Spearman Rho correlation analyses were performed. In addition, Pearson product-moment and Spearman Rho correlation analyses were performed to evaluate associations between medical characteristics of the very preterm group (GA, birth weight, SGA, length of hospital stay, PVL, and infection) and all dependent variables. To evaluate the effects of postdischarge formula on all dependent variables, analysis of variance was performed, including post-hoc Tukey tests to differentiate between the postdischarge formula (PDF) group, the standard term formula (SF) group and the human milk group. Effect sizes were expressed in terms of Cohen's d with values of 0.2, 0.5, and 0.8, referring to small, medium, and large effects, respectively and for correlations with values of .10, .30, and .50, referring to small, moderate, and large strength of relationships, respectively.[75] For all analyses α was set at .05.

RESULTS

Group characteristics

Group characteristics are shown in Table 3.1. As a consequence of our inclusion criteria, very preterm children had lower mean GA ($p < .001$) and mean birth weight ($p < .001$) than full-term children. There were no significant group differences with regard to sex ($p = .917$) and age at assessment ($p = .861$). The difference between groups on SES just escaped conventional levels of significance ($p = .073$). To explore the potentially confounding influence of SES, we

Table 3.1. Group characteristics of very preterm children and full-term children

Characteristic	Very preterm group	Full-term group	*p*
Age at assessment, years, M (SD)	9.2 (0.4)	9.2 (0.5)	.861
Estimated FSIQ, M (SD)	100.7 (11.2)	106.1 (12.5)	**.017**
Sex, *n* (% male)	26 (46)	25 (45)	.917
SES			.073
Low, *n* (%)	5 (9)	2 (4)	
Low intermediate, *n* (%)	22 (39)	12 (21)	
High intermediate, *n* (%)	16 (28)	18 (32)	
High, *n* (%)	14 (25)	24 (43)	
GA, weeks, M (SD)	30.2 (1.8)	39.8 (1.4)	**< .001**
Birth weight, grams, M (SD)	1293 (296)	3593 (535)	**< .001**
SGA, *n* (%)	15 (27)		
Length of hospital stay, days, M (SD)	50.3 (15.6)		
PVL			
None, *n* (%)	27 (47)		
Flaring and/or PVL grade I/II, *n* (%)	30 (53)		
Neonatal infection, *n* (%)	26 (46)		
Subependymal hemorrhage			
None, *n* (%)	50 (88)		
Grade I, *n* (%)	5 (9)		
Grade II, *n* (%)	2 (4)		
Neonatal Medical Index (NMI)			
NMI I, *n* (%)	1 (2)		
NMI II, *n* (%)	6 (11)		
NMI III, *n* (%)	28 (49)		
NMI IV, *n* (%)	15 (26)		
NMI V, *n* (%)	7 (12)		

Note. Very preterm group: $n = 57$; Full-term group: $n = 56$. There were no children with grade III or IV subependymal hemorrhage. FSIQ = Full-scale IQ; GA = gestational age; SGA = small for gestational age; PVL = Periventricular Leukomalacia. Bold numbers pertain to a significant *p*-value ($p < .05$).

added SES as a covariate to our main analyses. The interaction effects between group and SES on dependent variables were not significant, indicating that SES did not confound the group comparisons on dependent variables.

Somatosensory registration

Table 3.2 shows the results from the assessment of somatosensory registration. Compared to the full-term group, the very preterm group made significantly more errors on *Registration of Light Touch*. However, *Sensory Discrimination of Touch* as assessed by the ability to discriminate between sharp and blunt touch showed no difference between the two groups. The very preterm group performed worse on *Position Sense* of finger joints compared to the full-term group, indicating poorer kinesthesia in preterm children. No differences were found for finger gnosis, indicating that differences in *Position Sense* are not attributable to problems in finger identification. On the *Graphestesia* subtest, very preterm children made more errors than full-term children, indicating that preterm children are less efficient in copying tactile presented symbols.

Multisensory integration

Table 3.3 shows the results of MSIT performance. The main effects of task condition on MRT and accuracy measured the effects of 1) set-shifting as compared to maintaining set and 2) multisensory integration as compared to monosensory integration on set-shifting capacity. In the first analysis, both main effects were significant, indicating that set-shifting is associated with a

Table 3.2. Results of somatosensory registration

	Very preterm group		Full-term group					
	M	SD	M	SD	*Statistic*	*df*	*p*	*d*
Tactile Perception								
Registration of Light Touch	0.33	0.55	0.11	0.31	*U* = 1285		**.011**	0.34
Sensory Discrimination of Touch	0.65	0.81	0.43	0.68	*U* = 1360		.120	0.26
Kinesthesia								
Position Sense	0.44	0.78	0.16	0.46	*U* = 1314		**.023**	0.31
Graphestesia								
Graphestesia	10.12	3.76	8.54	3.77	*t* = 2.39	111	**.019**	0.42

Note. Very preterm group: *n* = 57; Full-term group: *n* = 56. Performance is measured in number of errors. *t* = *t*-value independent samples *t*-test. *U* = *U*-value Mann-Whitney U test. *d* = Effect size depicted as Cohen's *d*. Bold numbers pertain to a significant *p*-value ($p < .05$).

Table 3.3. Results of multisensory integration

	Group				Condition		Condition x Group		Group	
	Very preterm		Full-term							
	M	SD	M	SD	*F*(1,111)	*p*	*F*(1,111)	*p*	*F*(1,111)	*p*
Set-Shifting										
MRT					371.4	**< .001**	0.3	.587	0.0	.964
Set	743	92	736	88						
Visual Shift	943	141	948	138						
Accuracy					68.7	**< .001**	0.6	.433	0.7	.416
Set	0.89	0.09	0.90	0.06						
Visual Shift	0.80	0.16	0.82	0.13						
Multisensory Integration										
MRT					0.2	.631	0.0	.858	0.0	.895
Visual Shift	943	141	948	138						
Audiovisual Shift	940	130	942	149						
Accuracy					152.4	**< .001**	0.0	.908	1.0	.327
Visual Shift	0.80	0.16	0.82	0.13						
Audiovisual Shift	0.65	0.16	0.67	0.15						

Note. Very preterm group: $n = 57$; Full-term group: $n = 56$. MRT = Mean Reaction Time. Bold numbers pertain to a significant *p*-value ($p < .05$).

slower and less accurate performance as compared to maintaining set. In the second analysis, only the main effect on accuracy was significant, indicating that multisensory set-shifting is associated with a less accurate performance as compared to monosensory set-shifting. Group differences on set-shifting and multisensory integration were assessed based on interactions between group and task condition (*Set* and *Visual Shift*; *Visual Shift* and *Audiovisual Shift*, respectively) on MRT and accuracy. None of the interactions were significant, indicating that set-shifting capacity and multisensory integration of audio-visual information were not affected in very preterm children compared to full-term controls. Also no main effects of group on MRT and accuracy were found, indicating that the very preterm group did not significantly differ from the term control group in general task performance of audio-visual integration.

Sensory modulation

Table 3.4 shows the results on sensory modulation as assessed with the SP questionnaire. The very preterm group obtained lower scores than the full-term group on the *Total Score*, indicating that very preterm children overall had more sensory modulation difficulties. Compared to

Table 3.4. Results of sensory modulation

	Very preterm group		Full-term group					
	M	SD	M	SD	*t*	*df*	*p*	*d*
Sensory Profile								
Sensory Processing section	289.9	22.3	298.9	18.4	-2.047	108	**.043**	0.44
Sensory Modulation section	149.81	13.5	152.94	10.5	-1.093	108	.277	0.26
Behavioral/Emotional section	110.28	12.1	114.92	11.4	-2.060	108	**.042**	0.39
Total Score	549.9	44.8	566.8	37.0	-2.134	108	**.035**	0.41
Low Registration	67.7	6.7	70.6	4.0	-2.328	108	**.022**	0.52
Sensation Seeking	115.5	11.4	116.1	11.8	-0.414	108	.680	0.05
Sensory Sensitivity	88.4	7.3	92.1	5.7	-2.754	108	**.007**	0.56
Sensation Avoiding	125.4	12.0	128.8	10.4	-1.339	108	.183	0.30

Note. Very preterm group: n = 57; Full-term group: n = 53. d = Effect size depicted as Cohen's d. Bold numbers pertain to a significant p-value ($p < .05$).

the full-term group, the very preterm group scored lower on the *Sensory Processing* section and on the *Behavioral and Emotional Responses* section, but not on the *Sensory Modulation* section, indicating more difficulties in regulating the individual sensory systems and behavioral responses to sensory input and not in regulating competing sensory inputs in combination with movement and activity level. More specifically, compared to full-term children, very preterm children reached lower scores in the *Low Registration* quadrant, indicating higher thresholds (hyporesponsivity) for sensory stimuli along with passive self-regulation strategies (i.e. no seeking of additional sensory stimulation). On the other hand, the very preterm group also reached lower scores in the *Sensory Sensitivity* quadrant compared to the full-term group, indicating that very preterm children have lower thresholds (hyperresponsivity) for sensory stimuli along with passive self-regulation strategies (i.e. no avoidance of sensory stimulation). No significant differences were found for the other two quadrants (*Sensation Seeking* and *Sensation Avoiding*).

Sensory processing

The total number of positive results follows a binomial distribution.[74] The probability of 14 out 16 measures showing a difference would be only 2%. Looking at the three separate domains, we find that in the somatosensory registration domain there is a 6% probability (alpha = .06) of no difference, in the multisensory integration this is 69% and in the sensory modulation domain, a 0.4% probability. Thus, we conclude that it is very unlikely that the differences observed in somatosensory registration and the sensory modulation domains are in fact chance findings. However, the differences observed in the multisensory integration domain are not strong enough to conclude that very preterm children differ from full-term children.

Additional analyses

Associations between somatosensory registration, multisensory integration, and sensory modulation

Pearson product-moment or Spearman rho correlation analyses between dependent variables of somatosensory registration, multisensory integration, and sensory modulation were all weak ($-.15 < r < .12$) and not significant ($p \geq .108$), except for a weak but significant association between accuracy in the *Audiovisual Shift* condition and *Position Sense* ($r = -.23$, $p = .016$) and between the *Behavioral and Emotional Responses* section and *Graphestesia* ($r = -.22$, $p = .024$). Results were similar if these analyses were performed in each group separately (very preterm/full-term). These results indicate that somatosensory registration, multisensory integration, and sensory modulation are relatively independent aspects of sensory processing.

Associations between medical characteristics and somatosensory registration, multisensory integration, and sensory modulation

In the preterm group Pearson product-moment or Spearman rho correlation analyses between dependent variables of somatosensory registration, multisensory integration, and sensory modulation and medical characteristics (GA, birth weight, SGA, length of hospital stay, PVL, and infection) were all weak ($-.23 < r < .26$) and not significant ($p \geq .05$), with a few exceptions of significant moderately sized associations between: 1) SGA status and *Graphestesia* ($r = .34$, $p = .011$) and birth weight and *Graphestesia* ($r = .32$, $p = .015$), 2) GA and *Behavioral and Emotional Responses* section ($r = .30$, $p = .026$) and length of hospital stay and *Behavioral and Emotional Responses* section ($r = .34$, $p = .009$), 3) length of hospital stay and *Sensory Processing* section ($r = .28$, $p = .038$). Given the large number of correlations analyses, a Bonferroni correction was applied (.05/42 = .001), lowering the conventional statistical level of .05 to .001, leaving no significant correlations.

Effects of postdischarge formula on sensory processing

Analysis of variance found no differences between the children that had received postdischarge formula (PDF), standard term formula (SF) and human milk on the somatosensory registration tasks and on the MSIT. On the SP, group differences were found for the *Total Score* ($p = .037$), the *Behavioral and Emotional Responses* section ($p = .016$) and the *Sensation Avoiding* quadrant ($p = .013$). Post-hoc analysis on these three dependent variables all showed that the children who received PDF performed better than the children who received SF. The PDF group scored in between the SF group and the full-term group, although the PDF group did not significantly differ from the full-term group. These result indicate that the observed differences between

very preterm and full-term children on SP measures exist, despite positive effects of enhanced postdischarge formula.

DISCUSSION

This study explored the domain of sensory processing in very preterm school-age children. The results indicate that both somatosensory registration and sensory modulation are compromised in very preterm children, while multisensory integration, at least of audio-visual information, is not. Our findings further show that the different aspects of sensory processing were relatively independent and unrelated to the gravity and complications of very preterm birth. The findings of our study add to the existing literature that sensory processing difficulties in very preterm children persist at least until primary school age and therefore warrant sensory processing as part of follow up care in very preterm children up to school age. Simultaneously however, it is only fair to mention that we have found small to medium effect sizes, which require prudence interpreting the strength of these findings. Yet, in view of the fact that most of our measures point in the same direction and that the probability of the overall results to be due to random fluctuations is very low, it would be erroneous to have corrected our results for multiple comparisons, since this would have introduced the risk of falsely rejecting the existence of a difference between very preterm and full- term children.

In the somatosensory registration domain, we found that the very preterm group showed difficulties in tactile perception, kinesthesia and graphestesia. These findings may imply that very preterm children show a reduced ability to correctly register incoming somatosensory stimuli, which indicates that very preterm birth causes somatosensory hyposensitivity. This finding corroborates with the study of Demaio-Feldman (1994), in which very low birth weight, 7-year old children performed worse compared to a normative sample on somatosensory registration tasks, including graphestesia.[42] Our study further extends that finding by showing that children born very preterm also have impaired somatosensory registration when compared to age and gender matched term born peers. In contrast to our findings on the perception of light touch, no effects of very preterm birth were found on the sensory discrimination of touch. It seems possible that these results are due to the low sensory threshold in the task used, causing a floor-effect that reduced the chances of finding difficulties in this form of tactile perception in our sample of very preterm born children.

In the sensory integration domain, we found that very preterm children showed no difficulties in multisensory integration of auditory and visual information. These findings may seem in contradiction with frequently described visual-motor integration problems in preterm

children.[43,44] However, visual-motor integration is a far more complex ability, requiring dynamic integration of body scheme information with visual, proprioceptive and tactile information, both top-down and bottom-up.[76] Therefore, it is possible that the integration between sensory modalities is relatively spared in very preterm children, while integration between sensory and motor modalities is disrupted. This idea is in line with a study by Rose and colleagues (1998) finding no differences between very preterm and full-term children in visual-tactile integration.[34] Moreover, other modalities than audio-visual integration may be affected in very preterm children. Therefore, more research is needed in the sensory integration domain in very preterm children to further corroborate our findings.

In the sensory modulation domain, we found that very preterm children showed overall sensory modulation difficulties. More specifically, these difficulties were related to the individual sensory systems and to the behavioral responses to sensory input. Also, the very preterm children showed more signs of hyporesponsivity and hyperresponsivity, which is in accordance with previous findings.[54,59,77] However, our study is the first case-controlled study to show that sensory modulation difficulties persist at least until school age in very preterm children.

The finding that multisensory (audio-visual) integration is preserved while somatosensory registration and modulation is compromised in very preterm children is somewhat puzzling. Compromised somatosensory registration and modulation in preterm born children may be explained by smaller amounts of active tissue in somatosensory cortical regions[78] and white matter brain abnormalities.[25] This is also consistent with impaired white matter microstructure that has been observed in term born children with sensory processing difficulties.[9] However, it seems inconsistent that impaired multisensory integration has been observed in other disorders of affecting white matter integrity, such as pediatric traumatic brain injury.[61,79] Possibly, multisensory integration is less vulnerable for the effects of premature birth on early white matter development as compared to relatively late traumatic axonal damage. Unfortunately, we were unable to uphold this claim with our results, since we do not have data on the white matter integrity of our group of very preterm children. The weak associations between somatosensory registration, multisensory integration, and sensory modulation, found in the current study suggest that these domains are relatively independent aspects of sensory processing and may therefore not be affected at the same time.

Our study has some limitations. With half of the initial cohort willing to participate in this follow-up study, attrition was substantial. Although comparisons between participants and non-participants on demographic and medical characteristics did not reveal any evidence for selective drop-out, extrapolation of the results to the very preterm population requires caution. Secondly, assessment of children was carried out in two different environments. Very preterm

children were assessed at the pediatric outpatient clinic and full-term children were assessed at their schools. Although a friendly, quiet environment was created at the pediatric outpatient clinic, some distress of this hospital environment cannot be ruled out. Thirdly, we were unable to evaluate white matter integrity in our very preterm group, which would have contributed to understanding the possible cause of the sensory processing difficulties. Moreover, although only weak to moderate associations were found between sensory processing and the severity of preterm birth, this may also be attributed to the relatively low prevalence of risk factors for developing white matter abnormalities, including PVL, subependymal hemorrhage and infections in our very preterm group. Therefore, imaging studies linking white matter integrity to sensory processing difficulties in very preterm children are recommended. Additionally, more research is needed to understand and evaluate the small but beneficial effects of postdischarge formula on sensory modulation in comparison to standard formula. Lastly, the use of the SP questionnaire, although currently considered as gold-standard, provides a subjective measure of sensory modulation, since it is a parent-reported instrument.

In conclusion, we found that sensory processing difficulties in terms of somatosensory registration and sensory modulation are compromised in very preterm children, with small to medium effect sizes and that these difficulties persist at least until primary school age. As the sensory system is powerfully shaped by the amount and type of sensory experiences directly after birth,[15,17] developmental care interventions in NICU, including proven effective analgesia, kangaroo care and fine-tuned sensory stimulation, remain crucial.[53,80–82] Yet, the sensory system continues to be shaped throughout the course of life.[40] Therefore, signaling sensory processing difficulties is needed across the full childhood age range in very preterm children, especially since therapeutic interventions in sensory processing difficulties in school-age children may be effective.[83] Moreover, we suggest that sensory processing difficulties might be one of the pathways that lead to the plethora of well-known adverse neurocognitive and behavioral outcomes observed in very preterm children. Sensory processing difficulties have been found associated with problems in social participation, school functioning and both ADHD and ASD.[35,37,40] Indeed, also in very preterm children, sensory processing difficulties are related to social participation,[55] neurodevelopmental delay,[56] executive functioning[57] and symptoms of ASD.[54,58,84] Although our findings only pertain to part of the sensory processing domain and await replication, tailored interventions including counseling of parents and teachers on the expression of sensory processing difficulties in the home and school environment and referral of the very preterm child to occupational therapy, may be pivotal to downsize neurocognitive, social and behavioral problems in very preterm children.[37,40,83,85]

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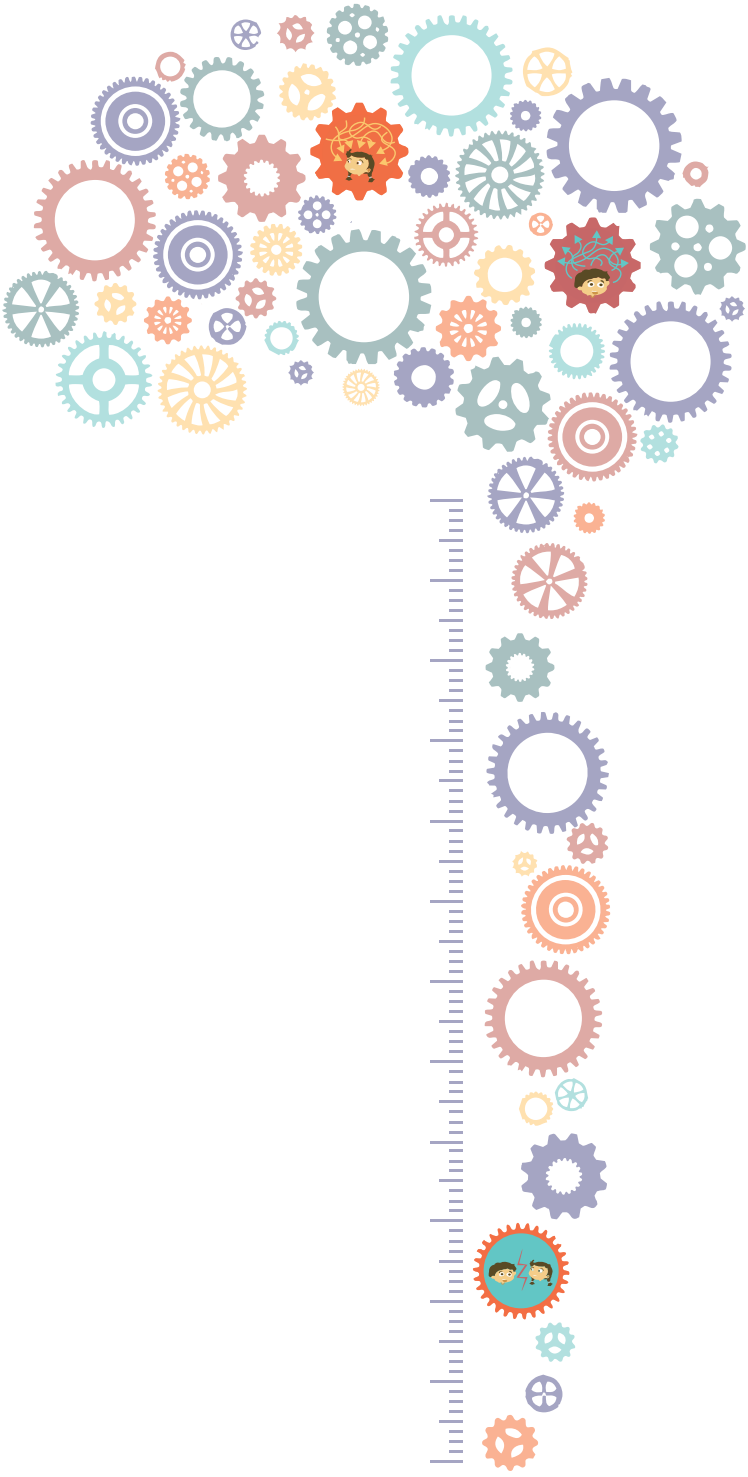

4

Attention deficit hyperactivity disorder and autism spectrum disorder symptoms in school-age children born very preterm

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ABSTRACT

Background Very preterm (VP) children face a broad range of neurodevelopmental sequelae, including behavioral problems.

Aim To investigate prevalence, pervasiveness and co-occurrence of symptoms of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in school-age children born very preterm.

Methods Using questionnaire and diagnostic interview data, parent and teacher reported symptoms of ADHD and ASD of 57 VP-children (mean age = 9.2 years) were compared with 57 gender and age matched full-term children using *t*-tests. Intra-class correlation coefficients quantified parent-teacher agreement. Correlation analysis investigated co-occurrence of ADHD/ASD symptoms. ADHD/ASD measures were aggregated using principal component analysis. Regression analyses investigated the contribution of perinatal risk factors, sex and SES to ADHD/ASD symptoms.

Results VP-children showed higher levels of parent and teacher reported attention problems, social impairment and compromised communication skills. Fair to strong agreement was found between parent and teacher reported ADHD and ASD symptoms, indicating pervasiveness of observed difficulties. Co-occurrence of ADHD and ASD symptoms in VP-children was found. Lower gestational age was associated with higher ADHD and ASD symptom levels, male sex with higher ADHD symptom levels and lower SES with higher ASD symptom levels.

Conclusion School-age VP-children show higher levels of ADHD and ASD symptoms, and attention, socialization and communication difficulties in particular. Routinely screening for these problems is recommended in follow-up care.

INTRODUCTION

Advances in perinatal and neonatal intensive care have markedly increased survival rates of very preterm infants (< 32 weeks of gestation). Unfortunately, a growing number of the surviving very preterm children struggle with neurodevelopmental problems and behavioral impairments.[1–3] In particular, symptoms of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD), are often observed in very preterm children.[4–6]

Very preterm children have a two to three-fold risk of developing ADHD at school-age and show higher rates of symptoms of ADHD than full-term children.[3,7,8] The inattentive type of ADHD is the most common subtype in very preterm children.[3,4,6] School-age very and extremely (< 28 weeks of gestation) preterm children also show higher levels of ASD symptoms than full-term children,[5,9,10] as well as higher rates of ASD diagnoses (5–9%)[11,12] in comparison to the general population (0.6%).[13] A growing body of evidence suggests that ADHD and ASD may have different clinical expressions in very preterm children than in full-term children, described as the "preterm behavioral phenotype".[3,6,14] In very preterm children, ADHD symptoms could be core attention problems with a neuropathological etiology related to the effects of preterm birth, whereas ASD symptoms may reflect primarily socialization difficulties.[3,6] Multiple studies acknowledge this neuropathological etiology by showing that ADHD and ASD symptoms in preterms are not only inversely related to gestational age (GA) and to birth weight, but are also associated with early brain damage in both white and grey matter[15–18] due to inflammation and hypoxia-ischemia.[19] However, evidence on the impact of GA on the development of ADHD and ASD is still inconsistent.[20,21] Also, precursors of brain abnormalities, including periventricular leukomalacia (PVL) and neonatal infections in very preterm children are inconsistently associated with ADHD and ASD symptoms[9,22–25] and in need of further exploration.

ADHD and ASD symptoms frequently co-occur both in the general population and in patients with ADHD and patients with ASD.[26,27] Visser and colleagues[26] suggest that attention problems form the linking factor between ADHD and ASD and the developmental pathway to both disorders. Therefore, it is important to study symptoms of ADHD and ASD in concert. However, studies that included both ADHD and ASD measures in preterms are scarce, and those studies that did, focused on ADHD or ASD diagnoses, not on symptoms, which would provide a more fine grained measure of the problems related to the two disorders.[5,9,10,28,29]

Children with the "preterm behavioral phenotype" may not show more problems on all symptom dimensions and therefore may fail to meet criteria for a full diagnosis of ADHD or ASD, yet the impact on daily functioning may be distinct.[3,30] Even if children qualify for an ADHD or ASD diagnosis, this may not fully capture the whole clinical presentation.[31] Additionally, the degree of pervasiveness of ADHD and ASD symptoms across settings is of clinical importance and

can be established with parent and teacher report.[32,33] Yet, many studies rely exclusively on parent reported symptoms,[4,14,34–36] with only a handful of studies including additional teacher reports.[5,10,29,30] Moreover, a great variety of assessment methods has been used to study ADHD and ASD in very and extremely preterm children. Most studies have used questionnaires allowing informants to provide dimensional symptom ratings of ADHD and ASD.[10,30,34,36,37] Only a few studies have employed a combination of questionnaires and diagnostic classification methods, with the use of standardized psychiatric interviews to assess ADHD4,[6,29] or comprehensive observational measures to diagnose ASD.[14,35,38] Including both diagnostic classification methods and dimensional measures is needed to assess both the presence or absence of the disorder of ADHD and ASD as well as the symptom severity of both disorders.

This current study adds to the body of knowledge by 1) comparing ADHD and ASD symptom levels in very preterm and full-term school-age children using both parent and teacher reported questionnaires and a diagnostic interview; 2) assessing co-occurrence of ADHD and ASD symptoms; 3) investigating pervasiveness of ADHD and ASD symptoms by assessing parent-teacher agreement. In addition, associations between ADHD and ASD symptoms and GA, neonatal infections, PVL, socio-economic status (SES) and sex in very preterm children are investigated.

METHODS

Participants

A sample of 57 very preterm children and 57 gender and age matched full-term children participated in the current study. The 57 very preterm children had participated in a randomized controlled trial (RCT) evaluating the effects of postdischarge formula, term formula, and human milk on growth and body composition between term age and six months corrected age[39] Eligible for inclusion in that RCT were all very preterm children admitted between August 2003 and July 2006 to the neonatal intensive care unit (NICU) of the VU University Medical Center, with at least one main caretaker understanding the Dutch language. Infants with congenital malformations or conditions known to affect growth and/or body composition (severe bronchopulmonary dysplasia, inborn errors of metabolism, cardiac or renal disease, necrotizing enterocolitis with substantial gut loss, grade IV intraventricular hemorrhage) were excluded. Baseline characteristics of the sample have been reported previously.[39]

Of the 152 infants included in the original RCT, 139 completed the study at six months corrected age and 122 were eligible for inclusion in the current study at 8–9 years of age. Very preterm

children with severe physical disabilities were excluded (*n* = 10). All other 112 children were contacted and invited to participate, to which 57 (51%) agreed (mean age = 9.2, SD 0.4). Reasons for non-participation (*n* = 55) were burden of the study (two-day psychological and medical assessment, including blood draw) (*n* = 19), cases where informed consent could be obtained from only one of the caretakers (*n* = 6), families lost to follow up (n = 5) or no reasons to decline participation were provided (*n* = 19). An additional six families declined participation due to the burden of recent psychiatric evaluation; four of these children were diagnosed with ADHD (7.2%) and two with ASD (3.6%). Of the 57 participating children 4 (7%) were diagnosed with ADHD and none were diagnosed with ASD. No differences were found between the group of participants and the total group of non-participants (*n* = 95) on sex, parental education, GA, birth weight, PVL and the presence of neonatal infections (all $p >$ .14). No differences were found between the postdischarge formula, term formula and human milk group on any of the dependent variables (all $p \geq .11$), with one exception at trend level for teacher ratings of general communication ($p = .085$).

The age- and gender-matched full-term control group was recruited from regular primary schools located in the same regions as schools attended by the very preterm children, and included children without histories of prematurity (GA > 37 weeks), perinatal complications, and neurological disorders as reported by parents. None of the full term control children were diagnosed with ADHD and/or ASD.

Socio-economic status (SES) was determined by classifying the highest level of parental education in a household on a four-point scale (low, low intermediate, high intermediate, high) with higher scores indicating higher levels of education and corresponding to higher SES.[40] Medical characteristics of the very preterm group were obtained from medical files. GA was expressed in weeks of gestation (range: 25–32) and birth weight in grams (range: 784–2065). Small for gestational age was defined as either birth length or weight < 2 SD. Length of stay was defined as days on NICU or high care unit from birth until discharge. Presence of PVL was defined as no PVL versus flaring and/or PVL grade I/II.[41] Presence of infection was defined as no infection versus blood-culture-proven infection. Subependymal hemorrhage was graded I–V.[42] The Neonatal Medical Index was graded I–V.[43]

Procedure

Very preterm children were assessed at the outpatient clinic of the VU University Medical Center, where parents completed the questionnaires addressing symptoms of ADHD and ASD. A trained research assistant and child psychologist administered the diagnostic interviews through telephone. Questionnaires completed by teachers were obtained through mail. Full-

term children were assessed at their schools and parent and teacher questionnaires were sent out by mail.

The present study was carried out between 2010-2015. Parents of all participating children provided written informed consent. The medical ethic committee of the VU University Medical Center approved the study protocol (#NTR2972).

Measures

Assessment of ADHD

Parent and teacher rating scales assessing ADHD symptoms included (1) the DSM-ADHD scale and the Attention Problems scale of both the Child Behavior Checklist (CBCL),[44] and the Teacher Report Form (TRF),[45] and (2) the Inattention and Hyperactivity/Impulsivity scale of the parent and teacher version of the Disruptive Behavior Disorders rating scale (PDBD and TDBD).[46] Psychometric properties have been reported for the CBCL/TRF and PDBD/TDBD.[46,47] More specifically, for the CBCL and TRF syndrome scales, including the Attention problem scale as well as for the DSM-oriented scales, including the DSM-ADHD scale, test-retest reliability ranged between r = .84 and r = .90 and internal consistencies varied between α = .81 and α = .86.[47] For the Inattention and Hyperactivity/Impulsivity scale of both the PDBD and TDBD test-retest reliability ranged from r = .79 to r = .87 and internal consistency varied between α = .89 and α = .93.[46] Raw scores served as dependent variables, with higher scores indicating more severe symptoms. In addition, in the very preterm group, the parent version of the Diagnostic Interview Schedule for Children - fourth edition (DISC-IV) was administered to assess the diagnosis of ADHD.[48]

Assessment of ASD

Parent and teacher rating scales to assess ASD symptoms included (1) the Total score of the parent reported Social Responsiveness Scale (SRS), which assessed socialization, communication, and repetitive behaviors associated with ASD,[49] and (2) the parent and teacher reported General Communication Score (GCS) and Pragmatic Communication Score (PCS) of the Children's Communication Checklist (CCC-2),[50] identifying general and pragmatic communication problems. Raw scores served as dependent variables, with higher scores indicating more severe symptoms. In addition, in the very preterm group the parent reported Social Communication Questionnaire (SCQ) was used to screen for the diagnosis of ASD using a cut-off score ≥ 15.[51] Adequate psychometric properties have been reported for the SRS, CCC-2 and SCQ.[49–51] In more detail; the Total score of the SRS shows high internal consistency (α > .90),[49] for the CCC-2 adequate test-retest reliability (GCS: r = .80; PCS: r =

.67) and high internal consistency (GCS: α = .89; PCS: α = .88) was found,[50] and for the SCQ also high internal consistency (α = .89) was reported.[51]

Assessment of IQ

In both the very preterm and the full-term group the full Scale Intelligence Quotient (FSIQ) was assessed using a four-subtest short form of the most recent available Dutch third edition of the Wechsler Intelligence Scales for Children (WISC-III),[52] including the subtests Similarities, Vocabulary, Picture Arrangement and Block Design. FSIQ as measured by this short form has high reliability (*r* = .93) and correlates strongly with Full Scale IQ (*r* = .92).[53]

Statistical analyses

Data were analyzed using IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, NY, USA). Dependent variables were screened for outliers (*Z*-score > 3.29 or *Z*-score < -3.29) which were rescaled according to Tabachnik & Fidell.[54] Due to non-compliance, questionnaire data were missing for 2–5% of parents and 5–14% of teachers for the dependent variables. Missing data were imputed using multiple imputation.[55]

Group characteristics of the very preterm and the full-term group (i.e. gender, age, SES, GA and birth weight) were compared using chi-square and t-tests. Group differences on IQ and parent and teacher ratings of ADHD (CBCL Attention Problems, CBCL DSM ADHD, PDBD Inattention, PDBD Hyperactivity/Impulsivity, TRF Attention Problems, TRF DSM ADHD, TDBD Inattention, TDBD Hyperactivity/Impulsivity) and of ASD (SRS Total score, CCC-2 General Communication, CCC-2 Pragmatic Communication) were tested using independent-samples t-tests. To enhance reliability of the ADHD and ASD measures, Principal Component Analysis (PCA) was used to aggregate 1) parent and teacher ADHD measures (ADHD component) and 2) parent and teacher ASD measures (ASD component). Pervasiveness of ADHD and ASD symptoms in the very preterm group was evaluated as agreement between all collected parent and teacher ratings, and was quantified using intra-class correlation coefficients (ICCs). The ICC assesses the reliability of ratings by comparing the variability of different ratings of the same subject to the total variation across all ratings and all subjects group.[56] ICC can be interpreted as follows: 0–0.2 indicates poor agreement; 0.3–0.4 indicates fair agreement; 0.5–0.6 indicates moderate agreement; 0.7–0.8 indicates strong agreement; and > 0.8 indicates almost perfect agreement.[57] Co-occurrence of ADHD and ASD symptoms was investigated using Pearson product-moment correlation analysis on the ADHD and ASD component scores. Backward regression analyses were used to investigate the contribution of sex, SES, GA, presence of infection and presence of PVL to ADHD and ASD symptoms in the very preterm group using the ADHD and ASD

component as criterion measures. Unique contributions were calculated with squared partial correlations. Effect sizes were expressed in terms of Cohen's *d* with values of 0.2, 0.5 and 0.8, referring to small, medium and large effects, respectively.[58] For all analyses α was set at .05.

RESULTS

Sample characteristics

Group characteristics are presented in Table 4.1. As expected, the very preterm group had lower mean GA ($p < .001$) and mean birth weight ($p < .001$) than the full-term group. In addition, mean estimated IQ was lower in the very preterm sample ($p = .017$, $d = 0.45$). There were no significant group differences for age at assessment ($p = .755$). Groups marginally differed in SES ($p = .068$), with somewhat higher SES scores in the full-term group. Pearson product-moment correlation analyses between SES and all dependent variables showed only weak associations (all $r < .293$), except for moderate associations between SES and parent reports (SRS, CCC-2) on ASD (all $r < .423$).

ADHD symptomatology

Parent ratings and teacher ratings on ADHD symptoms are presented in Table 4.2. Compared to the full-term group, the very preterm group showed higher parent ratings of ADHD symptoms (CBCL DSM ADHD; $d = 0.61$). The very preterm group obtained higher parent ratings on the CBCL Attention Problems ($d = 0.66$) and the PDBD Inattention scales ($d = 0.46$), but did not differ from the full-term group on the PDBD Hyperactivity/Impulsivity scale ($d = 0.16$), suggesting that symptoms of ADHD were limited to the symptom dimension of inattention.

Teacher reports converged with parent reports, except for the borderline significant TRF DSM ADHD scale ($d = 0.31$). The very preterm group obtained higher teacher ratings on both the TRF Attention Problems scale ($d = 0.41$) and TDBD Inattention scale ($d = 0.59$), but also on the TDBD Hyperactivity/Impulsivity scale ($d = 0.43$) compared to the full-term group, indicating that teacher reported ADHD symptoms combine inattention and hyperactivity/impulsivity problems.

On the aggregated ADHD component, the very preterm group showed higher ratings of ADHD symptoms than the full term group ($d = 0.55$). Sixteen percent of very preterm children ($n = 9$) qualified for a diagnosis of ADHD (ADHD-combined subtype: $n = 3$, ADHD-inattentive subtype: $n = 6$, ADHD-hyperactive/impulsive subtype: $n = 0$) as measured by the DISC-IV.

Table 4.1. Group characteristics

Characteristic	Very preterm group (*n* = 57)	Full-term group (*n* = 57)	*p*
Age at assessment, years, M (SD)	9.2 (0.4)	9.2 (0.5)	.755
Estimated FSIQ, M (SD)	100.7 (11.2)	106.0 (12.3)	**.017**
Sex, *n* (% male)	26 (46)	26 (46)	1.000
SES			.068
Low, *n* (%)	5 (9)	2 (4)	
Low intermediate, *n* (%)	22 (39)	12 (21)	
High intermediate, *n* (%)	16 (28)	19 (33)	
High, *n* (%)	14 (25)	24 (42)	
Gestational age, weeks, M (SD)	30.2 (1.8)	39.8 (1.4)	**< .001**
Birth weight, grams, M (SD)	1293 (296)	3585 (533)	**< .001**
Small for gestational age, *n* (%)	15 (27)		
Length of NICU stay, days, M (SD)	50.3 (15.6)		
PVL			
None, *n* (%)	27 (47)		
Flaring and/or PVL grade I/II, *n* (%)	30 (53)		
Neonatal infection, *n* (%)	26 (46)		
Subependymal hemorrhage			
None, *n* (%)	50 (88)		
Grade I, *n* (%)	5 (9)		
Grade II, *n* (%)	2 (4)		
Neonatal Medical Index (NMI)			
NMI I, *n* (%)	1 (2)		
NMI II, *n* (%)	6 (11)		
NMI III, *n* (%)	28 (49)		
NMI IV, *n* (%)	15 (26)		
NMI V, *n* (%)	7 (12)		

Note. There were no children with grade III or IV subependymal hemorrhage.
Abbreviations: FSIQ = Full-scale IQ; NICU = Neonatal Intensive Care Unit; PVL = Periventricular Leukomalacia.
Bold numbers pertain to a significant p-value ($p < .05$).

ASD symptomatology

Parent ratings and teacher ratings on ASD symptoms are presented in Table 4.2. Parent reports revealed the very preterm group to show higher scores on the SRS Total score ($d = 0.40$) and on the CCC-2 General Communication ($d = 0.46$) and Pragmatic Communication scale ($d = 0.46$), indicating more social impairment and communication problems than the full-term group. Likewise, teachers rated very preterm children to show more communication problems (CCC-2 General Communication; $d = 1.70$ and Pragmatic Communication; $d = 1.46$).

Table 4.2. Parent ratings and teacher ratings on ADHD and ASD symptoms

	Very preterm group (n = 57)		Full-term group (n = 57)			
Measure	M	SD	M	SD	p	Effect size[1]
Parent ratings of ADHD symptoms						
CBCL - DSM ADHD	3.8	3.1	2.1	2.4	**.002**	0.61
CBCL - Attention Problems	4.4	3.4	2.4	2.6	**< .001**	0.66
PDBD - Inattention	4.7	4.7	2.8	3.4	**.015**	0.46
PDBD - Hyperactivity/Impulsivity	3.7	3.6	3.1	3.8	.404	0.16
Teacher ratings of ADHD symptoms						
TRF - DSM ADHD	4.2	4.6	2.8	4.5	.099	0.31
TRF - Attention Problems	7.4	6.8	4.6	6.7	**.032**	0.41
TDBD - Inattention	4.0	4.5	1.8	2.8	**.003**	0.59
TDBD - Hyperactivity-Impulsivity	2.1	2.7	1.1	1.9	**.021**	0.43
ADHD Component	0.27	1.1	-0.27	0.84	**.004**	0.55
Parent ratings of ASD symptoms						
SRS - Total score	27.5	16.3	21.9	11.5	**.038**	0.40
CCC2 - General Communication	78.2	18.9	70.5	14.3	**.015**	0.46
CCC2 - Pragmatic Communication	40.1	10.1	35.7	9.2	**.022**	0.46
Teacher ratings of ASD symptoms						
CCC2 - General Communication	77.2	14.5	56.1	9.8	**< .001**	1.70
CCC2 - Pragmatic Communication	39.0	8.5	27.6	7.0	**< .001**	1.46
ASD Component	0.45	1.0	-0.45	0.74	**< .001**	1.02

Abbreviations: CBCL = Child Behavior Checklist; PDBD = Parent Disruptive Behavior Disorders; TRF = Teacher Report Form; TDBD = Teacher Disruptive Behavior Disorders; SRS = Social Responsiveness Scale; CCC2 = Children's Communication Checklist-2.
Bold numbers pertain to a significant p-value ($p < .05$).
[1] Effect sizes are depicted as Cohen's d.

On the aggregated ASD component the very preterm group showed higher ratings of ASD symptoms than the full term group (d = 1.02). None of the 57 very preterm children screened positive for ASD on the SCQ.

Pervasiveness of ADHD and ASD symptoms with parent-teacher agreement

Intra-class correlational analyses showed that agreement between scores for very preterm children as rated by parents and teachers varied for the different ADHD measures. For the CBCL and TRF Attention Problems scale the agreement was moderate (ICC = .50) and for the PDBD and TDBD Inattention scale the agreement was strong (ICC = .78).[56,57] The ASD measures showed fair agreement for the CCC-2 Pragmatic (ICC = .41) and General Communication scale (ICC = .39).

Co-occurrence of ADHD and ASD symptoms

The relationship between the aggregated ADHD component and the ASD component was investigated using Pearson product-moment correlation coefficient. There was a strong, positive correlation between the two components in the preterm group, r = -.58, n = 57, p = .01 and in the full-term group, r = -.49, n = 57, p = .01, indicating strong interrelatedness of ADHD and ASD symptoms.

Impact of neonatal risk factors on ADHD and ASD symptoms

Backward multiple regression analyses were performed on the ADHD and ASD component scores of the very preterm group, using sex, SES, GA, presence of infection, and presence of PVL as predictors. SES, presence of infection and presence of PVL were all not significant (all p > .406). GA and sex were significant predictors of the ADHD component score, explaining a total of 14% of variance $F(2,54) = 4.348$, p = .018, with GA providing a unique contribution of 11% explained variance and sex providing a unique contribution of 7% explained variance. Lower GA and male sex were related to higher ratings of ADHD symptoms. For the ASD component, sex, presence of infection and presence of PVL were all not significant (all p > .305). A 20% of variance $F(2,54) = 6.880$, p= .002, was explained by SES (14% unique contribution) and GA (8% unique contribution). Lower SES and lower GA were related to higher ratings of ASD symptoms.

DISCUSSION

This study investigated ADHD and ASD symptoms in very preterm school-age children in comparison to an age and gender matched full-term control group. Main findings were that the very preterm group showed higher scores on both parent and teacher reported ADHD and ASD measures than the full-term group, indicating higher symptom levels of both disorders in very preterm children. ADHD symptoms in the very preterm group were most pronounced for the symptom dimension of inattention, however teachers rated very preterm children to have more hyperactivity and impulsivity as well. Parent and teacher reported symptoms of ASD, including symptoms of social impairment and compromised general and pragmatic communication, were more frequent in the very preterm group as opposed to the full-term group. In the very preterm group 16% of children qualified for an ADHD diagnosis. None of the very preterm children screened positive for ASD. Pervasiveness of ADHD and ASD symptoms was underlined by fair to strong agreement between parent and teacher ratings. A strong correlation was found between the ADHD and ASD component scores, indicating

co-occurrence of ADHD and ASD symptoms. GA predicted both ADHD and ASD symptoms in the very preterm group. Additionally, male sex was related to higher levels of ADHD symptoms and lower SES was related to higher levels of ASD symptoms in the very preterm group.

Our finding that attention problems were more frequent in very preterm children is in accordance with other studies showing that preterm birth appears to be associated with only one of the two defining symptom dimensions of ADHD.[3,4,9] We found that very preterm children more often qualified for a diagnosis of ADHD (16%), as measured with the DISC-IV parental interview, than the reported average prevalence rate of 5%.[59] Importantly, this may even be an underestimation of the true ADHD prevalence in our initial study sample, given the attrition of children that had been diagnosed with ADHD (4/55, 7%). The percentage of children in our very preterm sample with an ADHD diagnosis is fairly consistent with other studies (7–17%).[4,5,28,66] Our results show that both ratings of ADHD symptoms and the number of children diagnosed with ADHD is substantially higher in very preterm children compared to term born children. Moreover, symptoms of inattention and the inattentive ADHD subtype, rather than hyperactivity and impulsivity, are predominantly found in our sample. These results are consistent with earlier studies reporting on the presence of predominantly inattentive symptoms in very preterm children.[3,4,6] Clearly, the observed attention problems may negatively impact on school functioning,[60] social skills,[61] self-esteem[62] and psychosocial functioning.[63]

With regard to the ASD measures, the very preterm sample showed more social impairment and less effective general and pragmatic communication in comparison to the full-term group, which bolsters previous findings.[12,14,29] Specifically, our study corroborates findings of Verhaeghe and colleagues[14] using the SRS to assess ASD symptoms, showing high levels of social impairment in very preterm children. However, none of the very preterm children in our study screened positive for ASD on the SCQ. The latter finding is somewhat remarkable, as three other studies have found significantly higher prevalence rates of ASD in preterm children using this instrument.[11,14,35] However, the study of Johnson et al.[11] and Verhaeghe et al.[14] report on extremely preterm children and have larger sample sizes.

The finding that preterm children show higher symptom levels of ADHD and ASD symptoms emphasizes the importance of a thorough dimensional assessment of the two disorders.[3,31] This is further supported by the overlap of ADHD and ASD symptoms,[26] also found in our study. As symptoms of ADHD and ASD co-occur, screening for only one of these disorders in preterm children could be inaccurate and incomplete. Moreover, the current study underlines the pervasiveness of the symptoms. Both parents and teachers rated very preterm children to have more problems than their full-term peers, affirming previous studies.[10,30] ADHD measures showed moderate to strong agreement between parent and teacher reports of

ADHD symptoms within very preterm children. Agreement was only fair for ASD measures. It is possible that symptom dimensions of ASD could strongly vary as a function of situational demands and could have a different burden on the home and school environment.[64] Both parent and teacher reports should therefore systematically be included in studies on ADHD and ASD symptoms in preterms.[32,64,65]

This study adds to the body of evidence that in very preterm children ADHD and ASD symptoms may be part of the "preterm behavioral phenotype"[3] with attention problems, rather than hyperactivity/impulsivity and with social impairment and communication problems as pivotal symptoms.[6,14,31,66] We speculate that the presence of profound attention problems in the absence of symptoms of hyperactivity and impulsivity in very preterm children, is related to the nature of the neurocognitive deficits in these children.[3,6] Earlier studies have shown a strong relationship between neurocognitive deficits in both working memory and processing speed and attention problems in very preterm children.[67,68] De Kieviet and colleagues[68] found that the attention problems of very preterm children were completely mediated by deficits in visual spatial working memory and processing speed. More generally, in her review, Diamond[69] claims working memory and processing speed to be the core cognitive deficits in ADHD, and in particular in children diagnosed with the attentive subtype of ADHD.[69] Neurocognitive deficits in very preterm children are supposed to result from the widespread white matter brain abnormalities[70] and alterations in brain development observed in these children.[71] Thus, there seems converging support for the idea that the distinctive compromised brain development of very preterm children may lead to attention problems in particular, that are best understood in terms of underlying deficits in working memory and processing speed.[3,68] Our finding that symptoms of ADHD and ASD co-occur in very preterm children also supports the existence of a "preterm behavioral phenotype" and are in line with the study of Hille and colleagues,[72] who found attentional, social and thought problems to be present in extremely preterm children, regardless of cultural background. Moreover, as attention problems have been suggested to form the linking factor in the co-occurrence of ADHD and ASD,[26,27] it could be argued that attention problems underpin socialization difficulties in very preterm children as well. Studies in children with ADHD show that inattention may limit adaptive social participation and may lead to social rejection.[61,73] Children with inattentive symptoms tend to miss social cues necessary for effective social interaction, may underperform during organized sports and games or are disliked because of shyness or sluggish responses.[61,73–75] Inattention may therefore be suggested as a risk factor for socialization difficulties in very preterm children. However, Visser and colleagues[26] warn that the unique and common underlying mechanisms of inattention in ADHD and ASD, in terms of alerting, orienting and executive control networks, remain to be elucidated. The same applies to the specific underlying mechanisms of inattention in very preterm children.

Recently, sensory modulation problems, defined as impaired regulation of the intensity of responses to sensory stimuli,[76] were found to be common in very preterm children and have been coined as one of the underlying mechanisms in understanding behavioral problems in very preterm children.[77]

Our finding that lower GA predicted both ADHD and ASD symptoms converges with other studies.[16,17,78] In addition, the association between male sex and symptoms of ADHD has been reported commonly.[79] Our finding that sex and ASD symptoms were not associated may seem somewhat surprising, since ASD is more common in boys than in girls[80] and studies on ASD in very preterm children also report this male dominance.[29,35] However, this is only found for a diagnosis of ASD, whereas elevated ASD symptoms have been found unrelated to sex.[9,14] Possibly, only the severe end of the spectrum of ASD symptoms is associated with male sex or sex ratios for elevated ASD symptoms may differ for different etiologies. In our study the presence of PVL and of infection showed no significant contribution to the prediction of ASD and ADHD symptoms. However, the low prevalence rate of infections and PVL in our sample and the dichotomous coding may, at least partly, explain why no significant effects were found. Indredavik et al.[81] found associations between ADHD symptoms, in particular inattention, and ventricular dilatation and white matter reduction, whereas Johnson et al.[11] found abnormal cerebral ultrasounds to be related to ASD in extremely preterm children. We found lower SES to be related to higher levels of ASD symptoms in the very preterm group. Studies on the association of SES on ASD in large population-based studies[82–85] show inconclusive evidence. A Finnish national case-control study found differential effects of SES on ASD subtypes.[82] Other findings range from higher ASD prevalence rates in high SES families in a large population-based American study, possibly explained by better access to health care services,[83] to higher ASD prevalence rates in low income families, in population-based Swedish and Japanese studies,[84,85] in countries with accessible healthcare systems that are independent of income, comparable to the health care system in our country (The Netherlands). However, the relationship between SES and preterm birth is rather complex, since especially low birth weight and low SES are highly associated even in countries with high social security levels, relatively small income differences and accessible medical care.[86] It therefore remains to be investigated if low SES in very preterm children is an additional risk factor for developing (symptoms of) ASD.

Some limitations of our study need to be addressed. First, attrition in this follow-up study was substantial with only half of the initial cohort willing to participate. Comparisons between participants and non-participants on demographic and medical characteristics did not reveal any evidence for selective drop-out. Still, generalization of the results to the very preterm population should be done with caution. Secondly, with our focus on symptoms rather than diagnoses we did not obtain diagnosis of ADHD and ASD in our full-term children. However,

the CBCL, PDBD/TDBD, SRS and CCC-2 are psychometrically sound and successfully used to distinguish between children with and without ADHD and/or ASD symptoms.[46,49,87,88] Thirdly, we are aware that we did not separately evaluate repetitive and restrictive interests, as we have done with communication problems. However, repetitive and restrictive interests were part of the Total score of the SRS. Finally, although IQ was lower in the very preterm group, we did not include IQ in our statistical analyses, since IQ is suggested to be statistically unfit as a covariate and is known to produce overcorrected and anomalous findings in research on neurodevelopmental disorders and psychopathology.[89,90]

In conclusion, the findings that very preterm children in comparison to full-term children show higher levels of ADHD and ASD symptoms highlights the importance of assessing ADHD and ASD symptoms in school-age very preterm children. Specifically, symptom assessment of attention problems, social impairment and communication problems rather than screening for ADHD and/or ASD should be the focus of follow-up care in very preterm children. More research is needed to reveal crucial underpinnings for the "preterm behavioral phenotype" of ADHD and ASD symptoms.

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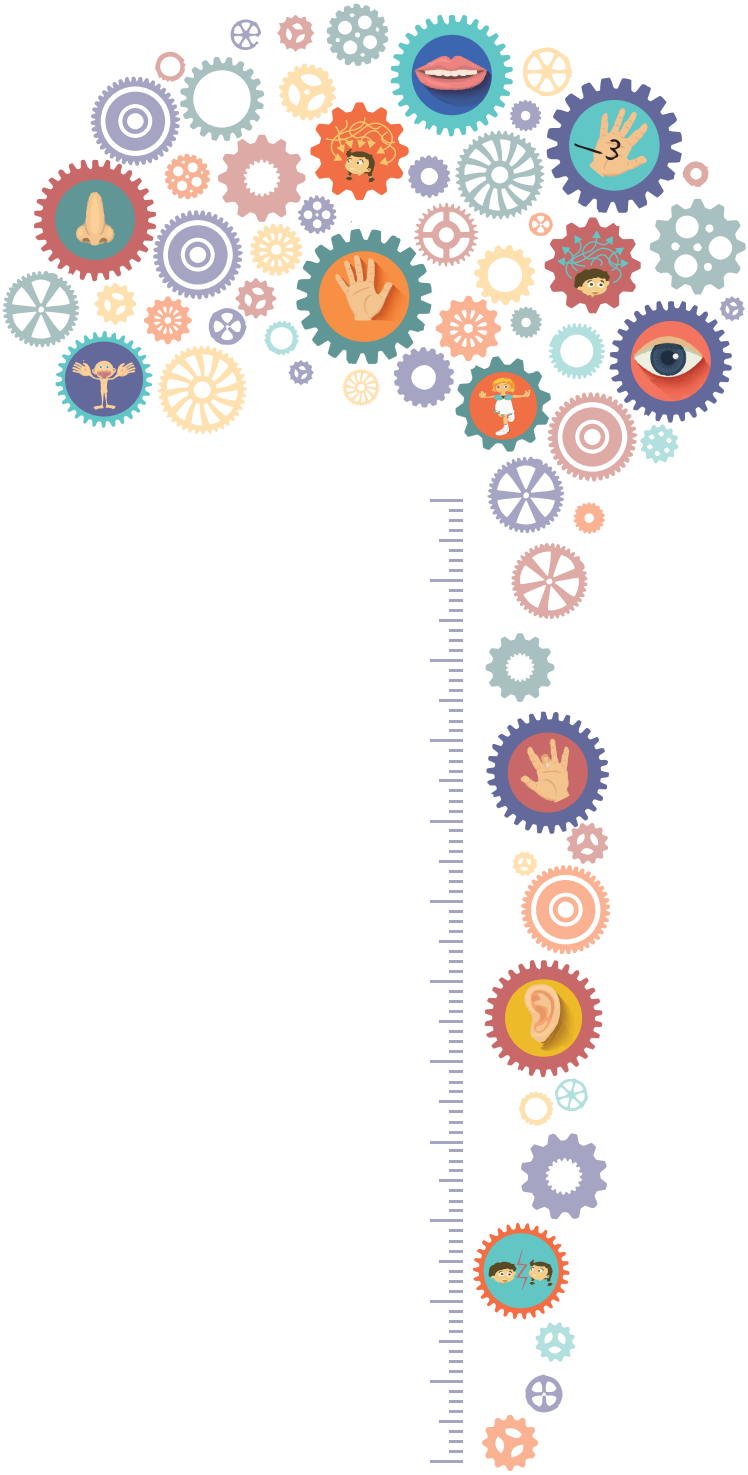

5

Understanding symptoms of ADHD and ASD in very preterm school-age children from a sensory processing perspective: a controlled neuropsychological study

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Submitted

ABSTRACT

Background Very preterm (VP) children are at risk for symptoms of attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and sensory processing difficulties.

Aims This study investigates whether sensory processing difficulties mediate the relationship between prematurity and ADHD and ASD symptom levels in VP children.

Method ADHD and ASD symptoms (reported by parents and teachers) of 57 VP children (mean age = 9.2), and 56 matched full-term (FT) children were aggregated to an ADHD and ASD component score by principal component analyses. Sensory processing was assessed using an aggregated component score of somatosensory registration tasks and a parent-reported sensory modulation questionnaire. Mediation analyses tested whether sensory processing difficulties mediate the relation between prematurity and aggregated ADHD and ASD symptom levels.

Results VP children showed more symptoms of ADHD ($p = .002$) and ASD ($p < .001$), and performed worse on sensory registration ($p < .001$) and modulation ($p = .035$). Moreover, sensory modulation partially mediated the relationship between prematurity and ADHD and ASD, while sensory registration did not.

Conclusion Sensory processing difficulties may play a key role in understanding ADHD and ASD symptoms in VP children. Follow-up care should include screening for sensory processing and behavioral difficulties.

INTRODUCTION

Almost 25% of very preterm (VP) born children (< 32 weeks gestational age) struggle with neurodevelopmental problems,[1] and behavioral difficulties in particular.[2,3] VP children show higher symptom levels of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) than full-term (FT) children and are two to three times more likely to develop ADHD at school age.[3–6] Moreover, ADHD and ASD symptoms frequently co-occur in both the FT population[7,8] as well as in the VP population,[3] with attention problems as the suggested linking factor to both disorders.[8]

Neurodevelopmental problems in VP children arise from the detrimental impact of VP birth on the developing brain.[9–11] Both primary pathological mechanisms, such as hypoxia-ischemia and infection,[12] and secondary harmful environmental influences related to treatment and stay at the neonatal intensive care unit (NICU)[11] compromise normal brain development and white matter development in particular.[5,13–15] Compromised connectivity of brain networks that facilitate efficient relay and integration of information throughout the brain,[16] puts VP children at risk for problems in information processing, including sensory processing difficulties.

It has been suggested that the white matter abnormalities of VP children might be key in understanding the ADHD and ASD symptoms of these children and that this relationship is mediated by sensory processing difficulties.[17] Indeed, ADHD and ASD symptoms in VP children have been associated with white matter brain abnormalities.[3,6,18] Moreover, sensory processing difficulties are highly present in VP children[17,19] and associated with white matter brain abnormalities in this population.[20–22] Evidence for difficulties in *registration* and *integration* of sensory stimuli is found in preterm infants,[19] and our recent systematic review evaluates sensory *modulation* difficulties,[17] described as an impaired regulation of the intensity of responses to sensory stimuli, resulting in behavioral hyporesponsiveness and/or hyperresponsiveness,[23] to be present in 14 out of 16 studies in preterm children. Adequate sensory processing is pivotal for normal child development in terms of perceiving, understanding and interacting with the environment and therefore strongly relates to behavioral functioning.[24] In fact, sensory processing difficulties are frequently associated with ADHD and ASD,[25–29] and may become evident in terms of hyperresponsiveness and hyporesponsiveness in multiple sensory modalities.[29–32] Taken together these findings suggest that difficulties in sensory processing might be the final common pathway related to ADHD and ASD symptoms in VP children.

Our previous work has shown that VP children show higher symptom levels of ADHD and ASD[33] and that sensory processing in terms of registration and modulation is also compromised in VP children in comparison to term born peers.[34] Thus far, no studies have investigated the impact of sensory processing difficulties on ADHD and ASD symptoms in VP children. Unraveling the

impact of sensory processing difficulties on symptoms of ADHD and ASD might enhance our understanding of the behavioral problems occurring in VP children and benefit interventions in this large group of children.

The current study aims to elucidate the impact of sensory processing on symptoms of ADHD and ASD in VP school-age children in comparison to FT children, using a comprehensive assessment battery including parent and teacher questionnaires on ADHD and ASD symptoms[35–39] and measures of sensory processing including behavioral somatosensory registration tasks[40] and a parent-reported questionnaire on sensory modulation difficulties.[41]

METHOD

Participants

A sample of 57 VP children and 56 gender and age matched FT children participated in the current study. The VP children had participated in a randomized controlled trial (RCT) evaluating the effects of postdischarge formula on growth and body composition between term age and six months corrected age (baseline characteristics of the sample have previously been reported).[42] Eligible for inclusion were all VP children (< 32 weeks gestational age and/or < 1500g) admitted between August 2003 and July 2006 to the NICU of the VU University Medical Center, Amsterdam, the Netherlands, with at least one main caretaker understanding Dutch or English. Exclusion criteria were infants with congenital malformations or medical conditions known to affect growth and/or body composition (i.e. severe bronchopulmonary dysplasia, inborn errors of metabolism, cardiac or renal disease, necrotizing enterocolitis with substantial gut loss, grade IV intraventricular hemorrhage). In the current study, VP children with severe physical/neurosensory disabilities were additionally excluded because of their inability to meet test situation demands. A total of 112 children were contacted and invited to participate, to which 57 (51%) agreed. The main reason for non-participation was the burden of the study (two-day psychological and medical assessment, including blood draw). No differences were found between the group of participants and the total group of non-participants on sex, parental education, gestational age (GA), birth weight, PVL and the presence of perinatal infections (all $p > .14$).

The FT control group was recruited from primary schools located in the same geographical regions as schools attended by the VP children, and included children without histories of prematurity (GA > 37 weeks), perinatal complications, neurological disorders and diagnoses of ADHD and/or ASD as reported by parents.

In both the VP and the FT group the full Scale Intelligence Quotient (FSIQ) was estimated using a four-subtest short form of the currently available Dutch version of the Wechsler Intelligence Scales for Children - third version (WISC-III)[43] including the subtests Similarities, Vocabulary, Picture Arrangement and Block Design. FSIQ as measured by this short form has high reliability (r = .93) and correlates strongly with Full Scale IQ (r = .92).[44]

Measures

Assessment of ADHD and ASD symptoms

To assess ADHD, raw scores of parent and teacher rating scales, including the DSM-ADHD scale and the Attention Problems scale of the Child Behavior Checklist (CBCL)[39]/Teacher Report Form (TRF),[38] and the Inattention and Hyperactivity/Impulsivity scale of the parent and teacher version of the Disruptive Behavior Disorders rating scale (PDBD and TDBD)[37] were aggregated into an ADHD composite score (*ADHD component*) by principal component analysis (PCA; one factor extraction, 70% of the total variance explained). To assess ASD, raw scores of parent and teacher rating scales, including the parent-reported Social Impairment scale of the Social Responsiveness Scale (SRS)[36] and the parent and teacher-reported General Communication Score (GCS) and Pragmatic Communication Score (PCS) of the Children's Communication Checklist (CCC-2),[35] were aggregated to an ASD composite score (*ASD component*) using PCA (one factor extraction, 65% of the total variance explained).

Assessment of sensory processing

Somatosensory registration

Raw scores of tactile perception, kinesthesia and graphestesia tasks were aggregated to a somatosensory registration composite score (*Registration component*) using PCA (one factor extraction, 40% of the total variance explained). Tactile perception was measured with two tasks, including the Registration of light touch, assessed by touching the child with a cotton wool on the skin of the forearm, which had been placed under a screen, and Sensory discrimination of touch, assessed by applying a pencil with a blunt or a sharp side to the forearm, which had been placed under a screen.[30] Kinesthesia (i.e. position sense of finger joints) was assessed by slowly stretching or bending one finger of the participant into a final joint position under a screen.[30] Graphestesia, a subtest of the Sensory Integration and Praxis Test[40] was assessed by drawing symbols with the index finger tip on the back of the child's hands under a screen, alternating the left and right hand. The child had to duplicate the symbol on the same hand with the index finger of the opposite hand. Performance on the somatosensory registration tasks was measured in number of errors.

Sensory modulation

Sensory modulation difficulties were investigated by the Sensory Profile (SP), which is a caregiver-completed questionnaire measuring sensory modulation abilities and the effect of sensory modulation on functional performance in daily life.[41] The SP contains 125 items using a 5-point rating scale. The *SP Total score* was used as a dependent measure, with lower scores indicating worse sensory modulation.

Procedure

VP children were assessed by a child psychologist (TB) and trained research assistant (AB) at the pediatric outpatient clinic of the VU University Medical Center, where parents completed the questionnaires. Questionnaires completed by teachers were obtained through mail. Assessment of FT children was performed likewise at their own school and parent and teacher questionnaires were sent out by mail.

The present study was carried out between 2010–2015. Parents of all participating children provided written informed consent. The medical ethic committee of the VU University Medical Center approved the study protocol (#NTR2972).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, NY, USA). Dependent variables were screened for outliers (-3.29 > *Z*-score > 3.29) which were rescaled according to Tabachnik & Fidell.[45] Due to non-compliance, there were three missing SP questionnaires. All children completed the somatosensory registration tasks. On ADHD and ASD measures 2–13% of questionnaire data were missing and these missing data were imputed using multiple imputation.[46]

Group characteristics (i.e. gender, age of the child, IQ, SES, GA and birth weight) between VP and FT children were compared using chi-square and *t*-tests. Group differences on the *ADHD component*, *ASD component*, *Registration component* and *SP Total score* were tested using independent-samples *t*-tests.

Mediation models (PROCESS macro for SPSS)[47] were used to investigate the possible mediating effect of somatosensory registration difficulties and sensory modulation difficulties on symptom levels of ADHD (*ADHD component*) and ASD (*ASD component*) in VP and FT children. The *Registration component* and *SP Total score* were separately inserted as mediator of the relation between group (VP, FT) as an independent variable and the *ADHD component* and

ASD component as separate dependent variables. Mediation occurred when the confidence interval of the indirect relation corrected for the direct relation did not include 0.[47] For all analyses α was set at .05.

RESULTS

Group characteristics

Group characteristics are presented in Table 5.1. As expected, VP children had lower mean GA and mean birth weight than term born controls. There were no significant group differences with regard to sex and age at assessment. Groups marginally differed in SES (p = .073), with higher SES in the FT group. SES did not show significant main effects, nor did SES significantly interact with group on the *ADHD component*, *Registration component* and *SP Total score*. On the *ASD component*, a significant main effect was found for SES with lower SES associated with higher ASD scores; however SES did not significantly interact with group on the *ASD component*.

VP children versus FT children on aggregated measures and SP

The VP group showed higher ratings of ADHD and ASD symptoms than the FT group on both the *ADHD component* (t (111) = 3.134, p = .002, d = 0.32) as well as the *ASD component* (t (111) = 5.335, p < .001, d = 0.55). In the domain of sensory processing, VP children showed higher scores than FT children on the *Registration component* (t (111) = 3.618, p < .001, d = 0.37), indicating that VP children made more errors on somatosensory registration tasks. Furthermore, VP children showed lower scores than the FT group on the *SP Total score* (t (111) = -2.134, p = .035, d = 0.41), indicating VP children had more sensory modulation difficulties.

Impact of sensory processing difficulties on ADHD and ASD symptoms

The impact of somatosensory registration on the relation between prematurity and symptoms of ADHD and ASD is depicted in Figure 5.1. The *Registration component* which significantly discriminated between the VP group and the FT group, was entered as a mediator of the relation between group (VP, FT) and the *ADHD component* and *ASD component*. As expected, membership of the VP group was related to higher *ADHD component* and *ASD component* scores and higher scores on the *Registration component*. However, the *Registration component* was neither related to the *ADHD component* nor the *ASD component*. The *Registration component* did not mediate the impact of VP birth on the *ADHD component*, *B* (SE) = -0.07

Table 5.1. Group characteristics of very preterm children and full-term children

Characteristic	VP group (*n* = 57)	FT group (*n* = 57)	*p*
Age at assessment, years, M (SD)	9.2 (0.4)	9.2 (0.5)	.861
Estimated FSIQ, M (SD)	100.7 (11.2)	106.1 (12.5)	**.017**
Sex, *n* (% male)	26 (46)	25 (45)	.917
SES			.073
Low, *n* (%)	5 (9)	2 (4)	
Low intermediate, *n* (%)	22 (39)	12 (21)	
High intermediate, *n* (%)	16 (28)	18 (32)	
High, *n* (%)	14 (25)	24 (43)	
Gestational age, weeks, M (SD)	30.2 (1.8)	39.8 (1.4)	**< .001**
Birth weight, grams, M (SD)	1293 (296)	3593 (535)	**< .001**
SGA, *n* (%)	15 (27)		
Length of hospital stay, days, M (SD)	50.3 (15.6)		
PVL			
None, *n* (%)	27 (47)		
Flaring and/or PVL grade I/II, *n* (%)	30 (53)		
Neonatal infection, *n* (%)	26 (46)		
Subependymal hemorrhage			
None, *n* (%)	50 (88)		
Grade I, *n* (%)	5 (9)		
Grade II, *n* (%)	2 (4)		
Neonatal Medical Index (NMI)			
NMI I, *n* (%)	1 (2)		
NMI II, *n* (%)	6 (11)		
NMI III, *n* (%)	28 (49)		
NMI IV, *n* (%)	15 (26)		
NMI V, *n* (%)	7 (12)		

Note. SES was determined by classifying the highest level of parental education in a household on a four point scale (low, low intermediate, high intermediate, high) with higher scores indicating higher levels of education and corresponding higher SES.[53] SGA is defined as either birth length or weight < 2 SD. Length of hospital stay is defined by the total number of days between admission to the VU University Medical Center and discharge from any hospital after potential transfers, including stay on the (neonatal) intensive/high care unit. Presence of PVL is defined by flaring on ultrasound and/or PVL grade I/II.[54] Presence of infection is blood-culture-proven. Subependymal hemorrhage is graded I–V.[55] The Neonatal Medical Index is graded I–V.[56] There were no children with grade III or IV subependymal hemorrhage.
Abbreviations: VP = very preterm; FT = full-term; FSIQ = full-scale IQ; SES = socio-economic status, SGA = small for gestational age; PVL = Periventricular leukomalacia.
Bold numbers pertain to a significant *p*-value ($p < .05$).

(0.05), 95% confidence interval (CI) = -0.19 to 0.03, or the *ASD component*, *B* (SE) = -0.07 (0.08), 95% CI = -0.27 to -0.05. These findings suggest that somatosensory registration does not contribute to ADHD and ASD symptom levels.

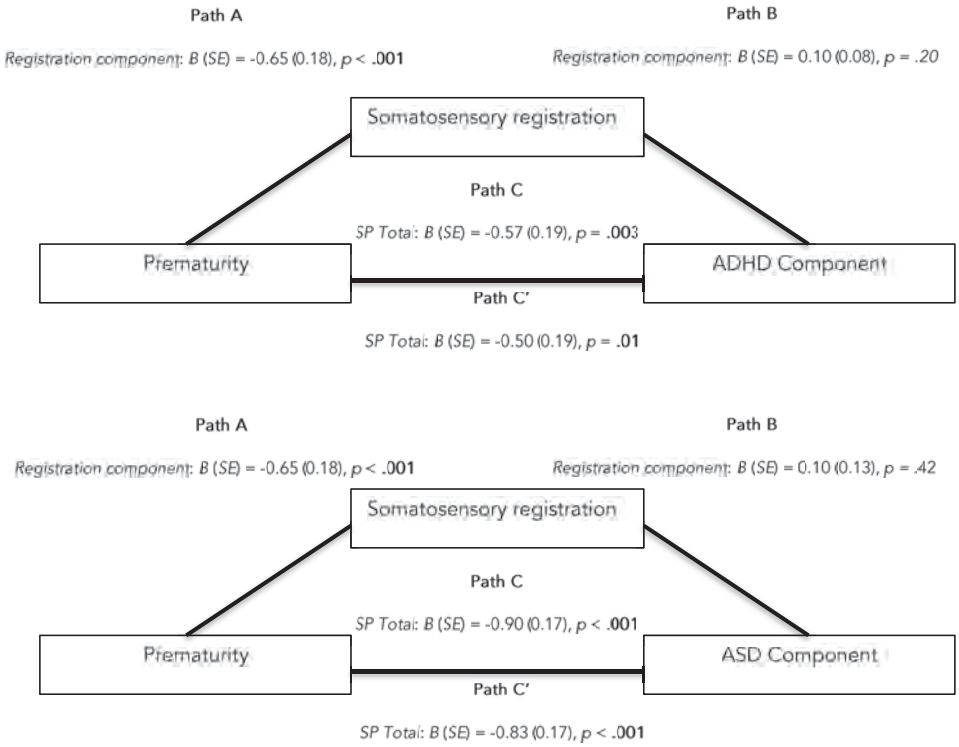

Figure 5.1. Mediation analysis investigating the role of somatosensory registration difficulties in the relation between prematurity and symptom levels of ADHD and ASD.
Note. The mediation analysis describes the relations between prematurity and ADHD/ASD symptom levels (Path C), between prematurity and somatosensory registration difficulties (Path A) and between somatosensory registration difficulties and ADHD/ASD symptom levels (Path B). Lastly, the relation between prematurity and ADHD/ASD symptom levels is described as corrected for somatosensory registration difficulties (Path C'). Abbreviations: ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; *B* (SE) = raw regression coefficient (Standard Error).

The impact of sensory modulation on the relation between prematurity and symptoms of ADHD and ASD is depicted in Figure 5.2. The *SP Total score*, which significantly discriminated between the VP group and the FT group, was entered as a mediator of the relation between group (VP, FT) and the *ADHD component* and *ASD component*. As expected, membership of the VP group was related to higher *ADHD component* and *ASD component* scores and a lower *SP Total score*. In turn, a lower *SP Total score* was related to both higher *ADHD component* and *ASD component* scores. Importantly, a lower *SP Total score* partially mediated the negative impact of VP birth on both the *ADHD component*, *B* (SE) = -0.20 (0.11), 95% CI = -0.45 to -0.03, and the *ASD component*, *B* (SE) = -0.22 (0.11), 95% CI = -0.43 to -0.02. These findings indicate that sensory modulation may contribute to ADHD and ASD symptom levels in children born VP.

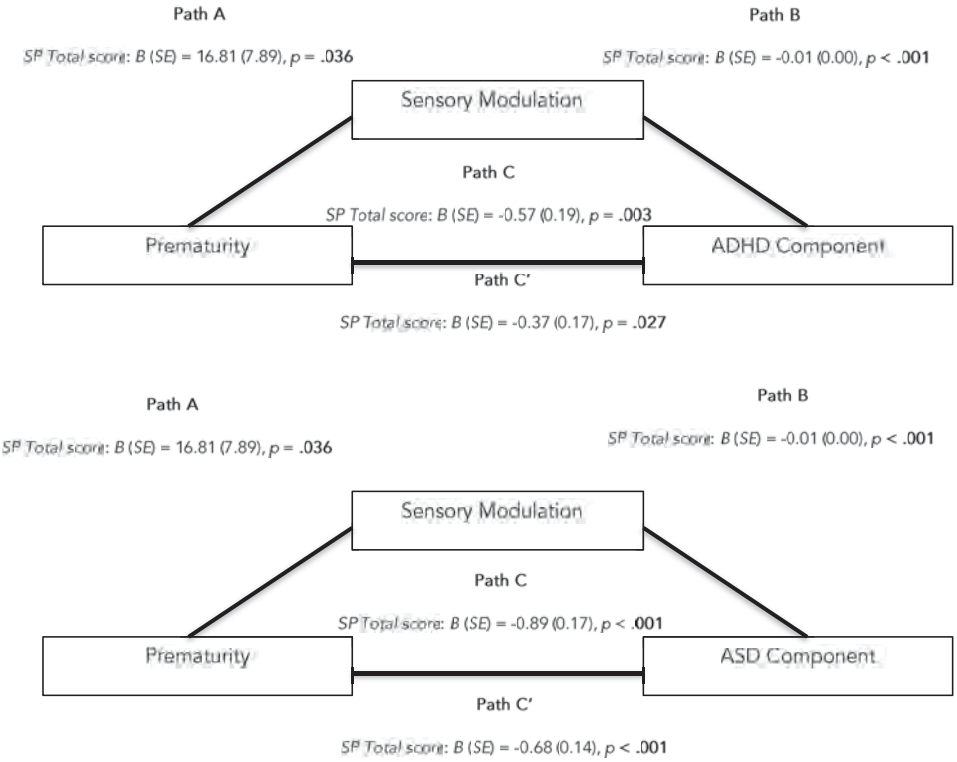

Figure 5.2. Mediation analysis investigating the role of sensory modulation difficulties in the relation between prematurity and symptom levels of ADHD and ASD.
Note. The mediation analysis describes the relations between prematurity and ADHD/ASD symptom levels (Path C), between prematurity and sensory modulation difficulties (Path A) and between sensory modulation difficulties and ADHD/ASD symptom levels (Path B). Lastly, the relation between prematurity and ADHD/ASD symptom levels is described as corrected for sensory modulation difficulties (Path C'). Abbreviations: ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; *B* (SE) = raw regression coefficient (Standard Error).

Exploratory analyses with neonatal complications

To explore if neonatal complications were relevant in the relation between prematurity and ADHD and ASD symptom levels, correlational analyses and mediation analyses were performed (PROCESS macro for SPSS).[47] In the preterm group Spearman rho correlation analyses between neonatal complications (SGA, PVL, infection and length of hospital stay) were all weak (-.12 < r < .23) and not significant ($p \geq .08$), with one exception of a significant moderately sized association between infection and length of hospital stay ($r = .42$, $p = .001$), indicating that these two indices of the severity of illness are somewhat related, but largely independent. For mediation analyses, subgroups of VP children were distinguished based on neonatal complications: VP children born SGA ($n = 15$) versus VP children born appropriate

for gestational age (AGA; *n* = 42); VP children with PVL (*n* = 30) and without PVL (*n* = 27), VP children with (*n* = 26) and without proven infection (*n* = 31), and children who stayed longer than 46 days at the hospital (*n* = 28) or shorter than 46 days (*n* = 29). The cut-off of 46 days divided the VP group in half. Table 5.2 shows the results of mediation models that were used to investigate the possible role of sensory modulation difficulties (*SP Total score* as mediator variable) in symptom levels of ADHD and ASD (*ADHD component* and *ASD component* as dependent variables), separately in all VP subgroups (SGA/AGA, PVL/no PVL, infection/no infection, hospital stay ≥ 46 days/hospital stay < 46 days) compared with the FT group (VP subgroups and FT groups as independent variables). For all neonatal complications (SGA, PVL, infection, hospital stay > 46 days) *SP Total score* partially mediated the negative impact of VP birth on both the *ADHD component* and the *ASD component*. Likewise, in absence of these neonatal complications, lower *SP Total score* did not mediate the impact of VP birth on the *ADHD component* and on the *ASD component*. These findings indicate that only in VP children who had at least one additional neonatal complication, sensory modulation difficulties contributed to ADHD and ASD symptom levels.

DISCUSSION

This is the first study that investigated the impact of sensory processing difficulties on ADHD and ASD symptom levels in very preterm school-age children. The results indicate that, in particular, difficulties in modulating the intensity of responses to sensory stimuli (behavioral hyporesponsiveness and/or hyperresponsiveness) may contribute to ADHD and ASD symptom levels, while the registration of somatosensory stimuli does not. The finding that sensory modulation difficulties are related to ADHD and ASD symptoms corroborates studies in FT children, that showed sensory modulation difficulties to be associated with both ADHD and ASD.[27–29] In fact, it is possible that disengaged (hyporesponsive) or overly sensitive (hyperresponsive) behavior in very preterm children is qualified as symptoms of ADHD and/or ASD. On the behavioral level, characteristics of ADHD and ASD show striking similarities with both hyporesponsive and hyperresponsive reactions of children with sensory modulation difficulties. For instance, hyporesponsive children react less readily and more slowly to sensory stimuli. They may seem oblivious and disengaged to their environment, tend to miss things and show little effort to capture additional input.[24,48] A comparison with attention problems as seen in ADHD and absent-minded and aloof behavior in ASD is easily made. Likewise, hyperresponsive children, readily triggered by sensory input, tend to be hyperactive or distractible, redirecting their attention from one stimulus to the next as seen in ADHD.[24] Conversely, these hyperresponsive children may become easily overwhelmed by sensory stimuli

Table 5.2. Results of mediation analyses for ADHD and ASD component with participants divided in groups according to medical characteristics and Sensory Profile Total score as mediator variable

	Path A			Path B			Path C'			Path C			Path C- Path C'		Mediation	
	B	SE	*p*	*B*	SE	*p*	*B*	SE	*p*	*B*	SE	*p*	*B*	SE	CI_{low}	CI_{high}
ADHD Component																
SGA	24.42	12.9	.062	-.01	.00	**< .001**	-.42	.32	.194	-.70	.37	.065	-.28	.17	**-.72**	**-.03**
AGA	7.15	4.51	.117	-.01	.00	**< .001**	-.18	.09	**.044**	-.26	.10	**.012**	-.07	.05	-.20	.01
PVL	20.96	9.58	**.031**	-.01	.00	**< .001**	-.24	.19	.205	-.48	.22	**.033**	-.24	.13	**-.57**	**-.04**
No PVL	6.10	5.24	.248	-.01	.00	**< .001**	-.27	.11	**.020**	-.33	.13	**.011**	-.07	.06	-.21	.03
Infection	24.10	10.08	**.019**	-.01	.00	**< .001**	-.38	.23	.108	-.63	.25	**.015**	-.25	.13	**-.58**	**-.06**
No infection	5.35	4.91	.280	-.01	.00	**< .001**	-.20	.10	**.042**	-.26	.11	**.025**	-.06	.06	-.20	.04
Length of stay (≥ 46 days) (> 46 days)	30.07	9.42	**.002**	-.01	.00	**< .001**	-.42	.23	.070	-.74	.24	**.003**	-.32	.14	**-.68**	**-.11**
Length of stay (< 46 days)	2.00	4.99	.700	-.01	.00	**< .001**	-.18	.10	.075	-.20	.12	.087	-.02	.06	-.15	.08
ASD Component																
SGA	24.21	12.9	.063	-.01	.00	**< .001**	-.77	.25	**.004**	-1.03	.29	**< .001**	-.26	.25	**-.54**	**-.03**
AGA	7.15	4.5	.117	-.01	.00	**< .001**	-.33	.08	**< .001**	-.43	.10	**< .001**	-.10	.06	-.23	.02
PVL	20.95	9.58	**.032**	-.01	.00	**< .001**	-.61	.16	**< .001**	-.89	.22	**< .001**	-.27	.13	**-.56**	**-.04**
No PVL	6.10	5.24	.248	-.01	.00	**< .001**	-.38	.09	**< .001**	-.45	.11	**< .001**	-.07	.06	-.19	.05
Infection	24.10	10.08	**.019**	-.01	.00	**< .001**	-.81	.18	**< .001**	-1.08	.22	**< .001**	-.28	.12	**-.55**	**-.07**
No infection	5.35	4.91	.280	-.01	.00	**< .001**	-.30	.08	**< .001**	-.37	.11	**.001**	-.07	.06	-.19	.05
Length of stay (≥ 46 days)	30.07	9.42	**.002**	-.01	.00	**< .001**	-.82	.18	**< .001**	-1.16	.21	**< .001**	-.34	.11	**-.59**	**-.15**
Length of stay (< 46 days)	2.00	4.99	.700	-.01	.00	**< .001**	-.29	.09	**.001**	-.32	.11	**.006**	-.03	.06	-.16	.09

Note. Mediation occurs when the CI of the indirect relation corrected for the direct relation does not include 0 (in bold). Abbreviations: *B* = raw regression coefficient; CI = confidence interval; ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; SGA = small for gestational age; AGA = appropriate for gestational age; PVL = periventricular leukomalacia. Bold numbers pertain to a significant *p*-value ($p < .05$).

with either fearful and cautious or negative and defiant behavior as a consequence, such as seen in ASD.[24] The hypothesis that sensory modulation difficulties are being interpreted as symptoms of ADHD and/or ASD is further supported by the common finding that VP children mainly show attention problems and social difficulties instead of qualifying for a full diagnosis of ADHD or ASD.[3]

Surprisingly, although the VP group showed affected somatosensory registration, these difficulties did not impact on ADHD and ASD symptom levels and therefore were not pertinent in the relation between prematurity and ADHD and ASD symptom levels, which was the case for sensory modulation. A possible explanation for this finding is that it is not so much the lower-order registration of somatosensory stimuli, but rather the higher-order regulation of responses to sensory stimuli, that is important in understanding symptoms of ADHD and ASD and subsequent adaptation to the environment. Brain circuits involved in higher-order regulation are far more complex and therefore more vulnerable to subtle white matter damage than lower-order registration circuits.[16,49]

Our findings further show that the presence of neonatal complications (i.e. SGA, PVL or infections) seem to play an important role in the relation between prematurity, symptom levels of ADHD and ASD and sensory modulation. According to the multiple-hit hypothesis,[50] being born very preterm in concert with neonatal complications may particularly compromise/change normal brain development and may enhance the risk for white matter brain abnormalities with subsequent neurodevelopmental problems, such as the sensory modulation difficulties and ADHD and ASD symptoms reported here. In addition, the finding that extended hospital stay is important in the relation between prematurity, symptom levels of ADHD and ASD and sensory modulation, not only suggests that longer hospital stay is associated with greater exposure to detrimental neonatal complications, but also supports the idea that the sensory challenging NICU itself, largely independent of other neonatal complications, may negatively affect long term neurodevelopmental outcome in very preterm children.[51]

A limitation of our study is the substantial attrition with half of the initial cohort willing to participate in this follow-up study. Although comparisons between participants and non-participants on demographic and medical characteristics did not reveal any evidence for selective drop-out, extrapolation of the results to the very preterm population requires caution. Another note of caution is the overlap in questionnaire items. Obviously, there is some overlap in items of the sensory modulation and ADHD and ASD measures, although not to such an extent that it explains the significant associations that were found.

In conclusion, sensory modulation contributed to ADHD and ASD symptom levels and might be considered as one of the pathways that lead to the well-known adverse behavioral

outcomes observed in VP children. Although this cautious statement calls for more research and replication, screening for sensory modulation difficulties and symptoms of ADHD and ASD should not be overlooked in VP children. Understanding ADHD and ASD symptoms from a sensory modulation perspective may provide additional leads for intervention and treatment in VP children.[28,52]

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PART TWO

6

Somatosensory functioning and experienced pain in ADHD-families: a pilot study

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ABSTRACT

Background An issue somewhat overlooked in children with Attention-Deficit/Hyperactivity Disorder is somatosensory functioning. Some studies show a deficit in the processing of tactile and kinesthetic stimuli, but more research is needed to confirm these findings. A related topic, namely the subjective experience of pain, has not been investigated. Also unknown is the somatosensory functioning and experienced pain of non-affected siblings of children with ADHD, which may shed light on the familiality of possible alterations in somatosensory functioning and experienced pain. Therefore, the present study aimed to investigate these aspects in children with ADHD and their non-affected siblings, and to investigate how these aspects were related to each other.

Method Somatosensory functioning (tactile perception and kinesthesia) and subjective intensity and emotionality of pain experiences were examined in 50 children with ADHD, their 38 non-affected siblings and 35 normal controls.

Results Both children with ADHD and their non-affected siblings showed deficits in tactile perception, though kinesthesia appeared unimpaired. Non-affected siblings reported a significant lower intensity and emotionality of past experienced pain than controls. The 'objective' tests of somatosensory functioning did not relate to the subjective sensation of pain.

Conclusions Alterations in tactile perception may relate to a familial susceptibility for ADHD. Clinicians should be aware of possible under reportage of experienced pain in siblings of children with ADHD. The intensity and emotionality of pain appears difficult to objectify with somatosensory test.

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a well-known psychiatric disorder that prevails in 3–5% of all school children,[1] more often in boys than in girls.[2] The core clinical symptoms of ADHD include inattention, hyperactivity and impulsivity.[3] However, many children with ADHD experience problems outside the core clinical domain, such as problems in sleep-wake rhythm (e.g. awaking during the night) and reduced motor coordination and balance.[3-6] This suggests there is more to ADHD than its core clinical features.

A somewhat overlooked area of secondary problems in these children is deficits in somatosensory functioning. Insight into the somatosensory functioning of children with ADHD is important, since optimal functioning of the somatosensory system is crucial for learning and the development of cognitive functions.[7] Somatosensory functioning refers to the processing of sensations arising from the body, which include tactile and kinesthetic information. Tactile perception refers to experiences derived from receptors in the skin. Kinesthesia refers to the perception of differences in limb positions derived from both skin receptors and muscle spindles.[8] Both systems are mediated by different nerve tracks (tractus spinothalamicus and tractus spinocerebellaris, respectively) and may therefore be differentially affected in an individual. Several studies have documented on abnormal somatosensory processing in children with ADHD.[7,9-14] Abnormalities in tactile perception have been observed,[7,9,12] as well as disturbances in kinesthetic acuity in some[10,15] but not all studies with ADHD children.[4] In sum, these findings suggest that some impairment might be present in processing somatosensory stimuli in (a proportion of) children with ADHD, which may pinpoint to overlapping abnormalities in the neurological substrate underlying ADHD and the processing of somatosensory stimuli.

On aspect related to somatosensory functioning that has not been examined in children with ADHD concerns the sensitivity for pain. This topic may be of interest in these children, since these children have an increased incidence of accidents[16] and medical procedures,[17] making them more prone to experiencing painful events. Pain is a complex phenomenon, composed of various aspects among which the sensory-discriminative aspects of pain, the emotional aspects of recent pain, and memory for past pain experience.[18-20] The sensory-discriminative aspect of pain refers to the ability to discriminate between sharp and dull pain and to indicate the location of pain.[18,19] The emotional aspects of recent pain determine partly the intensity with which pain is experienced and influence the medical help a patient seeks for its pain.[19] Knowledge about the patient's sensory-discriminative threshold for pain and memory for past pain experience is important, since both aspects may be related to the extent one is suffering from recent pain.[21,22]

Since little is known about the somatosensory functioning and emotional aspects of pain in children with ADHD, the aim of the present study was to investigate these issues in ADHD children. Somatosensory functioning was also investigated in their non-affected siblings. Research has shown that the disorder is highly heritable.[23,24] This may lead to siblings of children with ADHD having an enhanced risk for developing the disorder themselves[24] and its associated deficits. Even in non-affected siblings, ADHD-like deficits may be present.[25,26] By including not only children with ADHD, but also their non-affected siblings, light may be shed on whether certain deficits are part of a familial risk for the disorder or whether deficits are caused by the presence of the disorder itself.[27-29] In the first case, it is expected that non-affected siblings, sharing on average 50% of their genes with the affected child, would show the same deficit as the affected children. In the latter case, the deficit would only be observable in the affected, but not in the non-affected children. To our knowledge, somatosensory functioning and pain experiences have never been investigated in non-affected siblings of children with ADHD, making uncertain whether abnormalities in these areas may be part of a familial risk for the disorder or are a consequence of the disorder itself.

In the present study, we investigated somatosensory functioning (tactile perception and kinesthesia) and subjective experience of pain in children with ADHD, their non-affected siblings and controls in order to investigate whether possible alterations in these areas were familial in ADHD. Also, correlations between all measures were calculated to assess how these aspects were related to each other.

METHODS

Subject recruitment

The sample consisted of 50 children (37 boys, 13 girls) with the diagnosis of ADHD combined type, 38 non-affected siblings (22 boys, 16 girls) and 35 normal control children from a primary school (16 boys, 19 girls). The children with ADHD and their non-affected siblings participated in the Amsterdam part of the International Multicenter ADHD Genes study (IMAGE).[25,30] The IMAGE project is an international collaborative study that aims to identify genes that increase the risk for ADHD. Families with at least one child with ADHD and at least one additional sibling were recruited from 12 specialist clinics in eight European countries. At the Amsterdam site, 190 families agreed to participate of which 178 families fulfilled all the criteria.

During a certain period of the ongoing recruitment/testing, families were asked to participate in the present study as well, which was aimed at examining somatosensory functioning. This study

offered the unique opportunity also to investigate recent pain experience; a venipuncture was administered for DNA subtraction as part of the genetic study. Only children aged between 5 and 12 years were included in the present study. Exclusion criteria were an IQ < 70, a diagnosis of autism, epilepsy, general learning difficulties, brain disorders or known genetic disorders, such as Down syndrome or Fragile-X-syndrome. All children were of European Caucasian descent and were off medication for at least 48 h (stimulants) or longer (non-stimulants) past before testing.

Within an affected family, both the children already clinically diagnosed with ADHD as well as their siblings were similarly screened using the standard procedures of the IMAGE project.[25,30] Briefly, to identify children with ADHD symptoms, the parents and teachers Conners' long version rating scales[31] and the parent and teacher Strength and Difficulties Questionnaires (SDQ)[32] and were administered. T-scores ≥ 63 on the Conners'-N-scale (DSM-IV total symptom score) and scores > 90th percentile on the SDQ-hyperactivity scale were considered as clinical. Siblings were regarded as non-affected if their scores were in the non-clinical range on *both* the parent and teacher questionnaires (Conners'-N-scale: T-score ≤ 62, SDQ < 90th percentile). Subsequently, a semi-structured, standardized, investigator-based interview; the Parental Account of Children's Symptoms (PACS)[33] was administered to each child scoring clinically on any of the questionnaires completed by the parents or the teachers. No PACS interview was undertaken for non-affected siblings. The study was approved by the local medical-ethical committee and consent forms were signed by parents and children of 12 years and older.

The Conners' long version for both parents and teachers was completed for control children. Control children had to obtain non-clinical scores on both the parent and teacher version (Conners'-N-scale: T-score ≤ 62). Table 6.1 provides the characteristics of the three groups.

Materials

Assessment of somatosensory functioning

Assessment of tactile perception

Three aspects of tactile perception were measured: temperature discrimination, the sensory-discriminative aspects of pain, and light touch. Temperature was assessed by putting two plastic tubes filled with either cold (three times) or lukewarm water (three times) to the skin of the right forearm. The child was asked to indicate whether the temperature of the tube was cold or warm. Number of errors (maximum of 6) was used as dependent measure. The sensory-discriminative aspects of pain were assessed by applying a pencil with a blunt (three times) and a sharp side (pinprick; three times) to the right forearm. The child was asked to indicate whether the blunt or the sharp side was applied. Number of errors (maximum of 6) was used

Table 6.1. Demographics

	ADHD *n* = 50		Non-affected siblings *n* = 38		Controls *n* = 35			
	M	SD	M	SD	M	SD	$F_{2,120}$	Contrasts
Age in years	9.7	1.9	8.8	2.2	9.4	0.7	2.67	1 = 2 = 3
% male		74.0		57.9		45.7	7.14[a,b]	1 > 2 and 3
Conners' Parent								
DSM-IV Inattentive	72.5	9.7	48.5	8.6	46.4	9.7	103.09[b]	1 > 2 and 3
DSM-IV Hyperactive-Impulsive	77.5	10.5	50.6	8.6	49.1	7.3	134.00[b]	1 > 2 and 3
DSM-IV Total	76.7	8.8	49.4	8.4	48.3	6.3	174.70[b]	1 > 2 and 3
Conners' Teacher								
DSM-IV Inattentive	65.7	8.4	49.0	6.1	46.3	4.2	104.82[b]	1 > 2 and 3
DSM-IV Hyperactive-Impulsive	70.0	9.4	50.2	6.2	45.2	2.2	151.14[b]	1 > 2 > 3
DSM-IV Total	69.5	8.4	49.6	5.6	45.2	3.3	173.39[b]	1 > 2 > 3

Note. ADHD = Attention Deficit Hyperactivity Disorder; DSM-IV = Diagnostic and Statistical Manual for Mental Disorders; 1 = ADHD; 2 = Non-affected siblings; 3 = Controls.
[a] χ^2.
[b] $p < .05$.

as dependent measure. Light touch was assessed by touching the child (eight times) with a cotton wool on the skin of the right forearm. The child was asked to indicate the moment the cotton wool touched the skin. Dependent measure was the number of errors (maximum of 8).

Assessment of kinesthesia

Kinesthesia was assessed by testing position sense. The examiner slowly stretched (four times) or bended (four times) one finger (randomly chosen by examiner) of the participant into a final joint position. The subject (with closed eyes) had to indicate the finger that had been moved and its final position. Dependent measure was the number of errors (maximum of 8). To exclude the possibility that impaired finger gnosis caused an elevated number of kinesthesia errors, finger gnosis was assessed by lightly touching (but not bending or stretching) one of the fingers (randomly chosen by the examiner) of the child using the index finger of the examiner. Dependent measure was the number of errors (maximum of 4).

Assessment of subjective aspects of past and recent pain experiences

The subjective experience of past pain was assessed using the Children's Pain Inventory (CPI).[34] This questionnaire consisted of 16 descriptions of acute (nine items) and chronic (seven items) painful events that might have occurred in past daily or medical situations. The child

evaluated both the intensity as well as the emotional aspects of the painful events using two visual analogue scales: the Coloured Analogue Scale (CAS: intensity of pain) and the Facial Affective Scale (FAS: emotional aspects of pain).[34] The CAS had different colours on the front that were marked by scaled positions on the back (pink at the bottom [numeric value 0]: no pain and deep red at the top [numeric value 10]: maximum pain). The subject had to indicate the intensity of the past experienced pain by sliding a horizontal marker from the bottom to the top. Dependent measure was the mean intensity of past experienced pain for the 16 pain descriptions. The FAS consisted of nine line drawings of faces, each expressing a level of overt distress.[34] The children were required to indicate 'what they really felt inside' during the pain experience. The numerical values on the back of the nine faces have been determined in previous studies[35,36] and ranged from .04 (no pain: laughing face) to .97 (most severe pain: crying face). Dependent measure was the mean emotionality score for the 16 pain descriptions. The subjective experience of recent pain was also assessed. As part of the IMAGE study, children with ADHD and their non-affected siblings underwent a venipuncture at the VU-Medical center. The venipuncture was performed on the morning of the assessment and was used to extract DNA.[30] The intensity and emotionality of recent pain were assessed between 1 and 4 h after the venipuncture using the CAS and the FAS. Control children did not undergo a venipuncture.

Procedure

All tasks were carefully explained and demonstrated to the children before the actual testing took place. During all tasks of somatosensory functioning, children were asked to close their eyes. A *qualitative* examination of the child's somatosensory functions (temperature, sensory-discriminative aspects of pain, light touch, kinesthesia, and finger gnosis) was performed. The examination of temperature, sensory-discriminative aspects of pain, and light touch took place at the forearm and all somatosensory functions were tested at least three times. This procedure was based on a recent study in which a qualitative somatosensory examination appeared to be feasible in children of the same age as the children in the present study.[37] The rationale underlying the choice for a qualitative instead of a quantitative examination was that the former is more applicable for children in a clinical setting.[37] The forearm as the site of somatosensory examination is one of the most frequently used sites in this line of research,[38] since compared to other sites, its density in intra-epidermal nerve fibres is high.[39]

Testing of children with ADHD and their non-affected siblings took place at the VU University Amsterdam. Controls were tested in a quite room at their school. All children were off medication for at least 48 h (stimulants) or longer (non-stimulants) before testing to allow complete washout. At the end of the session, a gift worth approximately $5 was given. The study was approved

by the medical-ethical committee and an informed consent was obtained from the parents and children of 12 years.

Statistical analyses

For all analyses, a *p*-value of ≤ .05 was considered significant. The SPSS-PC program was used for data-analyses.[40] It was first assessed whether gender had to be included as factor in the analyses, since groups differed in gender ratio (Table 6.1). The effect of gender was studied with Chi squares carried out separately for each dependent variable within the control group. Subsequently, it was investigated whether children with ADHD deviated from control children, and whether non-affected siblings deviated from control children, separately for each dependent variable. Group comparisons for the measures of somatosensory functioning (not normally distributed) were performed using independent samples non-parametric tests (Mann-Whitney *U* tests). Group comparisons for the intensity and emotionality of subjective pain experiences (normally distributed) were performed using independent samples parametric tests (*t*-tests). Last, the correlations between all dependent measures were calculated using Spearman (for not normally distributed variables) and Pearson (for normally distributed variables) to assess the interrelatedness of the different somatosensory aspects and subjective pain experience.

RESULTS

No differences between control boys and girls were present for any of the dependent measures (*p*-values range from .25 to .41). Therefore, gender was omitted from the analyses. All results are presented in Table 6.2.

Group differences

Somatosensory functioning

Tactile perception

Data-analyses showed that children with ADHD made significantly more errors in temperature discrimination and the sensory-discriminative aspects of pain than controls. Although no significant differences between the ADHD group and control group were observed with respect to light touch, ADHD patients showed overall significantly more tactile perception errors than the control children. Like their affected siblings, non-affected siblings also appeared slightly less sensitive in temperature discrimination (trend) than controls and were also less accurate in the sensory discriminative aspects of pain. Their total tactile perception score was also worse

Table 6.2. Mean number of errors, standard deviations, Mann-Whitney *U*-tests and *t*-tests concerning the scores on somatosensory functioning and subjective pain experience

	ADHD		Non-affected siblings		Controls		ADHD versus controls		Non-affected siblings versus controls	
	M	SD	M	SD	M	SD	*z*/*t*	*p*	*z*/*t*	*p*
Somatosensory functioning										
Tactile perception										
Temperature	.23	.60	.08	.27	.00	.00	2.55	.01	1.69	.09
Sensory-discrimination of pain	.48	.88	.37	.75	.06	.34	3.15	.002	2.52	.01
Light touch	.14	.41	.16	.68	.09	.37	.96	.34	.37	.72
Total	.83	1.29	.61	1.24	.14	.49	3.61	.001	2.36	.02
Kinesthesia										
Bending/stretching fingers	.08	.35	.00	.00	.17	.75	.05	.96	1.46	.14
Control measure of finger gnosis	.27	.71	.05	.23	.09	.37	1.31	.19	.09	.93
Subjective pain experience										
Past pain										
Intensity acute	4.51	1.73	4.40	1.85	5.06	1.35	1.57	.12	1.72	.09
Intensity chronic	4.04	2.07	3.70	1.84	4.66	.99	1.64	.11	2.74	.01
Emotionality acute	.66	.16	.61	.17	.67	.13	.33	.74	1.93	.06
Emotionality chronic	.62	.28	.54	.16	.63	.11	.26	.80	2.6	.01
Recent pain (venipuncture)										
Intensity	3.61	3.08	3.79	3.31						
Emotionality	.57	.30	.54	.32						

Note. Experienced pain was assessed with the Children's Pain Inventory on which they rated the intensity (Colored Analogue Scale) and emotionality (Facial Affective Scale) of their past and recent pain. Controls did not undergo a venipuncture.

compared to controls. These findings suggest tactile perception to be impaired in children with ADHD and their non-affected siblings.

Kinesthesia

No group differences were present for kinesthesia or the control measure of finger gnosis, suggesting kinesthesia to be normal in children with ADHD and their non-affected siblings.

Subjective experiences of pain

No differences were observed between children with ADHD and controls with respect to intensity or emotionality of acute and chronic past pain experiences. Differences were observed, however, between non-affected siblings and controls; non-affected siblings reported a lower intensity and emotionality regarding acute and chronic previously experienced pain.

Relationship between the measures

Within the domain of tactile perception, temperature discrimination correlated significantly with sensory-discriminative aspects of pain ($r = .31$, $p = .001$) and light touch ($r = .20$, $p = .03$), although the latter two did not correlate significantly. This suggests children having difficulty with one aspect of tactile perception tended to have difficulty with other aspects of tactile perception. Within the domain of kinesthesia, finger bending/stretching correlated significantly with finger gnosis ($r = .23$, $p = .01$). Also significant correlations were found between past and recent experienced pain, ranging between .30 and .43 ($p < .01$), suggesting reports of past pain relate to current intensity and emotionality of pain. However, virtually no significant correlations were present between measures of somatosensory functioning on the one hand and experienced intensity and emotionality of past and recent pain on the other hand (except for one significant correlation between kinesthesia and intensity of past pain). This suggests that 'objective' testing of somatosensory functioning does not necessarily provide indication on the subjective aspects of pain.

DISCUSSION

The aim of our study was to investigate whether children with ADHD and possibly their non-affected siblings differed from normal control children with respect to somatosensory functioning (tactile perception and kinesthesia) and with respect to the subjective experienced intensity and emotionality of past pain. Also assessed was the relation between measures of somatosensory functioning and subjective pain experience.

Somatosensory functioning

Children with ADHD and their non-affected siblings committed, overall, more errors on tests demanding tactile perception than controls. Children with ADHD and to a lesser extent their non-affected siblings had more difficulty than controls in temperature discrimination. Furthermore, both groups made significantly more errors in sensory-discriminative aspects of pain (pinprick) compared to controls. These errors may imply that the children were less able to differentiate between warm versus cold and dull versus sharp, suggesting a hyposensitivity for processing of these types of stimuli. However, no group differences were present on the test of kinesthesia, nor on the control test of finger gnosis, which is in line with another study reporting on normal kinesthesia in ADHD.[4] This may suggest the underlying neural mechanisms of kinesthesia to be normal in ADHD. Alternatively, these discrepant findings may be explained by the fact that we only administered one test of kinesthesia. It may thus be possible that a general impairment in somatosensory functioning is present (and not limited to tactile stimuli only), the more so since several previous studies have shown abnormal kinesthesia in ADHD,[10,15] which would also relate to the high incidence of motor coordination and balance problems reported in ADHD.[6] Clearly, further research is required before form conclusions can be drawn, but preliminary evidence suggests some aspects of somatosensory functioning (i.e. tactile perception) to be abnormal in ADHD families.

Brain regions that are involved in tactile perception include the somatosensory cortex, the thalamus, and the insula.[18,41] Some studies have found abnormalities in the somatosensory cortex/post central gyrus in patients with ADHD, which may relate to the findings of decreased tactile perception in children with ADHD and their siblings; a recent voxel-based morphometric study observed a gray matter reduction in the somatosensory cortex of children with ADHD,[42] suggesting possible decreased sensitivity for the processing of somatosensory stimuli. Another voxel-based study showed an increased perfusion in, among others, the postcentral gyrus.[43] These authors suggest that an increased perfusion in the postcentral gyrus is a marker for disinhibition and a reflection of patient's inability to mediate incoming sensory stimuli.[43] In addition, a greater probability of hypoactivity in the right thalamus and greater probability of hyperactivity in the left thalamus was reported in patients with ADHD,[44] suggesting generalized abnormalities in the activity of the thalamus in ADHD. The somatosensory cortex, thalamus and insula are also part of the lateral pain system,[41] which is one of two systems in the central nervous system that mediates the processing of pain. Anatomical and/or functional abnormalities in these brain areas may, therefore, not only lead to deficits in somatosensory functioning, but may also lead to abnormalities in the experience of pain.

All in all, both anatomical and functional imaging studies as well as our findings seem to suggest that some aspects of somatosensory functioning may be abnormal in children with ADHD and their non-affected siblings. The fact that altered tactile perception was found in both children with ADHD as well as their non-affected siblings may suggests abnormalities in the processing of tactile stimuli relate to the familial susceptibility for the disorder. This might, in turn, be useful for molecular genetic research as well as clarifying the causal pathways leading from risk genes to observable ADHD symptoms.

Subjective experience of pain

Contrary to our expectations based on findings of altered somatosensory functioning in ADHD, children with ADHD did not differ from normal controls in the reported intensity or emotionality of past experienced pain. An explanation for this might be that in children with ADHD, the volume of the hippocampus is similar to the hippocampal volume of normal children.[45] The hippocampus is part of the medial pain system[18,19] which plays an important role in the memory for pain.[46] Since in our study children were asked to report on previously experienced pain, it is possible we assessed the memory for pain and possibly not (or to a lesser extent) the intensity and emotionality of the pain as it was actually experienced. In line with the findings of a possible decreased sensitivity to tactile stimuli in non-affected siblings, is their report on a *lower* level of past pain experience compared to controls. However, in that case, we would expect to find the same results in their affected siblings, since they showed similar impairments on the tests of tactile perception. Therefore, the lower level of experienced pain in non-affected siblings may also be explained by the observation that non-affected siblings may have been exposed to the physical aggressiveness of their affected siblings.[47] Against this background, 'normal' painful conditions that are experienced during daily life, like hurting one's knee after a fall (CPI), may be experienced as less painful by the non-affected siblings.

Since intensity and emotionality of past pain was correlated to the intensity and emotionality of recent pain, it may be expected that group differences are similar for past and recent pain. In that case, children with ADHD do not differ from controls in their intensity and emotionality of pain, yet non-affected siblings may experience pain with a lower level of intensity and emotionality. However, we do not know this for sure, since no recent pain assessment was performed in controls due to ethical concerns. Therefore, we can only speculate about alterations in actual pain experience in children with ADHD and their siblings, which in itself is interesting with respect to future research. One of the areas that is part of the medial pain system is the locus coeruleus,[48] a brain stem area which is the source of the noradrenergic system.[49] A dysfunction of the locus coeruleus through a disturbance of the number of alpha-2-noradrenergic receptors

has been described for ADHD.[50] Since the LC/noradrenergic system is part of a descending pain-suppressing system,[51] one could hypothesize that a deficit in the LC/noradrenergic system might cause a *lowering of the pain threshold* in ADHD. In other words, children with ADHD may respond more intensively to a painful stimulus than children without ADHD or may experience pain from a stimulus that is not painful in non-ADHD children with pain. Lowering of the pain threshold may also result from a hypoactive hypothalamic-pituitary-adrenal (HPA) axis which has been observed in children with ADHD.[52] A less active HPA-axis is related to a decreased activity in corticotropin-releasing hormone neurons, which normally produce analgesia.[53] Thus, two possible dysfunctions in the medial pain system of children with ADHD may lower the pain threshold and as a result may increase pain experience in ADHD. Possible dysfunctions of these two systems in non-affected siblings have not been examined thus far.

Interestingly, an *increase in the pain threshold*, resulting in a decrease in pain experience, might be characteristic for ADHD. Studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) showed hypoactivity in the anterior cingulate cortex (ACC).[54,55] The ACC is part of the medial pain system18 and reduced activity in this area may produce a decrease in pain experience. A decline in pain experience may also result from a reduction in the volume and cerebral blood flow of the prefrontal cortex which has been found in children with ADHD as well as in their non-affected siblings.[1,56,57] The prefrontal cortex plays a role in the processing of the emotional aspects of pain.[58] Taken together, hypoactivity in the ACC and PFC may cause a decrease in pain experience in ADHD. Future research is needed to clarify this.

Relationship between somatosensory functioning and subjective experience of pain

Within the domain of tactile perception, temperature discrimination correlated significantly with sensory-discriminative aspects of pain and light touch (though the latter two did not correlate significantly), suggesting children having difficulty with one aspect of tactile perception tended to have difficulty with other aspects of tactile perception. The same was true for correlations between past and recent experienced pain; past pain experience was positively correlated with the recent pain experienced during the venipuncture. The finding that past pain experience relates to recent pain experience is not new. In previous studies, pre-operative pain was significantly correlated with pain patients expected to experience after an operation[59] and with the pain patients recently experience after an operation.[22]

Overall, correlations between the more 'objective' tests of somatosensory functioning on the one hand and the subjective report on the intensity and emotionality of past and recent pain

on the other were not significant, suggesting 'objective' neurological tests of somatosensory functioning do not provide information regarding the subjective sensation of pain. The rationale for examining such a relationship is that in the pain literature, a combination of an increase in recent pain experience (medial pain system) and a decline in somatosensory functioning (lateral pain system) has been described.[21] More specifically, it has been hypothesized that a dysfunction of the lateral pain system may disinhibit areas of the medial pain system.[21] Disinhibition of the medial pain system is expressed as central pain.[21] It should be noted, however, that the cooperation between the medial and lateral pain system is weak,[18] which might explain why a relationship between somatosensory functioning and pain experience was not found in the present study.

Limitations

Some limitations were inherent to this study. First, larger sample sizes would have benefited the statistical power of the study to detect alterations in somatosensory functioning. However, this study was designed as an explorative pilot study and it is promising that alterations in somatosensory functioning in children with ADHD and their non-affected siblings can be observed in these relatively small samples. However, future research is needed to confirm these findings.

Second, recent pain experience was not recorded in control children due to ethical concerns. Therefore, no conclusions can be drawn as to whether recent pain experience in itself is different in children with ADHD and their siblings compared to controls. We have considered using children who underwent venipuncture within the scope of diseases other than ADHD as controls, but have decided not to do so; results of studies show that health status, well being and comorbidity such as asthma are predictors of pain experience.[60,62] In addition, disease-related sleep disturbances and depression are related to a decrease in pain threshold.[63] Only healthy children could, therefore, serve as a control group and studies on pain by venipuncture in this group have only been performed with neonates.[64]

Third, it may be hypothesized that the impairments in tactile perception found in children with ADHD are a result of having the disorder itself. That is, having a shorter attention span may have contributed to errors on the tasks measuring tactile perception. This may be true to a certain extent, yet one would expect at the same time that more errors would be committed by children with ADHD on all tasks, and not selectively on tasks of tactile perception, and one would expect non-affected siblings to perform normally on all tasks, since they do not exhibit more attentional problems than the control children. This appeared not to be the case; children with ADHD selectively made errors on the tasks measuring tactile perception, but not

kinesthesia, and non-affected siblings performed less accurately on the tactile perception tasks as well. These findings suggest that at least a part of the impairments in tactile perception ADHD is not an artifact.

Fourth, the examiner was not blinded to which group each child was in and except for the measurement of past and recent pain experiences, no standardized measurement methods were used. However, as far as the authors know, this is the first study that examined somatosensory functioning in both ADHD and their non-affected siblings. In other words, the nature of this study is explorative. For the reliability of this type of studies, blindness of the investigator is not a prerequisite. Nevertheless, the reliability of future studies would be improved by having the examiners blinded to the group the child is in and administering standardized somatosensory tests.

Clinical relevance of the present findings

In the first place, optimal functioning of the sensory-motor system is essential for learning and cognitive functioning for young children.[7] Recent epidemiological findings suggest that physical activity early in life may provide a cognitive reserve that protects against a decline in cognition at an older age.[65] In other words, disturbances in somatosensory functioning and with that, possibly in sensory-motor functioning, may hamper the development of a cognitive brain reserve in children with ADHD and their siblings. The more so since these children already suffer from cognitive problems.[3,25,26] Secondly, siblings experience past pain to a lesser extent. This finding might imply that clinicians should be alert, when siblings participate in activities that may normally provoke pain; not indicating pain does not automatically mean that there is no pain. In the third place, 'objective' tests of somatosensory functioning do not appear to be related to the subjective experience of pain. Thus, the intensity and emotionality of pain appears difficult to objectify with test. Pain assessment should, therefore, always focus on the personal experience of pain of the patient.

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7

Sex differences in tactile defensiveness in children with ADHD and their siblings

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ABSTRACT

Background Tactile defensiveness (TD) is a disturbance in sensory processing and is observed in some children with Attention-Deficit-Hyperactivity-Disorder (ADHD). TD has been examined in male children with ADHD and in children with ADHD without differentiating by sex. As males and females with ADHD may differ in the clinical expression of ADHD and associated deficits, the aim of our study was to examine sex differences in TD in males and with ADHD. Non-affected siblings were also examined, to investigate familiality of TD.

Method The Touch Inventory for Elementary-School-Aged Children was administered to 47 children with ADHD (35 males, 12 females; mean age 9y 8mo [SD 1y 11 mo]), 36 non-affected siblings (21 males, 15 females; mean age 8y 10mo [SD 2y 4mo]), and 35 control children (16 males, 19 females, mean age 9y 4mo [SD 6mo]).

Results & Conclusion Results indicated that females with ADHD displayed higher levels of TD than males with ADHD (who did not differ from control males). This suggests TD is sex specific and may contribute to the identification of ADHD in females, thus improving diagnostic and therapeutic strength in this under-referred group. Non-affected siblings were unimpaired, regardless of sex, which suggests that TD is specific to the disorder and not part of a familial risk for ADHD.

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD)[1] is a common neuropsychiatric developmental disorder, which is estimated to affect 3% to 11% of children and adolescents.[2] The core clinical symptoms of ADHD (inattention, hyperactivity and impulsivity) are often accompanied by associated symptoms, such as sleep problems, reduced motor coordination and balance.[2]

Sex possibly influences the clinical manifestation of ADHD and the extent to which associated symptoms of ADHD occur. Three studies found that females with ADHD showed relatively lower levels of hyperactivity, fewer diagnosis of conduct disorder and other comorbid disruptive behavior problems compared to males with ADHD.[3-5] However, it was also found that females with ADHD have greater intellectual impairment,[4,5] a higher prevalence of the predominantly inattentive subtype of ADHD,[3] and are more at-risk for substance use disorders.[3] One study found no sex differences with respect to impulsivity, academic performance, social functioning and/or fine motor skills.[4] Further study may help to determine whether differences exist between males and females with ADHD.

Relatively little is known about sex differences in disorders associated with ADHD, such as sensory processing disorders. Recent literature suggests that children with ADHD show a disturbance in sensory processing and integration of tactile stimuli.[6-9] One area of dysfunction in sensory processing disorders is called tactile defensiveness (TD).[10,11] TD is often observed in children with autism, learning disability, fragile X syndrome, emotional disturbances, and specific learning difficulties.[10-14] Individuals with TD show a tendency to 'react negatively and emotionally to certain touch situations'.[14] They avoid touch, interpret non-noxious touch, such as light, brief touch to the arms, face or legs, as threatening. They may try to avoid certain textures or types of clothing. Children with TD show an aversion to having their hair combed, nails cut by others, and avoid activities with a clear tactile component, such as finger painting.[15]

Four studies showed that children with ADHD exhibited higher levels of TD than control children.[6-9] However, three of these studies did not differentiate between males and females in the data-analyses[7-9] and one study included only males.[6] As sex may differentially affect the clinical manifestation of ADHD,[3,4] and as a recent twin study showed that relatively more females than males have extreme TD scores, the main goal of the present study was to assess TD in males and females with ADHD to examine whether levels of TD are comparable in both sexes.

A second aim of this study was to assess TD in non-affected siblings of children with ADHD to examine whether TD is a familial characteristic of the disorder. The reason for including non-affected siblings alongside affected children is that this allows for investigation of a possible shared aetiology of TD and ADHD. That is, non-affected siblings share part of the (genetic

and environmental) risk factors that have contributed to ADHD in their affected sibling. If TD arises partly from the same risk factors as ADHD, then one would expect to observe some TD in non-affected siblings, even in the absence of ADHD. If, however, ADHD and TD do not arise from the same risk factors but are merely associated with each other on a phenotypical level, then it is more likely that TD is observed only in affected children, but not in familially at-risk siblings.

METHODS

Participants

Children with ADHD and their non-affected siblings participated in the Amsterdam site of the International Multicenter ADHD Genes (IMAGE) study.[16] The IMAGE project is an international collaborative study that aims to identify genes that increase the risk for ADHD. Families with at least one child with ADHD and at least one additional sibling (regardless of possible ADHD status) were recruited from 12 specialist clinics in eight European countries. At the Amsterdam site, 190 families agreed to participate of which 178 families fulfilled all the criteria. Exclusion criteria were an IQ < 70, a diagnosis of autism, epilepsy, general learning difficulties (i.e. severe problems in multiple areas of academic learning), brain disorders or known genetic disorders, such as Down syndrome or Fragile-X-syndrome. All children were of European Caucasian descent.

This study was initiated as a pilot study on a subsample of the 178 families. Data collected a 6-month period of recruitment of the families were available for 47 children (mean age 9y 8mo, SD 1y 11mo) with the combined subtype of ADHD (35 males: seven were not on medication, 25 took stimulants, one took non-stimulants, two took a combination of stimulants and non-stimulants; and 12 females: four were not on medication, six took stimulants, two took non-stimulants) and 36 non-affected siblings (21 males, 15 females; mean age 8y 10mo, SD 2y 4mo). An additional 35 control children (16 males, 19 females; mean age 9y 5mo, SD 6mo) were recruited from elementary schools in the same geographical region as the participating families of the children with ADHD. Only children aged between 6–12 years were included in the present study. All children were off medication for at least 48 hours (stimulants) or longer (non-stimulants) before testing. The study was approved by the local medical-ethical committee and consent/assent forms were signed by parents and children of 12 years of age.

Within an affected family, the child clinically diagnosed with ADHD and the child's sibling were similarly screened using the standard procedures of the IMAGE project.[16,17] To identify

children with ADHD symptoms, the Conners' ADHD Rating Scale (parent and teacher long versions),[18] and the parent and teacher Strength and Difficulties Questionnaires (SDQ)[19] were administered. Children with T-scores ≥ 63 on the Conners' ADHD Total scale (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edn,[1] Total symptom score) and scores > 90th percentile on the SDQ hyperactivity scale were considered as clinical. Siblings were regarded as non-affected if their scores were in the non-clinical range on both the parent and teacher questionnaires (Conners' ADHD Total scale: T-score ≤ 62, SDQ < 90th percentile). Subsequently, a semi-structured, standardized, investigator-based interview; the Parental Account of Children's Symptoms (PACS),[20] was administered for each child scoring clinically on any of the questionnaires completed by the parents or the teachers. No PACS interview was undertaken for non-affected siblings. The Conners' Scale (long version) for both parents and teachers was completed for control children. Control children had to obtain non-clinical scores on both the parent and teacher version (Conners' ADHD Total Scale: T-score ≤ 62; see Table 7.1).

Tactile defensiveness

The Touch Inventory for Elementary-School-Aged Children (TIE)[15] was used to obtain a measure of TD. The TIE is a screening questionnaire for school-aged children aged between 6 to 12 years. It contains 26 items that involve common daily situations in which a child meets touch or stimulation. Children were presented with questions such as: 'Does it bother you to have your face washed?' and 'Does is bother you to go barefooted?' They were required to rate these situations on a 3-point scale in terms of the level of inconvenience: 'no', 'a little', 'a lot'. The TIE has a good internal reliability (a coefficient alpha of .79 and standardized alpha .79),[15] test-retest reliability (r = .91, p < .001),[21] and validity (discriminant analysis: p = .007, 85% correct classification).[15]

The English TIE was translated into Dutch for the current study using double translation procedures (i.e. from English to Dutch and back to English again by separate individuals who were fluent in English and Dutch) Any discrepancies were resolved after mutual agreement. A previous study has shown that mean test scores are similar in American children (English version of the TIE) and European children (non-English version of the TIE translated into native language of the children),[22] suggesting that careful translation of the TIE does not affect results. Scores could hypothetically range between 26 and 78, but the typical range is between 26 and 60 based on a sample of 415 children.[22] The same study showed that the mean score of the TIE was 41 with a SD of 7.8. Based on these data, a score of 57 and above (≥ 2 SDs) was regarded as a clinical score for TD. Scores of the TIE are referred to as TD-scores.

Table 7.1. Participants' attention-deficit-hyperactivity disorder screening scores by group

	ADHD group				Non-affected siblings				Controls					
	Males *n* = 35		Females *n* = 12		Males *n* = 21		Females *n* = 15		Males *n* = 16		Females *n* = 19			
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	$F_{5,112}$	Contrasts ($p < .05$)
Age, y:mo	10:0	1:7	10:0	1:1	9:0	2:2	8:11	2:2	9:7	0:6	9:4	0:8	2.0	*ns*
Conners' Scale Parent														
DSM-IV Inattentive	70.5	7.8	78.8	12.9	48.6	9.7	48.2	7.4	48.3	8.4	44.9	10.6	43.4	1 ≈ 2 > 3 ≈ 4 ≈ 5 ≈ 6
DSM-IV Hyperactive-Impulsive	77.2	8.8	78.2	15.7	50.7	9.5	49.7	7.6	50.1	9.7	48.2	4.5	50.6	1 ≈ 2 > 3 ≈ 4 ≈ 5 ≈ 6
DSM-IV Total	75.5	7.3	80.6	12.6	49.3	9.5	48.9	7.1	49.1	8.5	47.6	3.6	68.2	1 ≈ 2 > 3 ≈ 4 ≈ 5 ≈ 6
Anxious-shy	59.6	13.3	63.6	16.4	50.3	10.7	50.1	10.2	48.9	8.3	50.7	10.5	4.7	1 ≈ 2, 1 > 5, 2 > 3 ≈ 4 ≈ 5 ≈ 6
Conners' Scale Teacher														
DSM-IV Inattentive	63.4	5.7	72.4	11.3	47.0	5.3	51.0	5.6	46.9	5.9	45.7	2.0	56.7	2 > 1 > 3 ≈ 4 ≈ 5 ≈ 6
DSM-IV Hyperactive-Impulsive	68.1	9.2	75.4	9.7	49.9	5.9	49.8	6.0	45.0	2.7	45.3	1.7	64.5	2 > 1 > 3 ≈ 4 ≈ 5 ≈ 6
DSM-IV Total	67.1	6.7	75.8	10.1	48.3	5.6	50.5	4.3	45.7	4.3	44.7	2.2	84.9	2 > 1 > 3 = 4 = 5 = 6
Anxious-shy	61.6	11.0	60.7	13.4	56.1	8.6	53.5	11.0	53.2	9.1	57.9	13.4	2.1	*ns*

All values are mean (SD) unless otherwise indicated. ADHD = Attention Deficit Hyperactivity Disorder. DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edn.[1] Contrasts: 1 = Males with ADHD; 2 = Females with ADHD; 3 = Non-affected male siblings; 4 = Non-affected female siblings; 5 = Control males; 6 = Control females; ns = not significant.

Data analysis

Analyses were performed using SPSS (version 14.1). A mixed model was used with sex (two groups: males and females) and group (three groups: ADHD, non-affected siblings, and controls) as fixed factors. Family was used as random effect to account for within family correlation, since more than one child per family participated resulting in dependency of observations. The 'sex by group' interaction was implemented in the model to investigate whether sex differences on the TIE were similar between groups. Using 2 SDs as a cut-off (raw score ≥ 57), the percentage of children scoring extremely on the TIE was calculated for each group.

RESULTS

A mixed model with sex and group as fixed factors, the 'sex by group' interaction, and family as a random effect showed no main effect of sex (F (1, 117.8) = 0.97, p = .33), a significant main effect of group (F (2, 107.6) = 3.51, p = .03), and a significant 'sex by group' interaction (F (2, 117.3) = 4.14, p = .02). The latter finding implied that both main effects (sex and group) could not be interpreted separately from each other and analyses should be separated by group. When analyses were rerun, females had significantly higher TD-scores than males with ADHD (F (1, 47.0) = 10.27, p = .002) as well as compared to control females (F (1, 31.0) = 13.06, p = .001). Males with ADHD did not differ from control males (F (1, 48.0) = 0.01, p = .91). No sex difference was found when non-affected siblings were analyzed (F (1, 32.1) = 0.16, p = .70) or when controls were analyzed (F (1, 35.0) = 0.59, p = .45), and non-affected siblings did not differ from controls (F (1, 49.8) = 0.29, p = .59) (see Figure 7.1).

Using a cut-off score of 2 SD extreme TD scores were found in: one male with ADHD, two females with ADHD, one non-affected male sibling, one non-affected female sibling, one control male, but no control female.

DISCUSSION

The aim of the present study was to examine whether TD is comparable in males and females with ADHD, and whether TD is also present in non-affected siblings of children with ADHD.

Overall, children with ADHD had higher TD scores than control children, which is in line with previous studies.[6-9] These findings underline the importance of deficits associated with ADHD outside the spectrum of the core symptoms of inattention, hyperactivity, and impulsivity, and may suggest underlying abnormalities in the processing of somatosensory stimuli. Optimally-

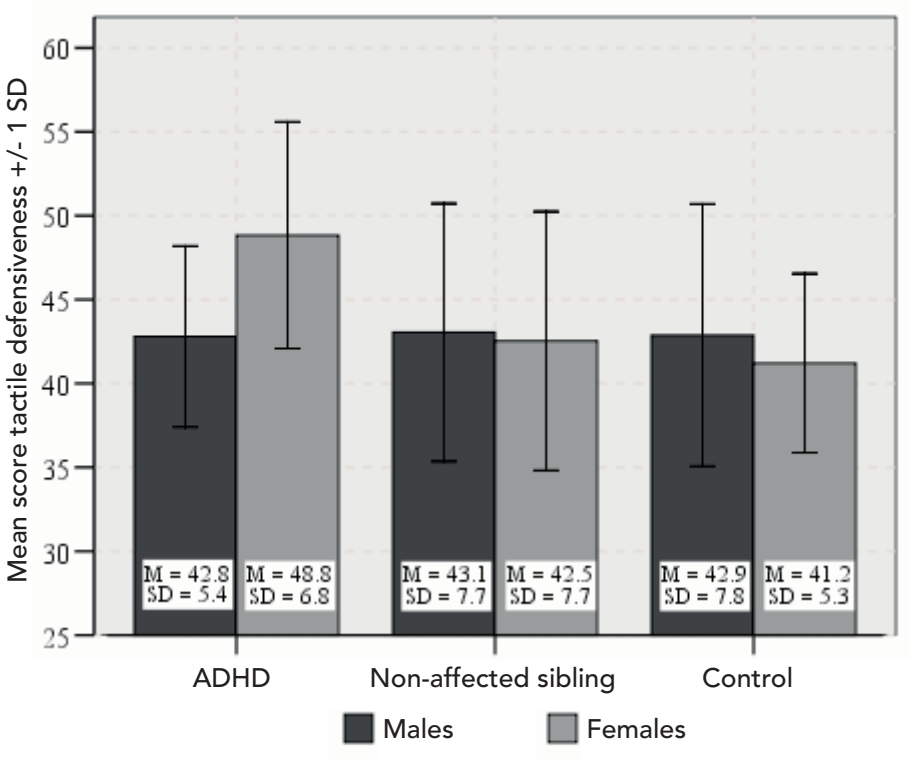

Figure 7.1. Mean (SD scores of tactile defensiveness (TD) in Children with ADHD, their non-affected siblings and controls for males and females separately. Compared with other groups, females with ADHD showed higher levels of TD.

functioning sensory processing enables an adequate range of performance and adaptation to daily environment.[8] In young children, poor sensory processing may cause difficulties in their social, cognitive, and sensory-motor development.[9] Moreover, problems in sensory processing may lead to difficulties in originating adequate responses in school, home and community settings.[7] Examining sensory processing in children with ADHD might prove valuable for intervention purposes.

The findings indicate that the levels of TD were different according to sex: females with ADHD portrayed more TD than males with ADHD. Moreover, the group of males with ADHD did not differ from the group of control males, whereas the group of females with ADHD differed from the group of control females. When the percentage of extreme scoring cases was calculated, about 17% of females with ADHD had extreme scores (possibly indicating TD), whereas only 3% of males with ADHD had extreme scores. In contrast to a previous study with males with ADHD,[6] the current study did not find elevated levels of TD in the group of males with ADHD.

An explanation for this might be that the present study and the study of Parush et al. differed in method of TD measurement. Parush et al.[6] used the Touch Inventory for Preschoolers (TIP) which is based on teacher reporting, whereas this study used the (TIE) based on self-report. As three of four previous studies[7-9] on TD in ADHD did not take the effect of sex into account, the current finding of sex differences for TD in ADHD cannot be compared to these previous studies.

There might be several explanations for the difference in TD between males and females with ADHD. Perhaps the most obvious explanation would be that females in general have higher levels of TD than males, so that the sex differences found in the current study are not unique to ADHD. Some evidence for this was found in a recent twin study[10] in which proportionally more females than males had extreme TD scores. However, in the same twin study it was reported that there was no difference between groups of males and females for mean TD scores. This is concordant with the current finding of an insignificant main effect of sex on TD scores. Thus, it appears that the sex differences for TD found in this study are specific to children with ADHD and not related to general sex differences for TD.

A second explanation for the elevated TD in females with ADHD compared to males with ADHD might be found in the relationship between TD, anxiety and inattention. The inattentive subtype is relatively more frequently diagnosed in females than in males with ADHD[3] and the inattentive subtype is more strongly associated with internalizing problems, such as anxiety, than the combined ADHD subtype.[5] Recently, it was found that TD correlated with a fearful temperament and anxiety.[10] Perhaps TD is an 'anxious' response to certain tactile situations, expressed in emotional responses to, or avoidance of, non-noxious touch and stimuli that are interpreted as threatening.[14,15] To examine whether inattention, anxiety, and TD were interrelated in the current sample, correlations between these measures were calculated, and all were significant < .05 (positive associations: .19–.44). Furthermore, females with ADHD differed more clearly from controls in their increased levels of anxiety (reported by parents) and inattention (reported by teachers) than males with ADHD. These findings support the explanation that a triad of symptoms (TD, anxiety, and inattention) co-occurs and that these symptoms appear more severe in females than in males with ADHD.

A third explanation for the increased levels of TD in females compared with males with ADHD might be specifically related to the sample of females with ADHD. It is known that fewer females with ADHD are diagnosed and referred for treatment than males with ADHD,[3] which may suggest that the females included in this study had a more severe form of ADHD than the males. This might translate into more severe levels of TD in females than in males. The current sample of females had higher scores on both the inattentive and hyperactivity/impulsivity scales (rated by teachers) than the sample of males with ADHD.

Furthermore, TD and anxiety did not appear to be uniquely associated with symptoms of inattention (see second explanation), but were also associated with symptoms of hyperactivity/impulsivity (correlations between hyperactivity/impulsivity and TD and anxiety were all positive and significant, ranging from .19 to .36 with all *p*-values < .05), this suggests that the elevated TD in females compared with males with ADHD might be related to a more severe form of general pathology in the females of this sample. This is concordant with previous findings of correlations between severity of psychopathology and TD.[8] However, the explanation of a generally more severe pathology in the females compared with males with ADHD in the current sample is contradicted by the equal raw scores of inattention and hyperactivity/impulsivity between both ADHD groups, suggesting comparable severity of ADHD symptoms in absolute terms between both ADHD group. Therefore, future research should seek to determine whether increased levels of TD in females compared with males with ADHD relate to higher levels of inattention and/or higher levels of overall psychopathology in females compared with males.

This appears to be the first study reporting on TD in non-affected siblings of children with ADHD to examine the familiality of TD. The group of non-affected siblings (males and females) had normal TD scores, which may suggest that TD found in ADHD is associated with the disorder at a phenotypical level but does not (wholly) relate to the same familial risk factors associated with ADHD.[17] However, it may also indicate certain causal factors not shared by affected and non-affected siblings. The finding that non-affected siblings had normal TD scores may be important for future research into the causal pathways leading up to ADHD, and to determine why certain children develop ADHD while other (at-risk) children do not.

There are some limitations to the interpretations of the current findings. The overall sample size and particularly the size of the group of females with ADHD, was relatively small. Future research using larger groups would help to clarify whether the current results can be replicated. Furthermore, only one (screening) measure of TD was used, and that measure was based on self-report. It is recommended that future studies apply a larger variety of TD measures, preferably also more experimental measures of TD to examine altered processing and/or appraisal of tactile stimuli.

Another limitation that should be noted is that even though the English version of the TIE was translated very carefully into the Dutch language, the Dutch translation of the TIE has not been investigated for validity and reliability, which should be carried out in future studies using this Dutch translation. However, this is unlikely to have influenced the results in the current study, as previous research has shown that mean test scores were similar in North American children (English version of the TIE) and European children (non-English version of the TIE translated into native language of the children),[22] suggesting careful translation of the TIE does not affect results.

Care should be taken when interpreting results based on group means. Although, overall, males with ADHD had TD scores comparable to those of control children, some extreme cases were present (just as in the non-affected sibling groups and control groups), suggesting that TD might be present in some males with ADHD, their non-affected siblings and even in typically developing control children. These cases should not be overlooked.

Conclusion

The current findings indicate that more females than males with ADHD suffer from increased levels of TD. Assessment of TD may contribute to an increased identification of ADHD in females who tend to be under-diagnosed,[3] enabling improved intervention. As non-affected siblings, both males and females did not display TD, TD does not appear to be part of a familial risk for ADHD.

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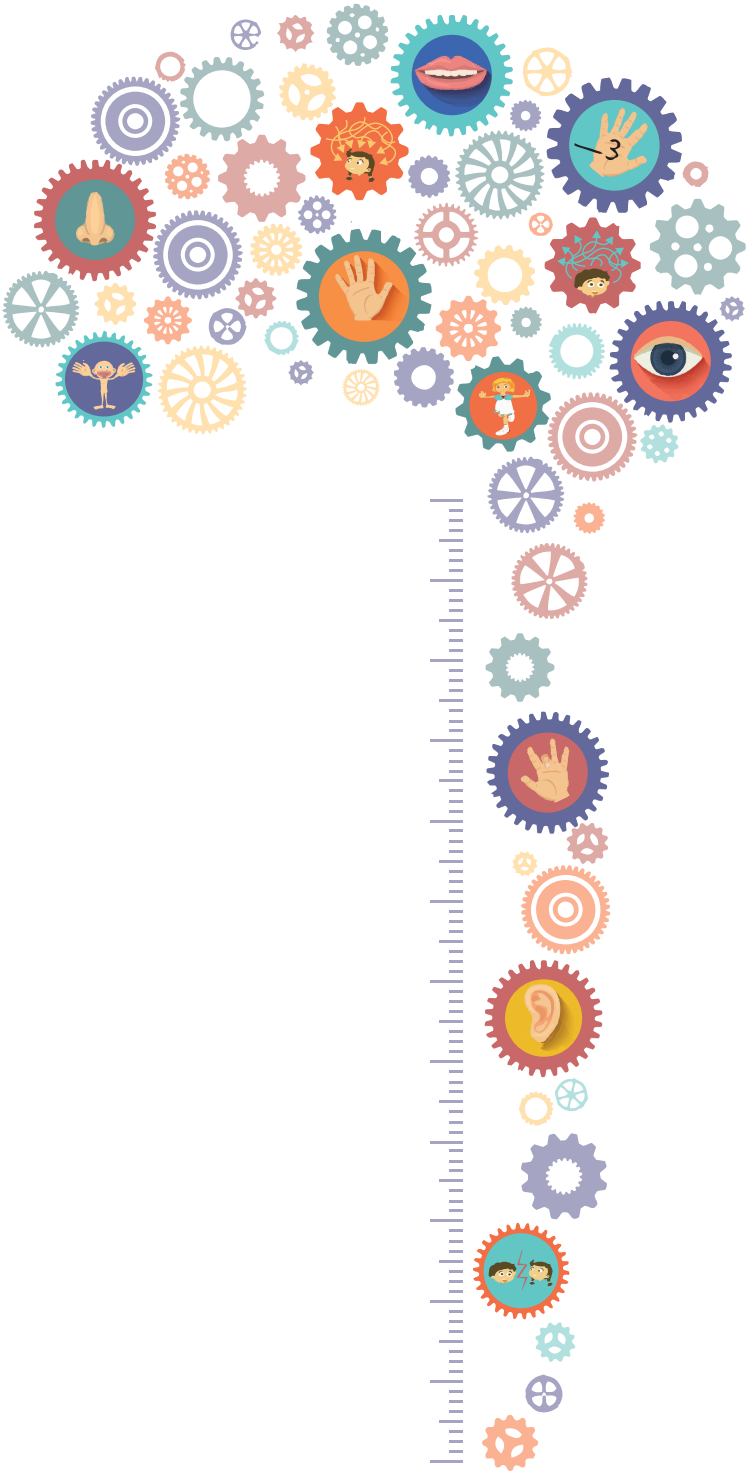

8

Summary and general discussion

ABOUT SVEN

When Sven is 9 years old, he and his parents receive an invitation to once again participate in the STEP study, a long-term follow-up study on nutrition, growth and development in very preterm born children. Sven's parents and teachers are asked to fill out behavioral questionnaires and Sven is invited for a comprehensive neurocognitive assessment, in addition to determining growth and health status of Sven. Sven is doing quite well in school. All his CITO-scores are average or just above, but he has some trouble focusing on his schoolwork. The teacher frequently has to check if Sven remembers the instructions and she recently talked to Sven's parents that he is unable to finish or plan the weekly school tasks. Last year the teacher even suggested that Sven may have symptoms of ADHD. His parents recognize Sven's absent-minded behavior; they have to help him remember what he needs to put in his soccer bag and getting ready for school is hard for him, because he gets distracted. They sometimes worry about him; he still is a sensitive child with car sickness and pickiness about clothes, although by now he can better explain why some clothes irritate him. Sven only occasionally brings home a friend, because he likes to be left alone for a while after school, but his parent sometimes wonder if he lacks some social skills.

Both Sven and his parents agree to participate in the follow-up study. A few weeks after the assessment the child psychologist of the follow-up study calls to discuss some elevated scores she found on the questionnaires. She explains to Sven's mother that Sven showed higher than average levels of attention problems, reported on the questionnaires by both his teacher and parents. On a social responsiveness scale Sven showed more difficulties compared to peers and on a questionnaire measuring sensory processing abilities in daily life, Sven scores fitted in a category called 'sensation avoiding'. Sven's mother recognizes the examples the child psychologist uses to illustrate Sven's behavioral difficulties and wonders if the explanation about Sven's difficulties would also be helpful for Sven's teacher. The child psychologist suggests making an appointment with Sven's parents at the hospital to talk about Sven's background some more, advise them on his behavioral difficulties and discuss a referral to occupational therapy. Afterwards, the child psychologist discusses Sven's difficulties with his teacher during a telephone call and refers Sven for occupational therapy, that he enjoys very much. Sven's parents feel that they now better understand Sven's sensitivity and behavioral difficulties.

This thesis is divided in two different parts. *Part one* covers studies on sensory processing difficulties and behavioral problems in very preterm born children. *Part Two* describes the context and basis of our hypothesis on the relation between sensory processing and behavioral difficulties by addressing sensory processing and pain experience in children diagnosed with attention deficit hyperactivity disorder (ADHD). The main aim of this thesis was to provide a detailed picture of sensory processing difficulties and behavioral problems, in particular symptoms of ADHD and autism spectrum disorder (ASD), in very preterm children and to unravel the impact of sensory processing difficulties on symptom levels of ADHD and ASD. To meet these aims, studies were undertaken to 1) systematically review the existing literature on sensory modulation difficulties in preterm children (< 37 weeks of gestation); 2) investigate the effects of preterm birth (≤ 32 weeks of gestation) on sensory processing, in terms of registration, integration and modulation; 3) investigate symptoms of ADHD and ASD in very preterm children by both parent and teacher report, and 4) study whether sensory processing impacts on symptom levels of ADHD and ASD in very preterm children. The main findings are summarized in Table 8.1. In this final chapter, results of the previous chapters are summarized and followed by a reflection on these findings. Furthermore, strengths and limitations of the studies, the clinical implications, and suggestions for future research are discussed.

SUMMARY OF MAIN FINDINGS

In Part one we addressed the nature of sensory processing difficulties in preterm and very preterm born children, in relation to behavioral problems. Chapter 3, 4, and 5 described the results of a group of 57 very preterm children and 57 full-term children in the age of 8–10 years. We set out with a systematic review of international peer-reviewed literature on sensory modulation difficulties in preterm children. Consistent evidence (89% of studies) emerged for substantial sensory modulation difficulties in preterm born children (**Chapter 2**). Conclusions were derived from 18 studies, including 1138 preterm born children and 493 full-term controls. It was found that preterm birth may lead to overresponsive and underresponsive behavioral profiles (low registration, sensation seeking, sensation avoiding, sensory sensitivity) across multiple sensory modalities (auditory, visual, vestibular, tactile and taste) and across different sensory modulation functions (response to tactile deep pressure, visual-tactile integration, adaptive motor functioning, ocular motor functioning and reactivity to vestibular stimulation). Five studies identified a relation between sensory modulation and behavioral difficulties including associations between sensory modulation and ASD, regulatory disorder, and difficult, fearful temperament. Additionally, predictors of sensory modulation difficulties were identified, including gestational age (GA), birth weight, white (and grey) matter abnormalities and length

Table 8.1. Overview of the main findings of this thesis

Chapter	Participants	Measures	Main findings
2	Systematic review sample of 1138 preterm born (< 37 weeks) children and 493 control children on sensory modulation	Systematic review results of 18 studies on sensory modulation, assessed with the TSFI, ITSP/SP and/or SRS	• Evidence for sensory modulation difficulties in preterm born children • Both underresponsive and overresponsive behavioral patterns exist • Multiple sensory modalities (auditory, visual, vestibular, tactile, taste) are affected • Some evidence on predictors for sensory modulation difficulties, including GA, BW, grey and white matter abnormalities, length of NICU stay
3	57 very preterm children 56 full-term children	*Registration:* Registration of Light Touch and Sensory Discrimination of Touch, Position Sense, Graphestesia (SIPT) *Integration:* MSIT *Modulation:* SP	• Very preterm children are less accurate on somatosensory registration tasks, including Registration of Light Touch, Position Sense and Graphestesia • No effect of very preterm birth on sensory discrimination of touch and multisensory integration efficiency • Very preterm children show more sensory modulation difficulties, including both underresponsiveness and overresponsiveness • Registration, integration and modulation are only modestly related
4	57 very preterm children 57 full-term children	*ADHD:* CBCL, TRF, PDBD, TDBD, DISC-IV *ASD:* SRS, CCC-2, SCQ	• Very preterm children show higher symptom levels of ADHD and ASD reported by parents and teachers • Very preterm children show more inattentiveness than hyperactivity/impulsivity • 16% of very preterm children qualify for a DISC-IV ADHD diagnosis • No very preterm children screen positive on the SCQ • ADHD and ASD symptoms co-occur and are pervasive in both home and school environment

Table 8.1. *Continued*

Chapter	Participants	Measures	Main findings
5	57 very preterm children 56 full-term children	*Registration:* aggregated scores of tactile perception, kinesthesia, graphestesia *Modulation:* SP *ADHD:* aggregated scores of CBCL, TRF, PDBD, TDBD *ASD:* aggregated scores of SRS, CCC-2	• Sensory modulation partially mediates ADHD and ASD symptom levels • Somatosensory registration is not pertinent in the relation between very preterm birth and symptom levels of ADHD and ASD • Neonatal complications, including infections, PVL and being born small for gestational age are relevant in the relation between prematurity and ADHD and ASD symptom levels
6	50 children diagnosed with ADHD 38 non-affected siblings 35 normal control children	*Registration:* Temperature Discrimination, Sensory Discrimination of Touch, Registration of Light Touch, Kinesthesia, *Pain experience:* CPI, CAS, FAS	• Children with ADHD, and to a lesser extent their non-affected siblings have more difficulties in temperature discrimination and sensory discrimination of touch compared to normal control children • Children with ADHD show a hyposensitivity in temperature discrimination and sensory discrimination • No effects of ADHD are found on registration of light touch, kinesthesia and subjective recent and past pain experience compared to normal control children • Somatosensory processing is not related to the subjective sensation of pain
7	47 children diagnosed with ADHD 36 non-affected siblings 35 normal control children	*Modulation:* TIE	• Sex differences are present in tactile overresponsiveness in children with ADHD • Girls, not boys, with ADHD show more tactile overresponsiveness • 17% of girls, versus 3% of boys with ADHD had extreme scores on tactile overresponsiveness

Note. ADHD = Attention Deficit Hyperactivity Disorder; ASD = Autism spectrum disorder; BW = birth weight; CAS = Colored Analogue Scale; CBCL = Child Behavior Checklist; CCC-2: Children's Communication Checklist; CPI = Children's Pain Inventory; DISC-IV = Diagnostic Interview Schedule for Children- fourth edition; FAS = Facial Analogue Scale; GA = gestational age; ITSP = Infant/Toddler Sensory Profile; MSIT = Multisensory Integration Test; PDBD = Parent version Disruptive Behavior Disorders rating scale; PVL = Periventricular Leukomalacia; SCQ = Social Communication Questionnaire; SIPT = Sensory Integration and Praxis Test; SP = Sensory Profile; SRS = Social Responsiveness Scale; TDBD = Teacher version Disruptive Behavior Disorders rating scale; TIE = Touch Inventory for Elementary School-aged children; TRF = Teacher Report Form; TSFI = Test of Sensory Functions in Infants.

of stay at the neonatal intensive care unit (NICU). Some caution is required in interpreting the results due to heterogeneity in gestational age, use of measurements and risk of selection bias, convenience sampling and high attrition rates. Moreover, only small numbers of children aged > 2 years are included and these findings await replication.

We thoroughly investigated three domains of sensory processing (registration, integration and modulation) in very preterm born children using a multimodal assessment battery including behavioral somatosensory registration tasks, a computerized multisensory integration task and a parent-reported sensory modulation questionnaire (**Chapter 3**). This extensive assessment revealed that, compared to the full-term group, both somatosensory registration and sensory modulation were compromised in very preterm school-aged children, with small to medium effect sizes, while multisensory (audio-visual) integration, was not. In the somatosensory registration domain, the very preterm group showed difficulties in tactile perception, kinesthesia and graphestesia indicating somatosensory hyposensitivity. In the sensory modulation domain, very preterm children showed higher levels of sensory modulation difficulties related to different sensory modalities and showed more signs of both underresponsiveness and overresponsiveness. Registration, integration and modulation of sensory stimuli were relatively independent and unrelated to the gestational age and complications of very preterm birth.

To evaluate behavioral problems, we investigated symptom levels and co-occurrence of ADHD and ASD using both parent and teacher reported questionnaires and a diagnostic interview very preterm born children and full-term born children (**Chapter 4**). Main findings were that the very preterm group showed higher symptom levels on both parent and teacher reported ADHD (mainly moderate effect sizes) and ASD (moderate and large effect sizes) measures compared to the full-term group and that ADHD and ASD symptoms co-occurred in very preterm children, indicated by a strong relation. Within the domain of ADHD symptoms, symptoms of inattention prevailed. In the very preterm group 16% of children qualified for an ADHD diagnosis. ASD symptoms, including social impairment and compromised general and pragmatic communication, were more frequent in the very preterm group as rated by both parents and teachers. None of the very preterm children screened positive for a full diagnosis of ASD. Pervasiveness of ADHD was underlined by moderate to strong agreement between parent and teacher ratings and low to moderate agreement on ASD symptoms. Furthermore, weak but significant associations between ADHD and ASD symptoms and GA were present, while male sex was exclusively and weakly related to higher levels of ADHD symptoms and lower SES was exclusively and weakly related to higher levels of ASD symptoms in the very preterm group.

We further addressed the relation between sensory processing difficulties and symptoms of ADHD and ASD in very preterm children by investigating whether symptom levels of ADHD

and ASD were mediated by sensory registration and sensory modulation (**Chapter 5**). We found that sensory modulation (underresponsiveness and/or overresponsiveness) partially mediated the relationship between preterm birth and ADHD and ASD symptom levels, while somatosensory registration did not. Furthermore, our findings showed that the presence of neonatal complications (i.e. small for gestational age [SGA], periventricular leukomalacia [PVL] or infections) was relevant in the relation between very preterm birth, symptom levels of ADHD and ASD and sensory modulation, as only in very preterm children who had at least one additional neonatal complication, sensory modulation difficulties impacted on ADHD and ASD symptom levels.

Taken together, the outcomes of the first part of this thesis confirm the presence of sensory processing difficulties in the domains of registration and modulation, as well as behavioral difficulties in terms of ADHD and ASD symptoms in very preterm children. Moreover, sensory modulation in particular was found to partially mediate symptoms of ADHD and ASD in very preterm children and might be considered as one of the pathways that lead to the well-known adverse behavioral outcomes observed in very preterm children.

In *Part Two* we described the context and basis of our hypothesis on the relation between sensory processing and behavioral difficulties by addressing sensory processing and pain experience in children diagnosed with ADHD in comparison to non-affected siblings and healthy control children. **Chapter 6** addresses somatosensory registration in terms of sensory discrimination and kinesthesia, and intensity and emotionality of pain experience. In the domain of somatosensory registration children with ADHD, and to a lesser extent their non-affected siblings, had more difficulty than controls (moderate effect sizes) in the sensory discrimination of warm versus cold and sharp versus blunt, suggesting hyposensitivity to these types of stimuli. Conversely, kinesthesia and finger gnosis showed no group differences, suggesting preserved perception of differences in limb positions in children with ADHD as well as in their non-affected siblings. The same was true for reported intensity and emotionality of pain experiences in which the children with ADHD did not differ from normal controls. However, non-affected siblings reported a significantly lower intensity and emotionality of past experienced pain than controls (moderate effect sizes). Somatosensory processing was not related to the subjective sensation of pain.

We examined tactile overresponsiveness in children with ADHD, and whether tactile overresponsiveness is present in non-affected siblings of children with ADHD (**Chapter 7**). We found that levels of tactile overresponsiveness were different according to sex; girls with ADHD showed more tactile overresponsiveness than boys with ADHD (large effect size). Moreover, the group of boys with ADHD did not differ from the group of control boys, whereas the group

of girls with ADHD differed from the group of control girls (large effect size). As non-affected siblings, both boys and girls, did not display tactile overresponsiveness, this does not appear to be part of a familial risk for ADHD.

In sum, the findings from the second part of this thesis illustrate that sensory processing in terms of somatosensory registration (temperature and sensory discrimination) is impaired in children with ADHD, while kinesthesia, finger gnosis and pain experience are not. Interestingly, tactile overresponsiveness is only present in girls with ADHD. These findings suggest underlying abnormalities in the processing of somatosensory stimuli in children with ADHD. Assessment of sensory overresponsiveness may contribute to an increased identification of ADHD in girls who tend to be underdiagnosed,[1] enabling improved intervention. Additionally, these findings underpinned our hypothesis to evaluate symptoms of ADHD (and given the frequently found sensory processing abnormalities, also ASD) in very preterm children from a sensory processing perspective.

GENERAL DISCUSSION

Heterogeneity in sensory processing difficulties

Effects of preterm birth on sensory processing have been studied more frequently in recent years.[2,3] On the basis of our review, we concluded that the vast majority of studies point to evident sensory modulation difficulties in preterm children across the full spectrum of gestational age (**Chapter 2**). We could not identify a clear profile of sensory modulation difficulties, as we found in our review that multiple sensory modalities were simultaneously impaired and that both overresponsiveness and underresponsiveness, with both active as well as passive self-regulation, were present in preterm born children. Our study into sensory processing further added to this lack of uniformity by concluding that in the domain of sensory modulation both overresponsiveness and underresponsiveness was present (**Chapter 3**). The observed heterogeneity in sensory modulation difficulties may be explained by the use of different measures, including a variety of parent-reported questionnaires in addition to child-administered tasks. However, even in studies that used the Dunn model to evaluate sensory processing (majority of reviewed studies), no clear profile emerged for one sensory modality nor for overresponsiveness or underresponsiveness. Another explanation for the heterogeneous findings might be differences between preterm children in terms of gestational age and birth weight, but also in neonatal risk factors, including the presence or absence of necrotizing enterocolitis, bronchopulmonary dysplasia, PVL and intraventricular hemorrhage. The extent to which very preterm infants have suffered from hypoxia-ischemia and inflammation leading

to disturbances in cerebral white matter integrity, as well as the extent of understimulation (due to parental separation) and overstimulation (nursery handling, pain, lights, noises) during NICU stay may be relevant in determining the profile of sensory processing difficulties. Some preterm children might have suffered more from overstimulation with excitotoxic damage and possible downregulation of the sensory system, while other preterms might have suffered more from understimulation with apoptosis and upregulation of the sensory system.[4,5] Consequently, overresponsiveness, as well as underresponsiveness, may be an offshoot of originally adaptive responses to the previously experienced overstimulation or understimulation.[6] However, after the NICU stay, these regulatory responses may become maladaptive, resulting in sensory processing difficulties later in life.[6,7] This is supported by the relatively high incidence of regulatory disorders among preterm infants.[8]

Additionally, our finding that multisensory (audio-visual) integration was preserved while somatosensory registration and modulation were compromised in very preterm children is puzzling (**Chapter 3**). However, Rose et al. (1998) also found no differences between very preterm and full-term children in multisensory (visual-tactile) integration.[9] A possible explanation is that the sensory domains of registration, integration and modulation are relatively independent aspects of sensory processing and may therefore not be impaired at the same time. This independency is underlined by weak associations between somatosensory registration, multisensory integration, and sensory modulation in our study in very preterm children. Another explanation is that the domains of sensory registration and modulation in particular are disturbed by specific brain abnormalities. Compromised somatosensory registration in preterm born children may be explained by smaller amounts of active tissue in somatosensory cortical regions[10] and sensory modulation difficulties may be explained by white matter brain abnormalities,[11] consistent with impaired white matter microstructure observed in term born children with sensory modulation difficulties.[12] However, it seems inconsistent that impaired multisensory integration has been observed in other disorders of affected white matter integrity, such as pediatric traumatic brain injury.[13,14] Possibly, multisensory integration is less vulnerable for the effects of premature birth on early white matter development as compared to relatively late traumatic axonal damage. Unfortunately, we were unable to uphold this claim with our results, since we do not have data on the white matter integrity of our group of very preterm children. Moreover, other modalities than audio-visual integration may be impaired in very preterm children. Therefore, more research is needed in the sensory integration domain in very preterm children to further corroborate our findings.

Understanding behavioral difficulties

While sensory processing is a relatively new domain in the research on very preterm children, ample evidence is available on behavioral difficulties in very preterm children. In the last decade a constellation of behavioral difficulties has been suggested to be present after preterm birth, described as the "preterm behavioral phenotype".[15] Johnson and Marlow (2010) characterize this phenotype by the presence of ADHD symptoms (inattention more than impulsivity/hyperactivity), social and emotional difficulties and a greater risk for internalizing rather than externalizing problems.[15] According to this phenotype, ADHD symptoms of inattention prevail symptoms of hyperactivity and impulsivity and are suggested to show a neuropathological etiology related to the effects of preterm birth, whereas ASD symptoms may reflect primarily socialization difficulties.[15,16] Multiple studies acknowledge this neuropathological etiology by showing that ADHD and ASD symptoms in preterms are not only inversely related to gestational age (GA) and to birth weight, but are also associated with early brain damage in both white and grey matter[17–20] due to inflammation and hypoxia-ischemia.[21] Our study on ADHD and ASD symptoms in very preterm children supports the existence of a "preterm behavioral phenotype", at least in terms of the ADHD symptoms and social difficulties, since our very preterm group indeed portrayed attention problems, rather than hyperactivity/impulsivity and social impairment and communication problems as pivotal symptoms (**Chapter 4**). Moreover, our finding of co-occurrence of ADHD and ASD symptoms in very preterm children further bolsters the "preterm behavioral phenotype" and converges with another study showing co-occurrence of attentional and social problems in extremely preterm children.[22] Attention problems may form the linking factor in the co-occurrence of ADHD and ASD,[23,24] and may underpin socialization difficulties in very preterm children as well. Studies in children with ADHD show that inattention may limit adaptive social participation and may lead to social rejection.[25,26] Children with inattentive symptoms tend to miss social cues necessary for effective social interaction, may underperform during organized sports and games or are disliked because of shyness or sluggish responses.[25–28] Inattention may therefore be suggested as a risk factor for socialization difficulties in very preterm children.

We speculate that the behavioral difficulties consistent with the "preterm behavioral phenotype" and defined by symptoms of ADHD and ASD, originate from sensory processing as a consequence of neonatal complications and NICU stay. With respect to sensory processing, our review showed that sensory modulation difficulties may be related to regulatory disorder and difficult, fearful temperament[8,29,30] and coincided with ASD.[31,32] Moreover, we found that sensory modulation in terms of underresponsiveness and overresponsiveness partially mediates ADHD and ASD symptom levels (**Chapter 5**). Although the explained variance of sensory modulation in ADHD and ASD symptom levels is fairly modest, we think that understanding behavioral difficulties in very preterm children is useful and meaningful in very preterm children from a clinical perspective.

We suggest that underresponsive and overresponsive behavior in very preterm children is (mis) labeled as symptoms of ADHD and/or ASD. Possibly the absent-minded ADHD-like and the aloof ASD-like behavior is primarily a reflection of underresponsiveness. Likewise, the sensory seeking behavior such as repetitive play and touching materials may be interpreted as restrictive and strange behavior in ASD and the fidgety or on the go behavior to seek sensory stimuli may be interpreted as hyperactive and distractible behavior consistent with ADHD.[33] Conversely, fearful and cautious overresponsive reactions to sensory stimuli may be interpreted as ASD-like behaviors and negative and defiant overresponsive reactions as ADHD-like behavior.[33] Understanding behavioral difficulties as part of the "preterm behavioral phenotype" from a sensory processing perspective is further supported by evidence in our studies on associations between ADHD and compromised somatosensory registration and tactile overresponsiveness and by extensive evidence on sensory processing difficulties from other studies in both ADHD and ASD.[33–40]

With respect to the different domains of sensory processing (registration, integration and modulation), it is the domain of modulation in particular, that is pertinent in the relation between very preterm birth and symptom levels of ADHD and ASD. Although the very preterm group showed impaired somatosensory registration, these difficulties did not relate to ADHD and ASD symptom levels. A possible explanation for this finding is that it is not so much the lower-order registration of somatosensory stimuli, but rather the higher-order modulation of responses to sensory stimuli, that is important in understanding symptoms of ADHD and ASD and subsequent adaptation to the environment. Brain circuits involved in higher-order modulation are far more complex, using extensive brain networks, both top-down and bottom-up, and are therefore more vulnerable to subtle white matter damage than lower-order registration circuits.[12,41] This is bolstered by a claim of Wallace and Stevenson, that low-level sensory functioning is unaffected in children with autism, since local cortical organization is preserved, while more extensive brain networks are impaired.[39]

In contrast to our findings that girls with ADHD showed higher levels of tactile overresponsiveness, we found no significant sex differences in sensory modulation in very preterm children. Although in our sample of very preterm children, sex was not a relevant predictor for sensory modulation difficulties, further studies are needed to assess these sex differences, as it is known that male sex is a risk factor for white matter injury[42] as well as more severe neurodevelopmental sequelae[43,44] in very preterm children.

According to the multiple-hit hypothesis,[45] being born very preterm in conjunction with neonatal complications may particularly compromise normal brain development and may enhance the risk for white matter brain abnormalities with subsequent neurodevelopmental problems,[42] such as the sensory processing difficulties and ADHD and ASD symptoms found in our studies.

We argue that the white matter abnormalities in very preterm children[11,46,47] show similarities to those found in children with a primary sensory processing disorder,[12] and that the impact of the sensory challenging NICU stay[48] is evident on both sensory processing and behavioral difficulties. In our review, we found some evidence that neonatal complications, including white (and grey) matter abnormalities and length of NICU stay, showed a dose-response relationship with sensory processing difficulties. This is supported by our finding that the presence of neonatal complications (i.e. being born small for gestational age, PVL, infections) is pertinent in the relation between very preterm birth, symptom levels of ADHD and ASD and sensory modulation, as only in very preterm children who had at least one additional neonatal complication, sensory modulation difficulties impacted on ADHD and ASD symptom levels. In addition, the finding that extended hospital stay is important in the relation between very preterm birth, symptom levels of ADHD and ASD and sensory modulation, not only acknowledges that longer hospital stay is associated with greater exposure to detrimental neonatal complications, but may also fit the idea that the sensory challenging NICU itself, largely independent of other neonatal complications, may negatively affect long term neurodevelopmental outcome in very preterm children.[49]

STRENGTHS AND LIMITATIONS

The studies presented in this thesis have both strengths and limitations. The very preterm children included in our studies are part of a large and representative sample of Dutch children born before 32 weeks of gestation (Study Towards the Effects of Postdischarge nutrition on growth and body composition of infants born ≤ 32 weeks of gestation and/or ≤ 1500 gram birth weight [STEP study]). Where the incidence of IVH, PVL and infections is relatively low in this group, other baseline characteristics including IUGR, SGA, BPD, length of NICU stay and SES are representative for the very preterm population. Moreover, recruitment of an equally sized full-term born control group, matched on sex, age and parental education, allowed meaningful comparison between very preterm children and full-term born children on behavioral and sensory processing measures. Another strength of our studies is that sensory processing was evaluated at multiple levels. Sensory processing included registration, integration and modulation, which allowed us to thoroughly differentiate between these three levels. Additionally, behavior was evaluated extensively, with multiple informants (parents and teachers) reporting on ADHD and ASD symptoms. Moreover, we used multiple questionnaires, a screening instrument and an interview, tapping into the same domain (ADHD and ASD). Finally, our studies in a group of children with a diagnosis of ADHD allowed us to provide a strong rationale for our finding that symptoms of ADHD are mediated by sensory modulation difficulties in very preterm children.

The presented studies also have some limitations. Since all very preterm children initially participated in a RCT on a postdischarge feeding intervention, it is possible that this has interfered with our results, as optimal feeding strategies aim to reduce long term growth deficits and risks for adverse developmental consequences later in life.[50] We analyzed the potential intervention effects by analyses of variance and found no meaningful effects of the intervention on any of our measures, except for a small but beneficial effect of postdischarge formula over standard term formula on sensory modulation. However, the observed differences between very preterm and full-term children on sensory modulation persisted, despite positive effects in the group of very preterm children receiving enhanced postdischarge formula. This suggests a robust difference between the very preterm and full-term group. Another concern is that our empirical studies on very preterm children are all performed in the STEP cohort, thereby capitalizing on the same group of children, so findings might be related to the idiosyncratic characteristics of our sample. For example, our STEP sample showed a relatively low prevalence of risk factors for developing white matter abnormalities, including PVL, subependymal hemorrhage and infections. Furthermore, our relatively small sample size of very preterm children prevented us from robustly studying the relation between neonatal risk factors and sensory processing difficulties and behavioral problems. Another limitation, unfortunately very common in follow-up studies in very preterm children, is the substantial attrition, with only half of the initial cohort willing to participate in this follow-up study. Of the 152 infants included in the original RCT, 112 children were still available for follow-up at 8–10 years of age, of which 57 (51%) agreed to participate in the current studies. However, no differences were found between the groups of participants and non-participants on sex, parental education, gestational age (GA), birth weight, PVL, and the presence of perinatal infections. Furthermore, regarding our choice of measures we consider the use of a screening instrument (SCQ) instead of a diagnostic interview on ASD as an inconsistency and shortcoming, since we did include a diagnostic interview on ADHD. However, the SCQ is a well validated alternative for the gold standard, but time-consuming, Autism Diagnostic Interview-Revised, and is widely used in studies on very preterm birth.[51–54] In addition, we have measured the domains of sensory processing with very different measures, in terms of parent report (modulation) versus child-administered tasks (registration and integration) and clinical measures (registration) versus a computerized task (integration). Yet, outside clinical diagnostic procedures on sensory modulation and a validated test for the infant age only (TSFI), no child-administered test is available for the domain of sensory modulation. Moreover, the three domains are very different in the demands they place on a child. Therefore some variety in measures will be inevitable.

With respect to the studies in the ADHD sample, larger sample sizes, especially for the group of girls with an ADHD diagnosis, would have benefited the statistical power of the studies to detect alterations in somatosensory functioning, tactile overresponsiveness and pain

experience. Another limitation of this ADHD sample is that some levels of sensory processing were not studied as thoroughly, with sensory integration missing in the measures and sensory modulation only represented by tactile overresponsiveness.

CLINICAL IMPLICATIONS

Our findings show that very preterm children are at risk for developing sensory processing difficulties and elevated symptom levels of ADHD and ASD. Moreover, we suggest that symptoms of ADHD and ASD, at least partly, originate from sensory modulation difficulties. In terms of long-term consequences of very preterm birth, sensory processing and behavioral difficulties are deemed as minor impairments. Yet, the impact of these minor impairments on adaptive functioning and quality of life in very preterm children may be substantial.[55,56] For instance, sensory processing and behavioral difficulties have been described to hamper normal development by interfering with social activities, play and leisure.[25,56–58] Although our studies found low to moderate effect sizes and the findings of the studies in this thesis await more research and replication, we believe that interpreting behavioral difficulties from a sensory processing perspective is useful in the follow-up care for very preterm infants.

In the last three decades the NICU stay of a very preterm infant has changed tremendously, starting with developmental care interventions from NIDCAP (Newborn Individualized Development Care and Assessment Program),[59,60] progressing to kangaroo care and (multi) sensory stimulation[61] and more recently to strong parent involvement in family integrated care for very preterm infants with promising results.[62] As the sensory system is powerfully shaped by the number and types of sensory experiences directly after birth,[63,64] interventions during NICU and High Care stay are crucial. Both developmental care interventions and family integrated care may mitigate sensory overstimulation and understimulation.[61,65–68] The use of proven effective analgesia diminishes procedural pain (overstimulation), especially when combined with parental holding of the infant or, if possible, with breastfeeding.[69] Kangaroo care, preventing tactile understimulation, has additional positive effects on both the infant and the parent, including better growth of the infant, decreased stress in mothers, and better mother-infant interaction.[61,67] Fine-tuned sensory stimulation, for instance by intensive parent involvement in the care for their preterm infant, may break down tactile (i.e. holding) and vestibular (i.e. handling/rocking) understimulation and normalize auditory stimulation (i.e. voices) and has shown positive effects on both infant (weight gain) and parent (stress levels).[68]

Yet, the sensory system continues to be shaped throughout the course of life.[35] Therefore, signaling sensory processing difficulties may be advisable across the full childhood age range

in very preterm children. In the Dutch follow-up care for children born very preterm, screening for sensory processing difficulties is not yet standard. The results of this thesis prompt the consideration of screening for sensory processing difficulties, at least at the level of modulation (overresponsiveness and underresponsiveness), and more in-depth screening of ADHD and ASD symptoms, in particular assessment of attention problems, social impairment and communication problems (rather than screening for a diagnosis of ADHD and/or ASD) in the follow-up care for very preterm children. Children with the "preterm behavioral phenotype" may not show difficulties on all symptom dimensions and therefore may fail to meet criteria for a full diagnosis of ADHD or ASD, yet the impact on daily functioning, especially in conjunction with sensory modulation problems, may be distinct.[15,70] Moreover, even if children qualify for an ADHD or ASD diagnosis, this diagnosis alone may not fully capture the whole clinical presentation nor lead to a tailored treatment indication.[71]

Understanding ADHD and ASD symptoms from a sensory processing perspective may provide additional leads for intervention and treatment in very preterm children.[35,72] Tailored interventions including counseling of parents and teachers by child psychologists on the expression of sensory processing and behavioral difficulties in the home and school environment and/or referral of the very preterm child to occupational therapy, may be pivotal to downsize behavioral difficulties in very preterm children.[33,35,57,73] Although counseling of parents is not extensively studied in the context of sensory processing difficulties, it is regarded as good clinical practice. Moreover, our experience in clinical practice suggests that if parents better understand the origin of the behavioral difficulties of their child, they will be more flexible and understanding in their parenting style; preventing conflicts, stress and miscommunication. The understanding of underresponsive and overresponsive behavioral patterns, as well as specific sensory processing problems across sensory modalities offers opportunities for interventions to lessen the impact on both the school and home environment. These interventions may include, but not be limited to, different seating arrangements in the classroom, selective use of headphones with or without music, addition of activating tactile materials during listening, shorter periods of working on one task, increase or decrease of distraction in a child's room (visual, auditory), specific use of materials and fitting for a child's clothes, and selective addition of types of new food.[33,74] Occupational therapy is an intervention that aims to improve the child's sensory responsivity across sensory modalities, social behavior, motor competence, and participation in daily life by stimulating the child to interact with sensory materials in an active, meaningful, and joyful manner in close collaboration with parents. Effectiveness of occupational therapy, although far from rigorously studied, has shown positive results in clinical practice and has also recently been proven effective in a small randomized controlled trial in children with sensory processing difficulties.[73]

FUTURE RESEARCH

Future research on sensory processing in preterm children is needed to replicate and extend the available results of this thesis. On both the registration and integration level, more studies are needed on the different sensory modalities. On the modulation level research should also include questionnaires on behavioral problems. Measures should best be a combination of child-administered tests and questionnaires. Parents should be considered as the primary informant to judge sensory processing in daily life of a very preterm child, and at the age of four also school teachers may be included as informants. Gathering information on self-report would be helpful in children above eight years of age. With respect to child-administered tests, both clinical and computerized measures may be used, complemented by quantitative sensory testing with brain evoked potentials, for instance to further explore sensory detection thresholds. Future studies would preferably be term-born controlled longitudinal studies combining sensory processing measures with behavioral measures tapping into ADHD and ASD to reveal crucial underpinnings for the "preterm behavioral phenotype". Imaging studies, including diffusion tensor imaging (DTI), are recommended to better understand the underlying brain abnormalities of sensory processing difficulties, linking white matter integrity and connectivity to the different levels of sensory registration, integration and modulation in very preterm children. Additionally, impact of NICU stay may be taken into account more thoroughly within prospective research designs, mapping for instance number of invasive and/or skin-breaking procedures, hours of kangaroo care, and neonatal pain measurements during hospitalization. Finally, although tailored interventions, such as parental counseling and referral to occupational therapy, are considered good clinical care, effectiveness of these interventions should be carefully evaluated. Scarcity of empirical research on therapeutic approaches targeting the sensory system, but also on parental sensitivity and parenting skills, illustrates the importance of collaborative, translational research. In the near future, we hope to evaluate effectiveness of parental counseling on sensory processing difficulties and regulatory problems in young infants by joining forces with clinicians (medical psychologists) and embedded scientists in the area of child development.

CONCLUDING REMARKS

The results of this thesis confirm the presence of sensory processing difficulties in the domains of registration and modulation, as well as behavioral difficulties in terms of elevated symptom levels of ADHD and ASD symptoms in very preterm children. Moreover, sensory modulation in particular may be related to symptoms of ADHD and ASD in very preterm children and might

be considered as one of the pathways that lead to adverse behavioral outcomes observed in very preterm children. Understanding ADHD and ASD symptoms from a sensory processing perspective may provide additional leads for intervention and treatment in very preterm children. Screening for sensory processing difficulties and symptoms of ADHD and ASD should therefore be considered to be included in the follow-up care in very preterm children.

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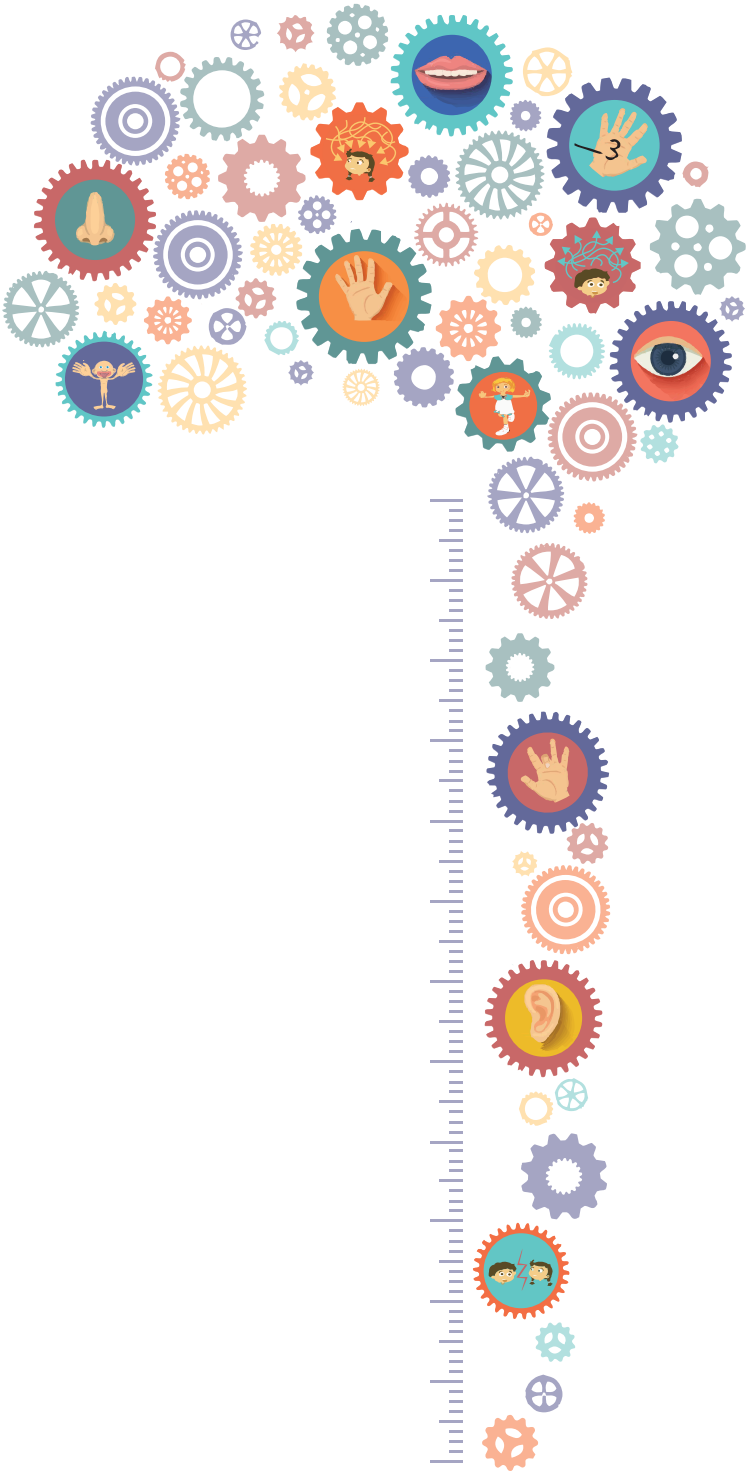


Nederlandse samenvatting

ACHTERGROND

Wereldwijd worden er elk jaar ongeveer 15 miljoen baby's te vroeg geboren. Vroeggeboorte is gedefinieerd als een zwangerschapsduur van minder dan 37 weken. Er wordt onderscheid gemaakt tussen matig vroeggeboren kinderen (zwangerschapsduur van 32–37 weken), ernstig vroeggeboren kinderen (zwangerschapsduur < 32 weken) en extreem vroeggeboren kinderen (zwangerschapsduur < 28 weken). Dit proefschrift gaat over ernstig vroeggeboren (zwangerschapsduur ≤ 32 weken) kinderen in Nederland.

In Nederland wordt 7,7% van alle kinderen te vroeg geboren en daarvan is 1,5% ernstig vroeggeboren, wat neerkomt op ongeveer 2500 baby's per jaar. Door verbeteringen in de neonatale zorg zijn de overlevingskansen van ernstig vroeggeboren kinderen gestegen tot inmiddels 96%. Echter, ongeveer een derde van deze ernstig vroeggeboren kinderen is bekend met ontwikkelingsproblemen op lange termijn, waaronder motorische (coördinatie) problemen, sensorische verwerkingsproblemen, lagere intelligentie, lager tempo van informatie verwerken, problemen in executief functioneren en internaliserende en externaliserende gedragsproblemen. Deze problemen zijn geassocieerd met hersenschade door o.a. hypoxisch-ischemische schade (schade die ontstaat doordat de hersenen worden voorzien van onvoldoende zuurstofrijk bloed) en het doormaken van infecties. Deze beide schadelijke condities kunnen leiden tot verstoring van de ontwikkeling van de witte en grijze hersenstof. De neonatale intensive care unit (NICU) waar te vroeg geboren kinderen na hun geboorte vaak weken verblijven, is een heel andere sensorische omgeving dan de baarmoeder en sensorische overstimulatie (fel licht, geluiden, verpleegkundige handelingen, pijnlijke medische procedures) en onderstimulatie (gemis aan o.a. vestibulaire en tactiele input door separatie van ouders) komen beide frequent voor. Het verblijf op de NICU kan de normale hersenontwikkeling verder verstoren door te vroege blootstelling aan deze afwijkende sensorische ervaringen.

Er is inmiddels veel onderzoek gedaan om ontwikkelings- en gedragsproblemen bij ernstig vroeggeboren kinderen te doorgronden. Toch is onze kennis hierover nog altijd incompleet. In dit proefschrift verkennen we sensorische informatieverwerking als een onderliggend mechanisme/substraat voor gedragsmoeilijkheden bij ernstig vroeggeboren kinderen. Sensorische informatieverwerking is het verwerken van informatie die ons via de zintuigen bereikt. Adequate verwerking van zintuiglijke (sensorische) informatie maakt het mogelijk om op efficiënte en gepaste manier te reageren op eisen en verwachtingen vanuit de omgeving. Voor kinderen is dit een belangrijke voorwaarde voor spelen, sporten en leren. Sensorische informatieverwerking bestaat uit *registratie*, *integratie* en *modulatie*. Problemen op het gebied van *registratie* bestaan uit verstoringen van het gewaar worden, discrimineren en interpreteren van sensorische prikkels. Problemen met *integratie* behelzen een verstoorde

	Zelfregulatiestrategieën/gedragsrespons	
Neurologische drempel	Passief	Actief
Hoge drempel	Gebrekkige registratie	Prikkelzoekend
Lage drempel	Gevoeligheid voor prikkels	Prikkelvermijdend

Figuur 1. Sensorische modulatie matrix.
(overgenomen uit: Dunn W. Sensory Profile: User's Manual. San Antonio, TX: The Psychological Corporation; 1999)

integratie van sensorische informatie uit de verschillende sensorische modaliteiten (auditief, visueel, vestibulair [evenwicht], tactiel, smaak, reuk, proprioceptie/kinesthesie [bewegingszin]). Problemen met *modulatie* beslaan een verstoorde regulatie van de intensiteit van reacties op sensorische prikkels leidend tot overresponsiviteit en onderresponsiviteit. Volgens het model van Dunn (zie Figuur 1) kunnen op het gebied van sensorische modulatie vier categorieën (ook wel kwadranten) worden onderscheiden: 1) Gebrekkige registratie, waarbij kinderen *hoge* prikkeldrempels laten zien met daarbij *passieve* zelfregulatiestrategieën; 2) Prikkelzoekend, waarbij kinderen *hoge* prikkeldrempels laten zien met *actieve* zelfregulatiestrategieën; 3) Gevoeligheid voor prikkels, waarbij kinderen *lage* prikkeldrempels laten zien met daarbij *passieve* zelfregulatiestrategieën, en 4) Prikkelvermijdend, waarbij kinderen *lage* prikkeldrempels laten zien met *actieve* zelfregulatiestrategieën.

Problemen in de sensorische informatieverwerking verstoren het adaptief functioneren en kunnen leiden tot gedragsmoeilijkheden. Zo worden ontwikkelingsstoornissen als attention deficit hyperactivity disorder (ADHD) en autismespectrumstoornis (ASS) geassocieerd met problemen in de sensorische informatieverwerking. Interessant is dat juist ernstig vroeggeboren kinderen een verhoogde kans op ASS en ADHD te hebben. ASS en ADHD zijn ontwikkelingsstoornissen die zich openbaren in de vroege kindertijd en forse beperkingen opleveren in het alledaags functioneren. ASS kent een wereldwijde prevalentie van ongeveer 0,6% en wordt gekenmerkt door beperkingen in sociale communicatie en sociale interactie in combinatie met repetitieve en eenzijdige patronen van gedrag, interesses en activiteiten. ADHD is een frequenter voorkomende ontwikkelingsstoornis (5%), waarbij aandachtsproblemen, hyperactiviteit en impulsiviteit kernsymptomen zijn. Bij ASS worden problemen op gebied van registratie, integratie en modulatie reeds frequent beschreven. Bij ADHD worden deze problemen eveneens gevonden.

Ons onderzoek binnen een groep schoolkinderen gediagnosticeerd met ADHD (**Hoofdstuk 6 & 7**) toonde reeds aan dat deze kinderen zowel problemen in tactiele registratie als tactiele modulatie (overresponsiviteit) lieten zien. Deze bevindingen vormden de basis voor onze hypothese dat problemen in sensorische informatieverwerking ook bij ernstig vroeggeboren kinderen geassocieerd zijn met, of zelfs verklarend zijn voor, kenmerken van ADHD en ASS.

DOELSTELLINGEN

Dit proefschrift heeft als doel een gedetailleerd beeld te schetsen van sensorische informatieverwerkingsproblemen en gedragsmoeilijkheden bij ernstig vroeggeboren kinderen, in het bijzonder ADHD en ASS (*Deel 1*). We zijn daarom gestart met een systematische review van de beschikbare literatuur over sensorische informatieverwerkingsproblemen in het volledige spectrum van vroeggeboorte (zwangerschapsduur < 37 weken). Vervolgens hebben we onderzoek gedaan naar de effecten van ernstige vroeggeboorte op sensorische informatieverwerking (op niveau van registratie, integratie en modulatie) en daarnaast op symptomen van ADHD en ASS. Tot slot hebben we onderzocht of sensorische informatieverwerkingsproblemen van invloed zijn op de ernst van de symptomen van ADHD en ASS bij ernstig vroeggeboren kinderen. Deze doelstellingen onderzochten wij van 2010 tot 2015 binnen een groep van 57 ernstig vroeggeboren 8–10-jarige kinderen, die bij geboorte geïncludeerd waren in een gerandomiseerd onderzoek naar de effecten van verrijkte voeding ("Study Towards the Effects of Postdischarge nutrition on growth and body composition of infants born ≤ 32 weeks of gestation and/or ≤ 1500 gram birth weight [STEP]"). Daarnaast nam een controlegroep van 57 à terme (zwangerschapsduur > 38 weken) geboren kinderen van dezelfde leeftijd en met dezelfde sociaal-economische achtergrond deel aan het onderzoek. In *Deel 2* van dit proefschrift beschrijven wij onze bevindingen over sensorische informatieverwerkingsproblemen bij een groep van 5–12-jarige kinderen, gediagnosticeerd met ADHD, in vergelijking met hun broers en/of zussen zonder ADHD en in vergelijking met een groep gezonde kinderen zonder gedragsmoeilijkheden. De bevindingen van dit onderzoek vormden de basis van de gedachtegang en hypothesevorming om ook bij ernstig vroeggeboren kinderen sensorische informatieverwerking te onderzoeken.

SAMENVATTING VAN DE BEVINDINGEN

In *Deel 1* vonden we middels een systematische review van beschikbare wetenschappelijke literatuur evident bewijs voor sensorische *modulatie*problemen bij vroeggeboren (zwangerschapsduur <37 weken) kinderen (**Hoofdstuk 2**). Onze conclusies waren gebaseerd op 18

studies, die in totaal 1138 vroeggeboren kinderen en 493 à terme geboren kinderen beschreven. Vroeggeboren kinderen laten zowel onderresponsiviteit als overresponsiviteit zien, verdeeld over de vier categorieën van Dunn (Gebrekkige registratie, Prikkelzoekend, Gevoeligheid voor prikkels, Prikkelvermijdend) en in meerdere sensorische modaliteiten (auditief, visueel, vestibulair, tactiel en oraal-sensorisch). Er bleek bovendien enig bewijs voor een relatie tussen sensorische modulatie en gedragsmoeilijkheden, waaronder ASS, een regulatiestoornis, en een moeilijk en/of angstig temperament. Voorspellers voor sensorische modulatieproblemen waren zwangerschapsduur, geboortegewicht, afwijkingen in de witte en grijze stof en duur van de NICU-opname.

In onze studie naar sensorische informatieverwerking (registratie, integratie en modulatie) in **Hoofdstuk 3** vonden we met een uitgebreide testbatterij dat 8–10-jarige ernstig vroeggeboren kinderen in vergelijking met à terme geboren kinderen moeilijkheden laten zien op gebied van tactiele registratie, kinesthesie (bewegingszin) en grafestesie (herkennen van tactiel aangeboden symbolen), wijzend op een somatosensorische hyposensitiviteit (ondergevoeligheid). Daarnaast bleek ernstige vroeggeboorte effect te hebben op sensorische modulatie in termen van onderresponsiviteit en overresponsiviteit. Sensorische integratie van audiovisuele informatie bleek binnen deze groep van ernstig vroeggeboren kinderen niet significant te verschillen van de prestaties van à terme geboren kinderen. Registratie, integratie en modulatie waren relatief onafhankelijk van elkaar en niet evident geassocieerd met de ernst dan wel complicaties van vroeggeboorte.

Hoofdstuk 4 laat zien dat symptomen van ADHD en ASS, gemeten met zowel ouder- als leerkrachtvragenlijsten, samen voorkomen bij ernstig vroeggeboren kinderen en bovendien in ernstigere mate optreden dan bij à terme geboren kinderen. ADHD-kenmerken waren het meest uitgesproken op het gebied van aandachtsproblemen. Binnen de groep ernstig vroeggeboren kinderen bleek 16% te voldoen aan een ADHD-diagnose. Wat betreft de ASS-kenmerken bleken sociale beperkingen en algemene en pragmatische communicatie meer aangedaan bij ernstig vroeggeboren kinderen dan bij hun à terme geboren leeftijdsgenootjes. Echter, geen van de ernstig vroeggeboren kinderen kwam in aanmerking voor een ASS-diagnose. Matige tot sterke overeenstemming tussen ouders en leerkrachten onderstreepten de pervasiviteit (optreden van klachten in meer dan één context/situatie) van de ADHD- en ASS-kenmerken.

In **Hoofdstuk 5** hebben we de relatie tussen sensorische informatieverwerking en kenmerken van ADHD en ASS geëxploreerd en gevonden dat niet zozeer sensorische registratie, maar wel sensorische modulatie (onderresponsiviteit en overresponsiviteit) gedeeltelijk verklarend is voor de ernst van zowel de ADHD- als de ASS-kenmerken.

In *Deel 2* beschrijven wij de context en basis voor onze hypothese dat sensorische informatieverwerking gerelateerd is aan kenmerken van ADHD en ASS bij ernstig vroeggeboren kinderen. In **Hoofdstuk 6** laten wij zien dat tactiele registratie (warm-koud discriminatie en punt-kop discriminatie) meer is aangedaan bij kinderen met ADHD, en in mindere mate ook bij hun broers en zussen, in vergelijking met kinderen uit de controlegroep. Dit wijst mogelijk op een hyposensitiviteit in tactiele registratie. Daarentegen presteren kinderen met ADHD niet anders dan gezonde controlekinderen (en dan hun broers en/of zussen) op kinesthesie en emotionele reacties op pijnprikkels.

In **Hoofdstuk 7** beschrijven wij vervolgens dat kinderen met ADHD op het gebied van tactiele modulatie meer overresponsiviteit laten zien dan hun broers en/of zussen en dan controlekinderen. Dit blijkt echter uitsluitend te gelden voor meisjes met ADHD en niet voor jongens met ADHD.

ALGEMENE DISCUSSIE

Heterogeniteit in sensorische informatieverwerkingsproblemen

In de afgelopen jaren zijn de effecten van ernstige vroeggeboorte op sensorische informatieverwerking vaker onderzocht. In ons review vonden we geen duidelijk profiel van sensorische informatieverwerkingsproblemen bij ernstig vroeggeboren kinderen en blijkt sprake van zowel onderresponsiviteit als overresponsiviteit, verdeeld over verschillende sensorische modaliteiten. Dit sluit aan bij onze eigen resultaten naar sensorische informatieverwerking bij ernstig vroeggeboren kinderen. Mogelijk wordt deze gevonden heterogeniteit in sensorische informatieverwerkingsproblemen verklaard door de manier waarop we meten, namelijk met inzet van verschillende meetinstrumenten, waaronder een combinatie van vragenlijsten middels ouderrapportage en tests/taken die bij kinderen zelf worden afgenomen. Daarentegen zien we eenzelfde variëteit aan bevindingen wanneer studies worden vergeleken die gebruik maken van hetzelfde meetinstrument, zoals de veelgebruikte *Sensory Profile*. Een andere verklaring voor het uiteenlopen van bevindingen zou kunnen zijn dat ieder ernstig vroeggeboren kind een eigen neonatale fase doormaakt. De opgelopen hersenschade varieert met de ernst en aanwezigheid van hypoxisch-ischemische schade en het al dan niet doormaken van één of meerdere infecties. Daarnaast kunnen onderstimulatie (door separatie van ouders) en overstimulatie (door verpleegkundig handelen, pijn, geluid, licht) sterk wisselen van kind tot kind. Als gevolg hiervan zouden overresponsiviteit en onderresponsiviteit initieel adaptieve reacties kunnen zijn van het sensorische systeem van het ernstig vroeggeboren kind op de sensorisch afwijkende situatie op de NICU. Op de langere termijn zouden deze over- en

onderresponsiviteit juist kunnen leiden tot sensorische informatieverwerkingsproblemen, hetgeen ook ondersteund wordt door de relatief hoge incidentie van regulatiestoornissen bij ernstig vroeggeboren kinderen.

Onze bevinding dat multi-sensorische (in ons geval: audiovisuele) integratie ongestoord is bij ernstig vroeggeboren kinderen, terwijl juist de tactiele registratie en modulatie aangedaan zijn, is opvallend. Verstoorde tactiele registratie en modulatie kunnen mogelijk verklaard worden door kleinere actieve gebieden in somatosensorische corticale gebieden en afwijkingen in de witte stof. Dit komt overeen met de witte-stofafwijkingen die geobserveerd worden bij kinderen met sensorische informatieverwerkingsproblemen. Een andere verklaring is dat registratie, integratie en modulatie relatief onafhankelijke aspecten van sensorische verwerking zijn, zoals wij ook vinden in onze studie bij zeer vroeggeboren kinderen en bij kinderen met ADHD.

Gedragsmoeilijkheden begrijpen bij ernstig vroeggeboren kinderen

Sensorische informatieverwerking is een relatief nieuw onderzoeksdomein bij ernstig vroeggeboren kinderen, terwijl gedragsmoeilijkheden inmiddels vrij uitgebreid bestudeerd zijn in deze groep. Enkele jaren geleden is er zelfs een suggestie gedaan voor een specifieke constellatie van gedragsmoeilijkheden bij ernstig vroeggeboren kinderen, genaamd "preterm behavioral phenotype", oftewel 'gedragsfenotype van de vroeggeborene'. Johnson en Marlow beschrijven dit fenotype als een constellatie van ADHD-symptomen (aandachtsproblemen > hyperactiviteit/impulsiviteit), sociale en emotionele problemen en een groter risico op internaliserende in plaats van externaliserende problemen. Ernstig vroeggeboren kinderen zouden voornamelijk aandachtsproblemen en sociale problemen laten zien, in plaats van uitgebreide ADHD- en ASS-symptomatologie. Deze problemen zouden een neuropathologische basis hebben en geassocieerd zijn met zwangerschapsduur, geboortegewicht en vroege hersenschade van grijze en witte stof. Resultaten van onze studie naar (symptomen van) ADHD en ASS ondersteunen het mogelijke bestaan van dit fenotype, omdat in onze groep ernstig vroeggeboren kinderen ADHD- en ASS-kenmerken samen voorkomen. Bovendien zien we in onze studie meer aandachtsproblemen dan hyperactiviteit en impulsiviteit terug, al dan niet in combinatie met sociale beperkingen en communicatieproblemen. Tevens sluiten we daarmee aan bij de recente suggestie dat aandachtsproblemen mogelijk de verbindende factor zijn tussen het samen optreden van ADHD en ASS in de algemene populatie, omdat aandachtsproblemen een remmende werking zouden hebben op sociale acceptatie. Kinderen met aandachtsproblemen missen gemakkelijk subtiele hints in sociale interactie, kunnen minder makkelijk meekomen bij strakker geregisseerde spelletjes en sportactiviteiten en worden soms buitengesloten vanwege vertraagde reacties en dromerigheid.

De gedragsmoeilijkheden die passen bij het gedragsfenotype van de vroeggeborene en die wij in onze studie identificeren als kenmerken van ADHD en ASS zijn mogelijk gerelateerd aan sensorische informatieverwerkingsproblemen als gevolg van neonatale complicaties en verblijf op de NICU. Wat betreft sensorische informatieverwerking vinden we in ons review dat sensorische modulatieproblemen gerelateerd zijn aan regulatiestoornissen, een angstig en moeilijk te kalmeren temperament en bovendien samengaan met ASS. Ons onderzoek toonde aan dat sensorische modulatie in termen van onderresponsiviteit en overresponsiviteit bijdraagt aan de ernst van ADHD- en ASS-kenmerken. Hoewel de verklaarde variantie van de ADHD- en ASS-kenmerken bescheiden is, zijn we ervan overtuigd dat het begrijpen van gedragsmoeilijkheden van ernstig vroeggeboren kinderen nuttig en betekenisvol kan zijn vanuit een klinisch perspectief. We stellen ons voor dat onderresponsief en overresponsief gedrag van ernstig vroeggeboren kinderen op gedragsniveau gelabeld kan worden in termen van ADHD- en ASS-symptomatologie, maar dat feitelijk verstoorde sensorische informatieverwerking ten grondslag ligt aan deze problemen en dat het dus cruciaal is om deze problemen vanuit dit perspectief te begrijpen. De dromerige indruk die inderdaad doet denken aan ADHD en het teruggetrokken gedrag dat doet denken aan ASS, zou feitelijk geduid kunnen worden als onderresponsiviteit. Op dezelfde manier zou prikkelzoekend gedrag (vanwege onderresponsiviteit), zoals repetitief spel, friemelen met handen, frequent aanraken van materiaal en continu in beweging zijn, begrepen kunnen worden als repetitief gedrag, passend bij ASS, of als hyperactief en ongericht gedrag, passend bij ADHD. Prikkelvermijdende en prikkelgevoelige reacties (vanwege overresponsiviteit), zoals voorzichtig, vermijdend en soms rigide gedrag zouden kunnen worden geïnterpreteerd als passend bij ASS of als dwingend of dwars gedrag bij ADHD. Het begrijpen van gedragsmoeilijkheden vanuit het perspectief van sensorische informatieverwerking biedt handvatten voor klinische toepassing en wordt eveneens onderschreven door onze bevindingen bij kinderen die gediagnosticeerd zijn met ADHD, waarbij ook problemen in tactiele modulatie en tactiele registratie aan de orde zijn.

KLINISCHE IMPLICATIES

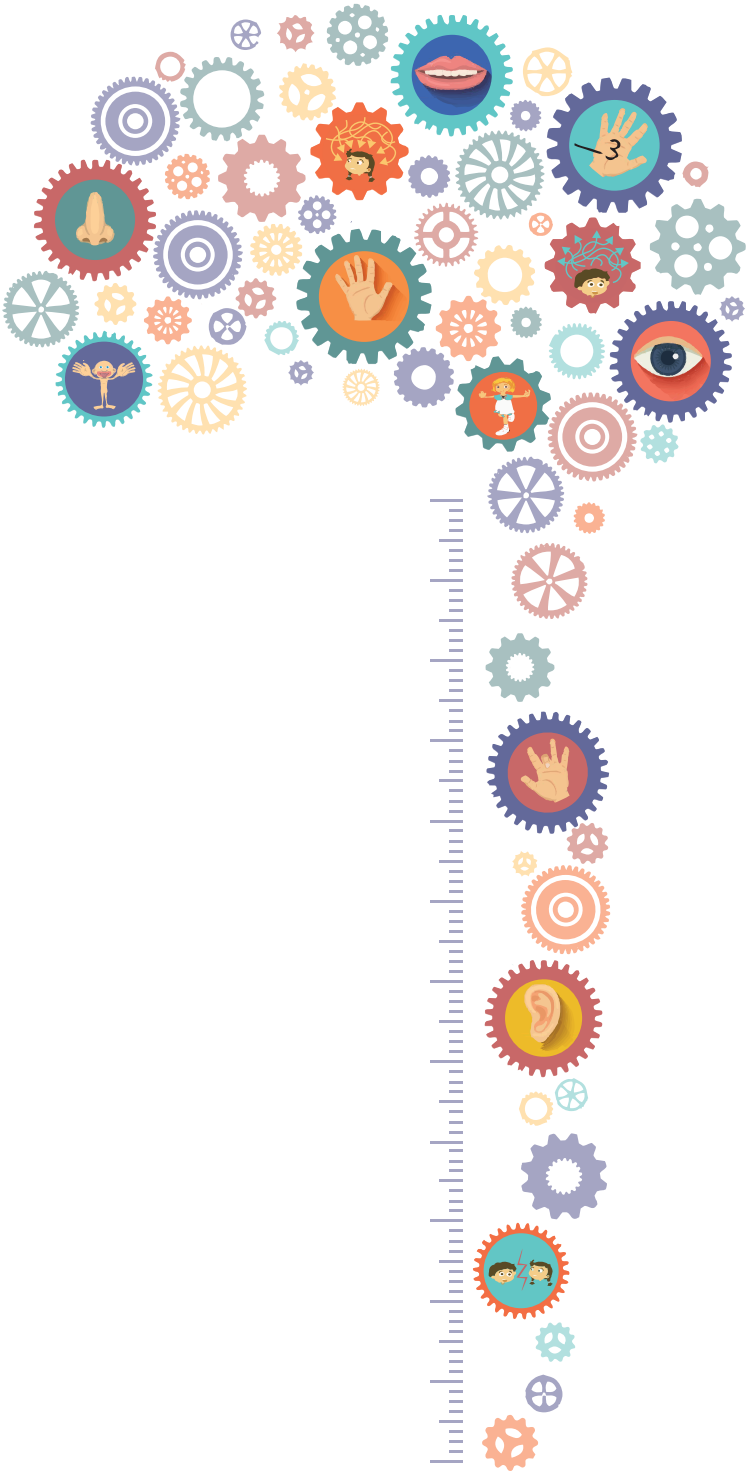
Onze bevindingen laten zien dat ernstig vroeggeboren kinderen een verhoogd risico hebben op het ontwikkelen van ADHD- en ASS-kenmerken en sensorische informatieverwerkingsproblemen. Het is zelfs zo dat deze sensorische informatieverwerkingsproblemen deels verklarend zijn voor gedragsmoeilijkheden bij ernstig vroeggeboren kinderen. Hoewel onze effectgroottes bescheiden zijn en meer onderzoek nodig is om onze bevindingen te repliceren, zijn wij ervan overtuigd dat het begrijpen van gedragsmoeilijkheden vanuit een sensorisch perspectief kansen biedt in de klinische zorg aan ernstig vroeggeboren kinderen.

In de afgelopen 30 jaar is het verblijf op de NICU voor een ernstig vroeggeboren baby enorm veranderd. Na de start van ontwikkelingsgerichte zorg volgens NIDCAP (Newborn Individualized Development Care and Assessment Program) in de jaren 90, werd het belang van frequent huid-op-huidcontact (buidelen) en het toevoegen van multi-sensorische stimulatie meer en meer duidelijk. Inmiddels heeft dit geleid tot een stevig bewustzijn voor de noodzaak van ouderbetrokkenheid, in zogeheten 'familiy integrated care'. Juist omdat het sensorische systeem sterk gevormd wordt door de hoeveelheid en de aard van de sensorische ervaringen direct na de geboorte, blijven interventies als effectief bewezen pijnbestrijding, buidelen, subtiel afgestemde sensorische stimulatie en intensieve betrokkenheid van ouders cruciaal. Het belang hiervan beperkt zich echter niet tot kort na de geboorte, want het sensorische systeem ontwikkelt zich ook gedurende de rest van het leven. Daarom is het belangrijk om sensorische informatieverwerkingsproblemen te signaleren en erkennen in zowel de babytijd als de schooltijd en misschien zelfs tot in de adolescentie. In het huidige nazorgtraject voor ernstig vroeggeboren kinderen in Nederland is nog geen plek ingeruimd voor specifieke screening van sensorische informatieverwerking. Gedragsproblemen worden voornamelijk globaal gescreend, zonder specifiek te kijken naar kenmerken van ADHD en ASS. Onze bevindingen pleiten voor het toevoegen van screeningsmaten gericht op sensorische modulatie en kenmerken van ADHD en ASS, in het bijzonder aandachtsproblemen en beperkingen in sociale interactie en communicatie. Het begrijpen van gedragsmoeilijkheden vanuit het perspectief van sensorische informatieverwerking biedt aanknopingspunten voor de behandeling van deze problemen. Op het individuele kind afgestemde interventies, zoals psycho-educatie aan ouders en leerkrachten over overresponsiviteit en onderresponsiviteit verdeeld over de sensorische modaliteiten, kunnen inzicht geven in problematische gedragspatronen van kinderen en kunnen deze doorbreken. Daarnaast kan verwijzing naar ergotherapie verlichting van problemen geven door de inzet van specifieke interventie op de verschillende modaliteiten om onder- en overresponsiviteit te normaliseren.

TOEKOMSTIG ONDERZOEK

Verder onderzoek naar sensorische informatieverwerking bij ernstig vroeggeboren kinderen is nodig om onze resultaten te repliceren en uit te breiden naar andere sensorische modaliteiten. Op het gebied van registratie is verder onderzoek nodig naar andere sensorische modaliteiten. Hetzelfde geldt voor multi-sensorische integratie, waar verder onderzoek licht zou kunnen werpen op de integratie van andere modaliteiten dan de audiovisuele integratie die wij hebben gemeten. Op het gebied van sensorische modulatie zou het zinvol zijn om naast ouderrapportage en leerkrachtrapportage ook zelfrapportage te includeren in onderzoek bij

kinderen boven de acht jaar. Toekomstig onderzoek zou longitudinaal ingericht moeten zijn, gebruikmakend van vergelijkingsgroepen van à terme geboren kinderen, waarin maten van sensorische informatieverwerking en gedragsvragenlijsten naar ADHD en ASS verder worden gecombineerd. Deze studies zouden bovendien gebruik moeten maken van beeldvormende technieken, waaronder diffusion tensor imaging (DTI) om de onderliggende hersenafwijkingen van sensorische informatieverwerkingsproblemen beter te begrijpen en integriteit en connectiviteit van de witte stof te verbinden aan de verschillende domeinen van sensorische registratie, integratie en modulatie. Het is daarnaast belangrijk om de impact van het verblijf op de NICU gedetailleerd mee te nemen bij het opstellen van risicoprofielen voor ontwikkeling van problemen in de sensorische informatieverwerking door bijvoorbeeld het aantal pijnlijke procedures, uren van buidelen en maten van neonatale pijn te registreren. Tot slot is het zinvol om interventies als psycho-educatie en ergotherapie te evalueren op hun effectiviteit bij ernstig vroeggeboren kinderen. Schaarste in empirisch bewijs voor therapeutische benaderingen die gericht zijn op het sensorische systeem en op pedagogische vaardigheden en sensitiviteit van ouders onderstrepen het belang van translationeel onderzoek, waarbij meerdere disciplines met elkaar samenwerken. In de nabije toekomst hopen wij de effectiviteit van psycho-educatie over sensorische informatieverwerkingsproblemen en regulatieproblemen aan ouders te onderzoeken, door de handen ineen te slaan met zowel klinisch werkende psychologen als psycholoog-onderzoekers. We hopen intussen psycho-educatie een vaste plaats te geven in de standaard geboden nazorg aan ernstig vroeggeboren kinderen.



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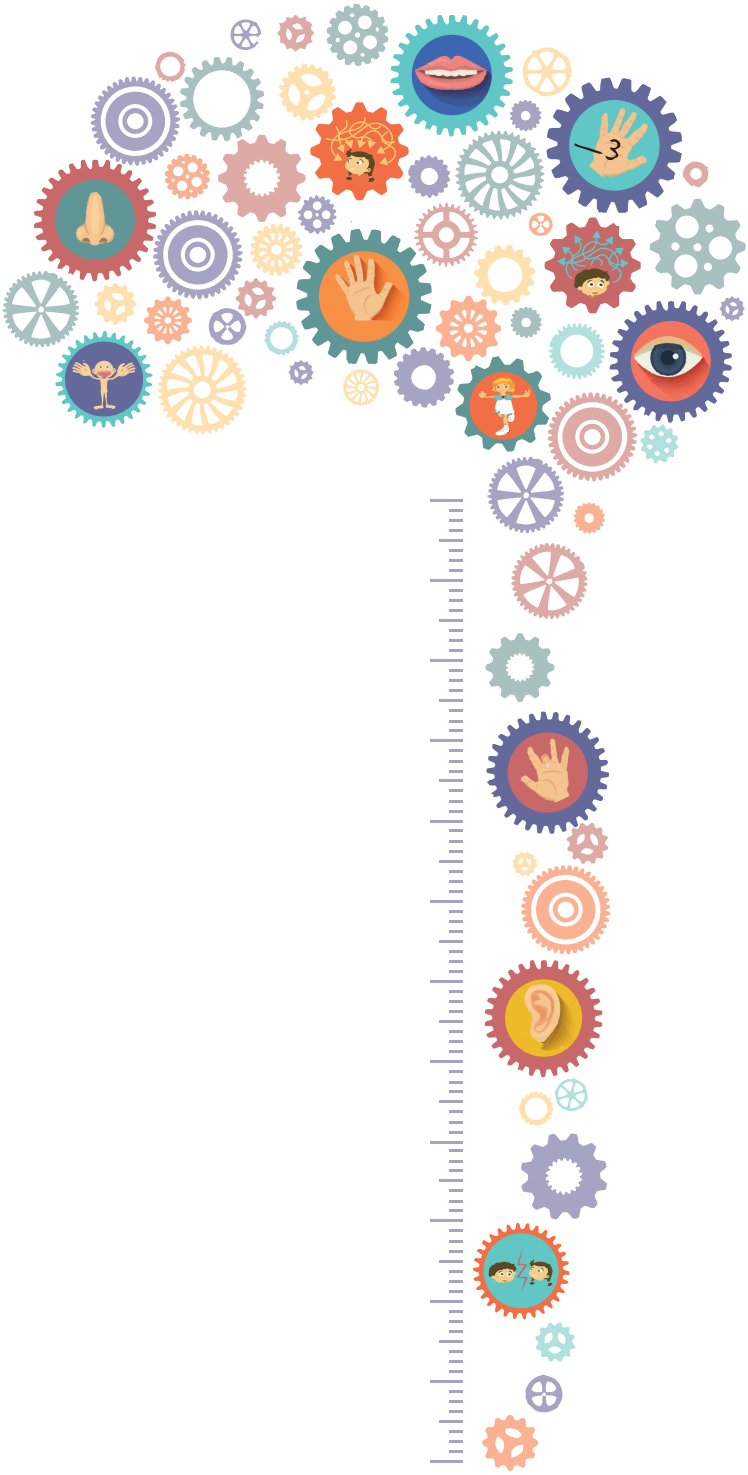

Dankwoord

En dan is het toch gewoon klaar. Van een ogenschijnlijk onschuldige vraag van Erik Scherder ('Zou je niet willen promoveren?') en een ontkennend antwoord ('Nee, ik wil graag de GZ-opleiding doen') naar een deeltijdpromotietraject. Patiëntenzorg combineren met het onderzoeken van een eigen klinisch ingegeven vraag klonk toch best goed en zowel het onderwerp als de aanpak maakten me enorm enthousiast. Al had ik nooit bedacht dat het tempo soms frustrerend laag zou zijn en dat ik mijn promotie pas in 2018 zou afronden. Maar ik had me ook niet kunnen voorstellen welke vrolijke life events er nog allemaal tussendoor zouden komen (trouwen, verhuizen & twee zonen op de wereld zetten).

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moeten we er nu een stukje voor rijden nu we niet meer een werkplek delen. Bedankt voor al je hulp de afgelopen en komende tijd! En maak er wat van daar in het Prinses Maxima Centrum (we zongen het al: 'juichend wachten ze je daar op').
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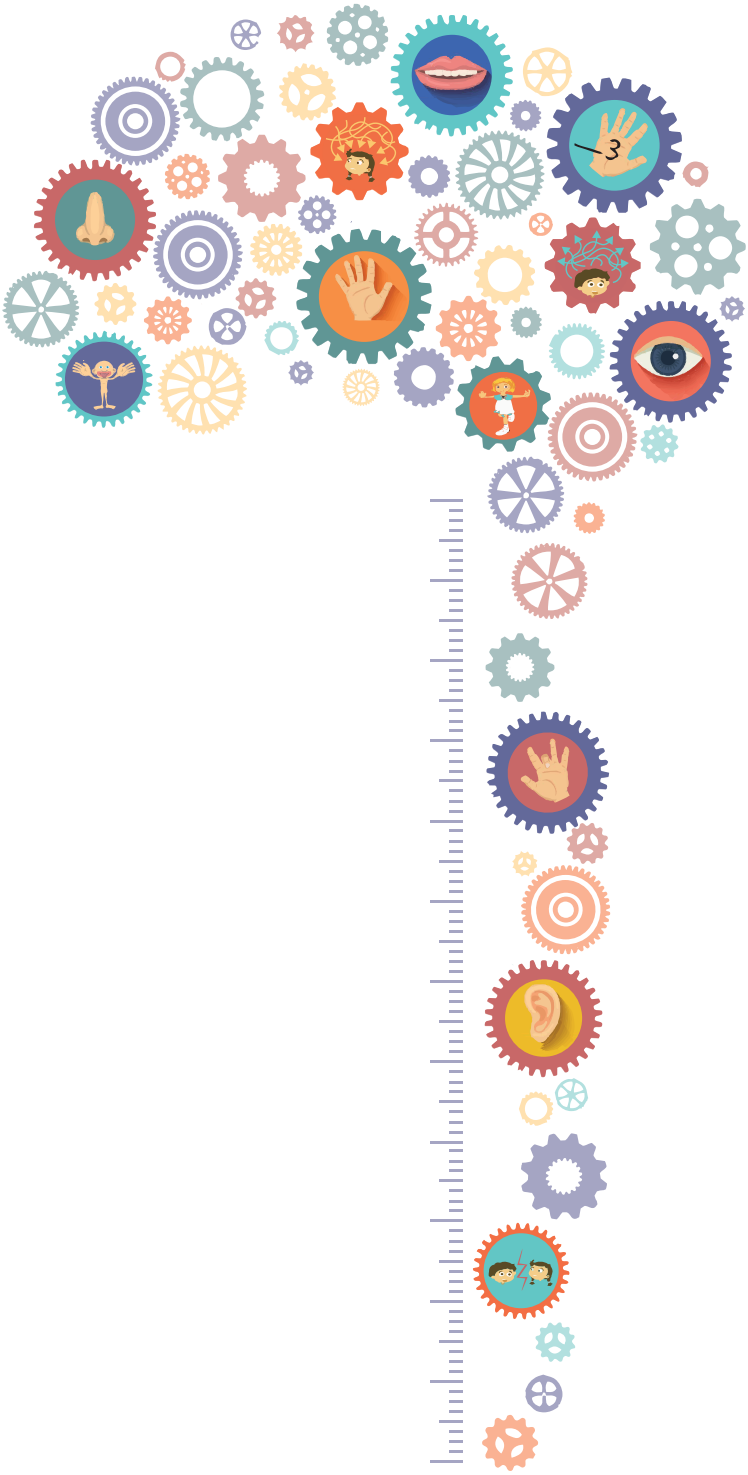
Mijn allerliefste Timme en Billy, gelukkig hadden jullie lang niet altijd door dat mama aan het werk was ('Waarom ga je naar zolder, mama?') of kwamen jullie lieve kusjes brengen ('Heb je het nu weer niet goed gedaan, mam? Zoveel rode strepen!'). De tijd doordeweeks tussen 18:00 en 20:00u voor ik weer aan het werk ging was een heerlijke verademing. Als jullie in mijn armen vliegen is er een boel vergeten. Ik ben trots jullie mama te zijn!



About the author

Tinka Bröring was born on March 6th, 1982 in Leiden, The Netherlands. She completed her high school education at Northgo College in Noordwijk, where she grew up with her mother, father and younger sister, Tanya. She started studying psychology at Leiden University in 2000. To pursue a double major in clinical neuropsychology (child and adult neuropsychology), she switched to VU University Amsterdam in 2002. She completed two clinical internships at the VU University Medical Center (VUmc) Amsterdam at the Department of Medical Psychology, Neuropsychology section (2004) and Pediatric Psychology section (2005) and graduated cum laude in 2006. As a follow-up on her master thesis, she worked on two papers on sensory processing in children with ADHD (Part two of this thesis) in close collaboration with Nanda Rommelse. Tinka worked at a mental health care center for children, Zonnehuizen Zeist, as a junior psychologist, before returning to the Pediatric Psychology section of the VUmc. There she started her two-year clinical training towards the Dutch health care psychologist registration (GZ-psycholoog), that she graduated from in 2009. During this training she became more and more interested in very preterm children and she started writing multiple grant proposals to finance the research that resulted in this thesis, supervised by professors Jaap Oosterlaan and Harrie Lafeber and dr. Kim Oostrom. To date, and during her PhD thesis, Tinka has been working as a child (neuro)psychologist at the Pediatric Psychology section VUmc, combining clinical patient care, research and teaching in bachelor and master courses of Medicine and Psychology and in Pediatric Nursing School. Between 2010 and 2012 Tinka also wrote a guidebook (literature review and practical guidance for parents and professionals) on emotional and behavioral functioning in children with cerebral palsy in collaboration with Johannes Verheijden and on behalf of the BOSK, organization for people with a physical handicap, which was published in 2012. Tinka will remain at the VUmc as a child (neuro)psychologist and is dedicated to the psychological care of very preterm and sick children. Tinka lives in Leiden together with Martijn and their two sons, Timme and Billy.

Tinka Bröring is geboren op 6 maart 1982 te Leiden. Ze groeide op in Noordwijk met haar vader, moeder en zusje, Tanya, en voltooide daar haar vwo op het Northgo College. Ze startte in 2000 met haar studie Psychologie aan de Universiteit van Leiden. Gegrepen door de neuropsychologie, maakte zij in 2002 de overstap naar de Vrije Universiteit in Amsterdam om daar een dubbele afstudeerrichting klinische neuropsychologie (Kind en Volwassene) te volgen. Bij de afdeling Medische Psychologie van het VU medisch centrum (VUmc) liep zij stage bij de sectie Neuropsychologie en bij de sectie Pediatrische Psychologie en zij studeerde in 2006 cum laude af. Naar aanleiding van haar afstudeerscriptie over sensorische informatieverwerking bij kinderen met AHDH publiceerde zij twee papers (Deel twee van dit proefschrift) samen met Nanda Rommelse. Na haar afstuderen werkte Tinka ondertussen als basispsycholoog bij Zonnehuizen, een kinder- en jeugdpsychiatrische instelling in Zeist. In 2007 keerde zij terug naar het VUmc en de sectie Pediatrische Psychologie, om aldaar de opleiding tot gezondheidszorgpsycholoog Kind en Jeugd af te ronden in 2009. Tijdens deze GZ-opleiding raakte Tinka geïnteresseerd in de problematiek van vroeggeboren kinderen en schreef zij meerdere financieringsaanvragen om het onderzoek te kunnen opzetten dat uiteindelijk resulteerde in dit proefschrift, dat werd gesuperviseerd door professoren Jaap Oosterlaan en Harrie Lafeber en dr. Kim Oostrom. Daarnaast schreef Tinka van 2010 tot 2012 in opdracht van de BOSK, organisatie voor mensen met een fysieke beperking, samen met Johannes Verheijden een boek voor ouders en professionals over gedrag en emotie bij kinderen met cerebrale parese. Tinka is inmiddels 11 jaar met veel plezier werkzaam bij de sectie Pediatrische Psychologie VUmc, waar zij patiëntenzorg (o.a. baby-peuterbehandelingen en neuropsychologische diagnostiek/behandeling) combineert met onderzoek en onderwijs aan de bachelor- en masteropleiding Geneeskunde en Psychologie en post-hbo-opleiding Kinderverpleegkunde. Zij zal zich ook in de toekomst blijven inzetten voor de psychologische zorg aan ernstig vroeggeboren en zieke kinderen. Tinka woont in Leiden samen met Martijn en hun twee zonen, Timme en Billy.