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.
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<th>Chapter</th>
<th>Participants</th>
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<th>Main findings</th>
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| 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, Graphesthesia (SIPT)  
Integration: MSIT  
Modulation: SP | • Very preterm children are less accurate on somatosensory registration tasks, including Registration of Light Touch, Position Sense and Graphesthesia  
• 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

<table>
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<th>Chapter</th>
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<th>Main findings</th>
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<tr>
<td>5</td>
<td>57 very preterm children 56 full-term children</td>
<td><strong>Registration</strong>: aggregated scores of tactile perception, kinesthesia, graphesthesia  <strong>Modulation</strong>: SP  <strong>ADHD</strong>: aggregated scores of CBCL, TRF, PDBD, TDBD  <strong>ASD</strong>: aggregated scores of SRS, CCC-2</td>
<td>• 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</td>
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<tr>
<td>6</td>
<td>50 children diagnosed with ADHD 38 non-affected siblings 35 normal control children</td>
<td><strong>Registration</strong>: Temperature Discrimination, Sensory Discrimination of Touch, Registration of Light Touch, Kinesthesia,  <strong>Pain experience</strong>: CPI, CAS, FAS</td>
<td>• 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</td>
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<tr>
<td>7</td>
<td>47 children diagnosed with ADHD 36 non-affected siblings 35 normal control children</td>
<td><strong>Modulation</strong>: TIE</td>
<td>• 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</td>
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**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 graphesthesia 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, 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. 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. Consequently, overresponsiveness, as well as underresponsiveness, may be an offshoot of originally adaptive responses to the previously experienced overstimulation or understimulation. However, after the NICU stay, these regulatory responses may become maladaptive, resulting in sensory processing difficulties later in life. This is supported by the relatively high incidence of regulatory disorders among preterm infants.

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. 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 and sensory modulation difficulties may be explained by white matter brain abnormalities, consistent with impaired white matter microstructure observed in term born children with sensory modulation difficulties. 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. 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”. 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. 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. 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 due to inflammation and hypoxia-ischemia. 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. Attention problems may form the linking factor in the co-occurrence of ADHD and ASD, 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. 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. 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 and coincided with ASD. 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 overresponsive 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 injury42 as well as more severe neurodevelopmental sequelae43,44 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\textsuperscript{11,44,47} show similarities to those found in children with a primary sensory processing disorder,\textsuperscript{12} and that the impact of the sensory challenging NICU stay\textsuperscript{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.\textsuperscript{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. 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. 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. For instance, sensory processing and behavioral difficulties have been described to hamper normal development by interfering with social activities, play and leisure. 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), progressing to kangaroo care and (multi) sensory stimulation and more recently to strong parent involvement in family integrated care for very preterm infants with promising results. As the sensory system is powerfully shaped by the number and types of sensory experiences directly after birth, interventions during NICU and High Care stay are crucial. Both developmental care interventions and family integrated care may mitigate sensory overstimulation and understimulation. The use of proven effective analgesia diminishes procedural pain (overstimulation), especially when combined with parental holding of the infant or, if possible, with breastfeeding. 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. 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).

Yet, the sensory system continues to be shaped throughout the course of life. 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. 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.

Understanding ADHD and ASD symptoms from a sensory processing perspective may provide additional leads for intervention and treatment in very preterm children. 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. 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. 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.
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.

REFERENCES


