Neurofeedback Treatment in Children and Adolescents with Autism
Addressing the Controversy

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Chapter 1

Introduction

The ten year old Yurre and his mother Ginette are on a holiday in London and they visit Trafalgar Square. Ginette explains:\footnote{Cited from ‘De Dinoman en het Muziekmeisje’, a book about raising two children with autism written by Ginette Wieken (www.ginettewieken.nl).} “During his meeting with the pigeons on the square, Yurre suddenly puts his arms around me, buries his head in my neck, and stays like that for a while. Surprised, I hug him back, however without really getting a response. This really is one of his autistic hugs. He bends forward such that our lower bodies and legs do not touch. The hug seems to take forever. ‘Is something wrong, dear?’ I whisper. ‘No’, he whispers back and he strokes his nose across my cheek. I notice that other people are looking at us, but what do I care! My son is hugging me! ‘Yur, you aren’t crying, are you?’ ‘No’ ‘But is everything alright?’ I inquired worriedly. ‘Mam, stop keep asking me what the matter is. I am just loving you.’ My eyes start to water. ‘I just felt it and now it is all taking very long, I think’ he adds accurately. Then suddenly he lets go, pays no attention to me anymore, and is already carrying another pigeon on his arm.”
Yurre has Asperger syndrome, which is one of the disorders in the autistic spectrum. He has difficulties with expressing his feelings: he hugs his mother awkwardly while keeping a distance between his body and his mother's. Furthermore, he ends his hug abruptly and continues his pigeon activities without paying any attention to his mum anymore. Yurre's autistic disorder can not be cured, but there exist many behavioral training programs to change his abnormal patterns of behavior. Neurofeedback is claimed to be such a training program. The current dissertation examines whether children like Yurre may benefit from neurofeedback. Although neurofeedback can be applied to adults as well, the present dissertation focuses on children and adolescents with a disorder in the autistic spectrum aged between 8 and 18 years. The children and adolescents who participated in the studies described in this dissertation all have intelligence scores in the average to above average range. Before going into detail about the studies that were conducted, I will start this introduction with describing autism spectrum disorder (ASD) and the treatments available and offered to children and adolescents with ASD. Furthermore, I will critically review the scientific status of neurofeedback as a treatment for children and adolescents with ASD, both worldwide and specifically within the Netherlands. Finally, I will briefly introduce the upcoming chapters of this dissertation.

1.1 Autism: a pervasive developmental disorder
According to the American Psychiatric Association (APA; 2000) and the World Health Organization (1993), a diagnosis of ASD is given if qualitative abnormalities in social interactions and verbal and nonverbal communication are observed, along with restricted and stereotyped patterns of behavior, interests, and activities. Three subtypes of ASD can be distinguished: autism, Asperger disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS). These subtypes vary in severity and age of onset. Autism is seen as the most severe disorder, whereas PDD-NOS is a milder form. The diagnosis Asperger disorder is given to children with normal intelligence and (close to) adequately developed communication skills. In autism, qualitatively abnormal behavior is manifested before the age of three. In PDD-NOS and Asperger disorder, abnormalities in behavior can also be manifested after age three. Table 1 provides an overview of the diagnostic criteria for autism as defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR; APA, 2000). The prevalence of ASD has been estimated at 1 in 100 (Baird et al., 2006; Nederlandse Vereniging voor Autisme [Dutch Association for Autism], 2011).

Table 1.
DSM-IV-TR diagnostic criteria for autism.

<table>
<thead>
<tr>
<th>Criteria for Autistic Disorder</th>
</tr>
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<tbody>
<tr>
<td>A total of six or more manifestations from 1, 2, and 3, below:</td>
</tr>
<tr>
<td>1. Qualitative impairments of social interaction (at least two manifestations)</td>
</tr>
<tr>
<td>a. Marked impairment in the use of multiple types of nonverbal behavior such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interactions;</td>
</tr>
<tr>
<td>b. Failure to develop peer relationships appropriate to developmental level;</td>
</tr>
<tr>
<td>c. Lack of spontaneous seeking to share enjoyment, interests or achievements with other people (e.g. by lack of showing, bringing or pointing out objects of interest); and</td>
</tr>
<tr>
<td>d. Lack of social or emotional reciprocity.</td>
</tr>
<tr>
<td>2. Qualitative impairment of communication (at least one manifestation)</td>
</tr>
<tr>
<td>a. Delay in, or lack of, development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gestures or mime);</td>
</tr>
<tr>
<td>b. In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others;</td>
</tr>
<tr>
<td>c. Stereotyped and repetitive use of language or idiosyncratic language; and</td>
</tr>
<tr>
<td>d. Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level.</td>
</tr>
<tr>
<td>3. Restrictive and stereotyped patterns of behavior, interests, and activities (at least one manifestation)</td>
</tr>
<tr>
<td>a. Encompassing preoccupation with one or more restricted, repetitive, and stereotyped patterns of interest that is abnormal either in intensity or focus;</td>
</tr>
<tr>
<td>b. Apparently inflexible adherence to specific, nonfunctional routines or rituals;</td>
</tr>
<tr>
<td>c. Stereotyped and repetitive motor manerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements); and</td>
</tr>
<tr>
<td>d. Persistent preoccupation with parts of objects.</td>
</tr>
<tr>
<td>Delays or abnormal functioning, with onset before the age of 3 years, in at least one of the following areas: Social interaction; Language as used in social communication; and Symbolic or imaginative play.</td>
</tr>
<tr>
<td>A determination that Rett's disorder or childhood disintegrative disorder does not account better for the observed symptoms.</td>
</tr>
</tbody>
</table>
1.1.1 The neurobiology of autism

ASD is recognized as a neurobiological condition with a strong genetic component. Twin studies, for example, reported high concordance in diagnoses of monozygotic twin pairs (73 to 93%) and lower concordance in dizygotic twin pairs (0 to 31%) and reported high heritability for ASD (Ronald & Hoekstra, 2011). Research investigating the brains of individuals with ASD with structural and functional imaging techniques revealed accelerated growth in head circumference of ASD brains during early childhood (Courchesne, Redcay, & Kennedy, 2004). This accelerated growth was found to reflect increases of cerebral gray and white matter in children with ASD in the age of six to 24 months (Courchesne et al., 2004). Accelerated growth in head circumference was confirmed by studying postmortem brain weights (DiChicco-Bloom et al., 2006). Postmortem studies additionally reported a variety of microscopic changes in the brains of individuals with ASD. The most consistent findings were decreased cerebellar Purkinje neurons and cerebral cortex dysgenesis (DiChicco-Bloom et al., 2006). Functional neuroimaging studies examined the neural systems involved in disturbed social interactions of individuals with ASD and reported reduced neural activity during the perception of facial expressions, joint attention, empathy, and social cognition in brain regions that normally govern these specific functions (DiChicco-Bloom et al., 2006). For example, individuals with ASD lack activation of fronto-temporal regions when deriving socially relevant information from visual stimuli as compared to normal controls (Baron-Cohen et al., 1999).

Electroencephalography (EEG) studies have revealed abnormal patterns of EEG activity in individuals with ASD as compared to normal controls. It seems that children with ASD show increased delta and theta power in frontal and central regions of the brain (Chan, Sze, & Cheung, 2007; Murias, Webb, Greenson, & Dawson, 2007; Pop-Jordanova, Zorcce, Demerdzieva, & Gucev, 2010). In addition, decreased alpha power was reported in children with ASD (Chan et al., 2007; Murias et al., 2007), as well as increased beta (Murias et al., 2007) and gamma power (Orekhowa et al., 2007). Although largely similar EEG abnormalities are seen in ADHD (Barry, Clarke, & Johnstone, 2003), the EEG patterns in ASD were suggested to be qualitatively different from EEG patterns in ADHD (Clarke, Barry, Irving, McCarthy, & Selikowitz, 2011). Another consistent finding of EEG studies concerns abnormal patterns of connectivity in children with ASD as compared to normal controls. That is, over-connectivity was reported within local, short-distance networks of the ASD brain, whereas long-distance brain areas of children with ASD showed under-connectivity (Wass, 2011). Abnormal EEG patterns in children with ASD were furthermore revealed by research investigating evoked response potentials (e.g. Gandal et al., 2010) and measures of EEG complexity (Bosl, Tierney, Tager-Flusberg, & Nelson, 2011). Epileptiform EEG abnormalities or paroxysmal EEG were repeatedly found in children with ASD, both in children with and without clinical epilepsy (Ekinci, Arman, Isik, Bez, & Berkem, 2010; Yasuhara, 2010). Finally, dysfunctions of the mirror neuron system were reflected in the EEGs of children with ASD (Dapretto et al., 2006; Oberman et al., 2005). Mirror neurons are motor neurons that fire when a person watches the actions of others. In children with ASD, mirror neurons are dysfunctional while observing others and attempting to imitate their emotional expressions. Although children with ASD are able to perform such tasks, they show no mirror neuron activity in the inferior frontal gyrus, an area that was inversely related to symptom severity in the social domain (Dapretto et al., 2006; Oberman et al., 2005).

1.1.2 Clinical characteristics of autism

Children and adolescents with ASD show limitations in all of the life domains that are relevant to children and adolescents, i.e., (1) learning and applying knowledge; (2) general tasks and demands; (3) communication; (4) mobility; (5) self-care; (6) domestic life; (7) interpersonal interactions and relationships; (8) major life areas; and (9) community, social, and civic life (ICF-CY, 2007). These limitations have profound impact on the levels of participation of children and adolescents with ASD. The limitations that are most typical to children and adolescents with ASD can be situated within the domains ‘communication’ and ‘interpersonal interactions and relationships’. Concerning ‘communication’, Loveland and Tunali-Kotoski (2005) described the qualitative abnormalities in understanding and expressing verbal and non-verbal messages of children and adolescents with ASD, such as their inability to direct attention by pointing and their tendency to repeat others’ or one’s own speech. In addition, they described that conversations with children with ASD often focus on limited topics that are solely of interest to the child and that their speech may be pedantic and formal in situations where another style would be more appropriate (Loveland & Tunali-Kotoski, 2005). Regarding the domain ‘interpersonal interactions...
and relationships, children and adolescents with ASD have limited capacity to engage in relationships and they often do not understand the principles of reciprocity and sharing of interests that are inherent in friendship. Furthermore, they do not adequately use eye contact and have difficulties in reading social cues of their conversation partners (Van Engeland & Buitelaar, 2008).

1.1.3 Cognitive theories of autism

The clinical characteristics of children and adolescents with ASD are based on impairments in a variety of cognitive functions. Three different theories have been proposed to explain these cognitive dysfunctions, which are 'theory of mind deficit', 'executive dysfunctions', and 'weak central coherence' (Hill & Frith, 2003). Theory of mind has been defined as the ability to understand the minds of others. Individuals with ASD show deficits in understanding intentions, thoughts, and actions of others (Colle, Baron-Cohen, & Hill, 2007). Central coherence refers to the tendency to process incoming information in its context for higher level meaning. Children and adolescents with ASD are believed to have weak central coherence, which might explain their tendency to focus on details instead of on whole objects or situations (Happé, 1997). Executive dysfunctioning is a widely accepted cognitive explanation for many of the limitations of individuals with ASD. Deficits in executive functions such as planning, impulse control, working memory, and flexibility might result in rigid and pervasive behavior, preferences for routine behavior, and problems in daily life management (Hill, 2004).

1.1.4 Treatments for children with autism: evidence based versus controversial

There is general agreement on the efficacy of one type of treatment for children with ASD. This type of treatment is based on applied behavior analysis (ABA; Matson & Smith, 2008; Peters-Scheffer, Didden, Korzilius, & Sturmey, 2011). ABA is a method that uses behavior modification techniques to teach skills and to unlearn unwanted behavior in intensive one-to-one therapy sessions. Lovaas (1987) was the first to show the positive effects of ABA based training in young children with ASD. High rates of aggressive and self-stimulatory behaviors were reduced by behavior modification techniques such as ignoring, time-out, and shaping of socially acceptable behavior. Positive behavior such as appropriate toy play, verbal requests, and interactive play with peers were taught by using reinforcement. The children who participated in Lovaas’ ABA based training displayed an average improvement in IQ score of 20 points, as compared to children in the control group who received no such behavior modification program. Although Lovaas’ study received many critical comments, the results of this first study have been replicated numerous times in well designed studies (see for a meta-analysis Peters-Scheffer et al., 2011).

In the past years, dozens of other treatments have been offered to children and adolescents with ASD and their parents. Using the Google search engine to perform an internet search (search terms ‘autism’ and ‘treatment’) resulted in more than 60 different types of treatment, such as dolphin therapy, music therapy, and the use of fish oil, among other things. These treatments were all proposed as efficacious for the treatment for children with ASD. However, many of these treatments can be labeled as controversial for several reasons. As Jacobson, Foxx, and Mulick (2005) have postulated: “Treatments or therapies may be … controversial because (a) their underlying theoretical (or at least stated) rationales are baseless, or require assumptions of their effectiveness; (b) there is little or no unambiguous evidence of their benefits; (c) the research underlying their use does not meet conventional standards of quality or specificity; or (d) there are much simpler and better verified explanations for apparent, superficial effects of their use.” (Jacobson et al., 2005, p. xiv).

Despite the lack of scientific evidence, many controversial treatments are popular and have been preferred over evidence based approaches. Vyse (2005, pp. 10-12) suggests that this popularity arises if: (1) the effectiveness of available therapies is incomplete or (2) the best available treatment is onerous or distasteful for parent or client. These two conditions are also relevant for the popularity of controversial treatments for clients with ASD, since ABA based treatments do not entirely take away the symptoms of ASD and since ABA based treatments are expensive, demanding to administer, and take years to complete. In addition, Vyse described that controversial treatments are popular if: (3) the controversial treatment is supported by ideology or (4) the controversial treatment is promoted by proprietary professional groups. Regarding ideology, for example the belief in beneficial effects of nutrition has instigated the popularity of gluten-free diets. An example of a treatment for ASD that is promoted by professional groups despite the absence of scientific evidence is sensory integration therapy.
1.2 Neurofeedback

Neurofeedback was recently defined by the International Society for Neurofeedback and Research as follows: "Neurofeedback, also known as EEG-biofeedback, is a process in which sensors are placed on the scalp and devices are used to monitor and provide moment-to-moment information that is fed back to the individual about his or her physiological brain activity for purposes of improving brain functioning" (Hammond et al., 2011). Figure 1 illustrates the set up of a neurofeedback session in clinical practice. Detailed information about the application of neurofeedback in clinical practices can be found in chapter two of this dissertation.

1.2.1 Origin of neurofeedback

The origin of neurofeedback goes back to the 1960s when Joseph Kamiya successfully trained human individuals to control alpha waves. Alpha waves are oscillations in the 8 to 12 Hz frequency range that are predominantly generated in occipital and parietal lobes and can be recorded during wakeful relaxation with eyes closed. In the experiment by Kamiya, participants were instructed to indicate whether they thought they were 'in alpha', i.e., whether their brain produced alpha as the dominant frequency, each time a tone sounded. Initially the participants answered correct in about fifty percent of the trials. After repeatedly receiving feedback on whether the
1.2.2 Neurofeedback in the Netherlands

Neurofeedback was moved to Europe in 1997, when the American experts on neurofeedback visited the first meeting of the Biofeedback Foundation of Europe (BFE) in Davos, Switzerland. This is where Dutch psychologists were first introduced to neurofeedback and became enthusiastic about it. After visiting national and international conferences and workshops about neurofeedback, they started to apply neurofeedback in clinical practices in the Netherlands. Other therapists followed soon. Currently there are about 200 practices in the Netherlands (Mulder, 2010). At the same time, neurofeedback therapists have united themselves in professional organizations such as the neurofeedback section of the Nederlands Instituut van Psychologen [Dutch Association of Psychologists] (NIP). Since the year 2000, this neurofeedback section aims to inform psychologists, clients, and health care insurers in the Netherlands about neurofeedback and to stimulate research investigating its efficacy. In order to enlarge the quality of neurofeedback in the Netherlands, the neurofeedback section of the NIP set up a register for approved neurofeedback therapists. In order to be registered a minimum of theoretical knowledge, practical skills, and hours of supervision is required, in accordance with the criteria of international organizations, i.e., the Biofeedback Certification International Alliance (BCIA), the Association for Applied Psychophysiology and Biofeedback (AAPB), the International Society for Neurofeedback and Research (ISNR), and the European Society of Applied Neuroscience (SAN).

1.3 Research findings on neurofeedback in autism and critical comments

After an intermezzo about neurofeedback and its history, the discussion about neurofeedback is now further illustrated by earlier research projects and their critics. At the start of the research project that resulted in this dissertation, there were four studies published in international, scientific journals that had investigated the effects of neurofeedback in children and adolescents with ASD (Coben & Padolsky, 2007; Jarusiewicz, 2002; Scolnick, 2005; Sichel, Fehmi, & Goldstein, 1995). These studies were generally consistent in their findings considering the effects of neurofeedback on symptoms of ASD, cognitive functions, and EEG activity.
many clients are enthusiastic, researchers are questioning the efficacy of neurofeedback (Van der Bles, 2007). Subsequently, Huitema and Eling (2008) expressed their doubts on the scientific evidence for the application of neurofeedback in the Dutch Tijdschrift voor Neuropsychologie [Journal of Neuropsychology]. They pointed to the fact that neurofeedback in the Netherlands is mainly practiced and promoted by commercial organizations who might have conflicts of interest. Furthermore, they concluded that studies that investigated the effects of neurofeedback in diverse clinical populations had methodological shortcomings and therefore their conclusions may not be reliable. In that same journal issue, de Hen and Geurts (2008) criticized the use of neurofeedback as a treatment for children with ADHD. They concluded that the observed effects in attention, impulsivity, and hyperactivity after neurofeedback training might also have been caused by the cognitive training provided during neurofeedback, the reward frequency or the intensive contact between client and therapist. Finally, the working mechanism of neurofeedback was discussed in De Psycholoog [The Psychologist] (Eling & Maes, 2009). The authors discussed whether operant conditioning of physiological processes like EEG activity is possible, since most of these processes occur unconsciously. They suggested that neurofeedback training might result in changes in behavior as a result of, for example, relaxation and that changes in EEG activity are only consequences of these behavioral changes.

### 1.4 Consequences of critical comments on neurofeedback in the Netherlands

In 2008, the Dutch College voor Zorgverzekeringen [Health Care Insurers Board] (CVZ) concluded that "On the basis of the available scientific literature, the application of neurofeedback in the treatment of ADHD and epilepsy does not meet the scientific and practical requirements as meant in article 2.1, subsection 2 of the Health Insurance Act. The same goes for the application of neurofeedback to anxiety disorders, autism/autism spectrum disorders, tinnitus, and other psychological problems (Coben & Padolsky, 2007; Jarusiewicz, 2002; Scolnick, 2005; Sichel et al., 1995), whereas children in the control groups did not (Coben & Padolsky, 2007; Jarusiewicz, 2002). In addition, improvements in self-esteem, empathy, and flexibility were reported after neurofeedback, as well as reductions of anxiety, temper tantrums, and mood changes (Scolnick, 2005). Neurofeedback was also demonstrated to have positive effects on the cognitive functions of children with ASD. That is, Coben and Padolsky (2007) reported that neurofeedback resulted in significantly improved executive functions, visual perceptual functions, and language skills. Finally, it was reported that training to decrease theta power and to increase low beta power resulted in structural changes in the EEG (Scolnick, 2005; Sichel et al., 1995). That is, in both studies the previously elevated theta to beta ratios were reduced after neurofeedback training, i.e., changed in the direction of normality.

Although these previous studies provided support for the effectiveness of neurofeedback in clinical practice, there are still doubts about the scientific evidence of neurofeedback. That is, the previous studies investigating the effects of neurofeedback in ASD are of low methodological quality. The conclusions of these studies were based on a single case study (Sichel et al., 1995), a description of five cases (Scolnick, 2005), and two non-randomized controlled group studies (Coben & Padolsky, 2007; Jarusiewicz, 2002), whereas at least two independent studies comparing neurofeedback to a credible sham therapy, a pill, or a bona fide treatment are needed for labeling a treatment as being efficacious and specific (APA, 1995). Next, the positive effects on the children’s autistic behavior were based on parent reports in all studies. These parents may have been inclined towards a positivity bias matching their expectations of the treatment and the investments of their child and of themselves, which involves two or three weekly visits to a clinic. Another critical comment on neurofeedback is that the outcomes of previous studies may not be a result of neurofeedback per se, but could reflect unspecific effects of neurofeedback, i.e., effects of the implicit training of attention and the intensive one-to-one contact with the therapist during neurofeedback sessions (Gevensleben et al., 2009; Heinrich, Gevensleben, & Strehl, 2007).

Since neurofeedback arrived in the Netherlands, multiple critical comments have been written about this new form of treatment in the Dutch media. In 2007, the Dutch newspaper Trouw published an article about neurofeedback, concluding that although
or physical disorders" (CVZ, 2008). In this citation, the CVZ refers to the Health Insurance Act written by Mr. Hoogervorst, former Minister of Health, Welfare, and Sports (Staat der Nederlanden, 2005), where it was stated that criteria for services to be reimbursed by health care insurers are defined by "current scientific and practical requirements". As a consequence of the controversial character of neurofeedback, the CVZ decided that "Hence, neurofeedback is not recognized as one of the services to be reimbursed in the framework of the health insurance legislation" (CVZ, 2008). In response to the request of the NIP to revise this decision taking into account three recent scientific studies on neurofeedback and ADHD, a reassessment concerning the application of neurofeedback in ADHD was done in 2009. This reassessment confirmed the former conclusions of the CVZ regarding the lack of scientific evidence for the efficacy of neurofeedback in ADHD as follows: "After studying this literature, the CVZ concludes that with respect to neurofeedback as a treatment for children with ADHD, there are insufficient reasons to revise the decision that was taken in 2008 with regard to neurofeedback for children with ADHD". As a result, neurofeedback was added to a list of 40 other therapies for children with ASD that are not reimbursed by most of the health care insurers in the Netherlands (CVZ, 2010). As the author of this dissertation I understand the perspective of the CVZ regarding the controversial status of neurofeedback and I recognize the urgent need for scientific research on the efficacy of neurofeedback for children and adolescents with ASD.

1.5 The current dissertation: aim and outline

1.5.1 Aim of the dissertation

The aim of this dissertation was to investigate the efficacy of neurofeedback treatment for children and adolescents with ASD. We focused on the efficacy of neurofeedback on three levels: symptoms of ASD, executive functions, and EEG activity.

1.5.2 Outline of the dissertation

Chapter two provides a detailed description of neurofeedback treatment as it is used in clinical practices. The chapter starts with a description of what a neurofeedback session entails, what the client's task is during a session, and how frequency components and scalp locations that are used during neurofeedback training are chosen. Furthermore, the cognitive and neuronal mechanisms that might play a role in neurofeedback are explained.

Chapter three describes the results of a first pilot study investigating the effects of neurofeedback in seven 8 to 12 year old children with PDD-NOS. The study was conducted in a private practice for neurofeedback, i.e., Neurofeedback Nijmegen. The treatment plan that was used was adopted from neurofeedback treatment of individuals with ADHD. Before and after treatment, the children's symptoms of ASD were rated by their parents, their performance on a range of executive function tasks was measured, and 19-channel EEGs were recorded. These measures were compared with the same measures taken of a matched waiting list group in order to find the effects of the treatment.

The long term maintenance of the effects of neurofeedback found in the pilot study is described in chapter four. That is, symptoms of ASD and executive functions of the participants of the pilot study who had neurofeedback training were additionally assessed twelve months after neurofeedback training ended. These measures were compared with the measures of the initial study, i.e., the measures taken before treatment started and immediately after treatment ended.

Chapter five describes the results of a randomized controlled study, in which 20 8 to 12 year old students with ASD from PI-school Entréa, Nijmegen, and Stichting Maashorst, Reek, were randomly allocated to a neurofeedback or a waiting list group. Treatment plans in this study were individualized and based on the initial 19-channel EEG recording of each participant. All neurofeedback sessions were provided at the own school of the participants, thereby reducing the therapy load for both the participants and their parents. In addition to parent ratings of symptoms of ASD, teachers filled out questionnaires rating the symptoms of ASD of the participants. Furthermore, executive functions and EEG activity were measured in all participants before and after treatment and in a six months follow-up.

Chapter six describes the results of a randomized controlled study with six
months follow-up that controlled for treatment expectancy of participants and for unspecific effects of neurofeedback training, i.e., the implicit training of attention and the intensive one-to-one contact with the therapist during neurofeedback. Thirty-eight 12 to 18 year old students with ASD of VSO Mariëndaal, Arnhem, were randomized over three groups: a neurofeedback (or EEG-biofeedback) group, a skin conductance (SC) -biofeedback group, and a waiting list group. Participants in the neurofeedback and the SC-biofeedback group received similar biofeedback sessions in which feedback was provided of the EEG (neurofeedback group) or SC (SC-biofeedback group). Participants, parents, and teachers were blinded for treatment allocation to EEG- or SC-biofeedback groups. All participants were assessed on symptoms of ASD, executive functions, and 19-channel EEG before and after treatment and after six months.

Chapter seven provides a general discussion that reviews the main findings of the above mentioned studies. Implications for scientific research and clinical practice are discussed and I will comment on the status of neurofeedback as a treatment for children and adolescents with ASD.

Chapter 2
What is Neurofeedback?

Neurofeedback is defined as “a process in which sensors are placed on the scalp and devices are used to monitor and provide moment-to-moment information that is fed back to the individual about his or her physiological brain activity for purposes of improving brain functioning” (Hammond et al., 2011). This chapter provides a detailed description of neurofeedback as it is often used in clinical practice. In addition, the cognitive and neuronal mechanisms that may be involved in neurofeedback are discussed.

2.1 The practice of neurofeedback

In a typical neurofeedback session, a client sits in front of a computer screen while his or her electroencephalographic (EEG) activity is recorded by one or more electrodes. Figure 1 shows an example of the set up of a neurofeedback session in which a Nexus-4 device (MindMedia, the Netherlands) was used.

Before a client can start with neurofeedback treatment, a treatment plan needs to be determined specifying the frequency component (or components) that is to be altered and the exact locations on the scalp at which training will take place. In the field of neurofeedback, such a treatment plan is often referred to as a treatment protocol. The frequency components and locations for training of such a treatment plan are typically determined by comparing a 19-channel EEG recording of the client with a normative database containing the EEG spectra of typically developing individuals of the same age.

Typically, an EEG recording is collected using a stretchable electrode cap that contains multiple electrodes to map the distribution of brain waves over multiple sites on the scalp. Each of the electrodes is connected to the client’s scalp using a conductive electro gel. Figure 2 shows an example of the experimental setup of an EEG assessment using the Mitsar EEG 201 System (Mitsar Medical Diagnostic Equipment, Russia). Following the correct preparation of all electrodes in the cap, a client’s EEG is recorded for several minutes in one or more conditions. The conditions eyes opened and eyes closed are usually included in the EEG assessment. In these conditions, the client is instructed to sit still on a comfortable chair while keeping the eyes opened or closed. Next to the recording of EEG in these rest conditions, the EEG may be recorded in task conditions like reading or math.

Raw EEG recordings are analyzed to construct a quantitative EEG (QEEG) containing the absolute and relative power spectra of the client’s EEG per electrode. Relative power expresses the ratio of power in a particular frequency band relative to the total power across frequencies. The client’s absolute and relative QEEG data may be subsequently compared with a normative database containing EEG data of healthy individuals of the same age to estimate possible deviations from normality. Two databases that are often used are NxLink designed by John, Prischep, and Easton (NxLink, Ltd.) and NeuroGuide, designed by Thatcher (Applied Neuroscience, Inc.). These databases produce color-coded maps and data in digital form, providing information on a client’s deviations from the norm group. The output of such a database comparison may be used to guide the selection of the frequency components and the location for the subsequent neurofeedback treatment.

Figure 3 shows part of the output of the NeuroGuide database revealed by comparing the QEEG of a 15-year old girl with Asperger disorder to this database. The maps indicate that, relative to the database, power in the theta range over central and frontal electrodes exceeds the population mean, i.e., a population of girls of the same age without an autism spectrum disorder (ASD), by more than one and a half standard deviations. As a consequence, neurofeedback might, in this case, target the inhibition of 3 to 7 Hz power over fronto-central scalp regions.
In addition to the method of using a database to determine possible frequency components and locations for training, a neurofeedback treatment plan may also be specified by visual inspection of the raw 19-channel EEG recording of the client. This procedure requires extensive knowledge of the raw EEG. A raw EEG signal is composed of separate brain waves with different frequencies and amplitudes, often arranged in separate frequency bands, i.e., delta (1-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz), and gamma (above 30 Hz). These frequency bands can be identified in the raw EEG on the basis of the unique waveform patterns of each frequency band. Figure 4 shows an example of raw EEG data of a 10-year old boy with PDD-NOS in WinEEG software (Mitsar Medical Diagnostic Equipment, Russia). This example includes raw EEG activity measured by electrodes across several frontal sites. Visual inspection of this EEG fragment reveals clear theta activity at electrode Fz, which is indicated by the arrow.

Instead of using individualized treatment plans wherein the frequency component and treatment location are determined on the basis of an individual’s EEG characteristics, neurofeedback treatment may also be guided by predefined treatment protocols. Probably the best known protocol is the theta/beta protocol that is used often in the treatment of ADHD. This protocol prescribes the inhibition of theta power while beta power is enhanced at frontal or central, midline regions (Monastra et al., 2005). This protocol was developed after the finding that 85 to 90% of the individuals with ADHD have elevated theta power and reduced beta power over frontal and central, midline cortical regions of the brain (Monastra et al., 2005). Although the theta/beta protocol was originally applied to individuals with ADHD, this neurofeedback protocol has also been applied successfully to individuals with ASD (Jarusiewicz, 2002; Scolnick, 2005; Sichel, Fehmi, & Goldstein, 1995; Thompson, Thompson, & Reid, 2010).

After a treatment plan has been established, the actual neurofeedback treatment may commence. In each neurofeedback session, an electrode needs to be attached to the selected treatment location by using conductive electrode paste. In addition, reference and ground electrodes are to be attached. Often the reference electrode is located somewhere on the head at a location where little or none of the frequency component that is selected for treatment is found, e.g. at an earlobe or at the bone behind one of the ears, i.e., the mastoid. The ground electrode is typically placed somewhere on the body, e.g. at the mastoid. Figure 5 provides an example of electrode configuration during a typical neurofeedback session, showing an EEG electrode that is used for feedback attached to the scalp and a reference electrode attached to the left mastoid.

During a neurofeedback session, information about the level of the EEG frequency component that was selected for training is fed back to the client. Although in principle feedback may take any form or modality, many neurofeedback therapists use a bar graph on the computer screen to reflect the ongoing changes in EEG power over time. Figure 6 shows an example of such a computer screen created with BioTrace software (MindMedia, the Netherlands). The larger the amplitude of the recorded EEG
activity is, the higher the bar graph on the computer screen will be presented. In this way, the bar graph informs the client about the amplitude of his or her EEG activity, almost immediately after it occurs. A criterion line is drawn together with the bar graph representing a concrete goal for the trainee. That is, depending on the treatment plan (i.e., decrease or increase the activation in a particular frequency range), the client may be directed at keeping the bar graph amplitude below or above the criterion line. At first, meeting the criterion is accidental, but over time participants may learn to maintain the bar graph below or above the indicated criterion.

Whenever the client manages to keep the bar graph below or above the criterion line for a minimal amount of time, visual and auditory rewards are provided, often in the form of a film clip presented next to the bar graph. Film clips are usually presented with corresponding music or sound and are chosen according to the age and interests of the client. Clients can also be rewarded by a counter that counts the number of seconds the criterion is met. If desired, the bar graph can change color when the EEG activity is not within the desired range or the film clip can shrink to remove the reward. Some clients with ASD show resistance to the combination of many different rewards, such as a shrinking film clip, music, a counter, and a color changing bar graph. Therefore, the exact form in which the reward is presented should reflect the preferences of the client.

A typical neurofeedback session consists of training and rest intervals. During training intervals, the client's goal is to move the bar graph below or above a criterion line. These training intervals are alternated with rest intervals, in which the client can relax for a short time. The length of the training intervals depends largely on the attention span of the client. Clients with a larger attention span may be presented with longer training intervals. A training interval of three minutes was chosen often in the treatment of individuals with ASD. If necessary, the length of training intervals may be adapted during the course of the training. Training and rest intervals are alternated manually or by predefined scripts. Clients with a high need for structure, like many clients with ASD, might benefit from the accuracy that is provided by such a script.

Neurofeedback training is usually provided in psychological practices and typically takes place twice or thrice per week. Some neurofeedback therapists provide home training programs. The number of sessions is determined by the specific complaints of the client and on the progression of the client during the training. Neurofeedback for individuals with ASD generally includes 40 to 60 sessions (Thompson et al., 2010).

2.2 Cognitive and neuronal mechanisms underlying neurofeedback

Although the number of publications about the effects of neurofeedback is growing, little has been written about the cognitive and neuronal mechanisms underlying
neurofeedback. In the present section we present an overview of the cognitive mechanisms that might permit the technique of neurofeedback to result into altered EEG activity and the possible neuronal mechanisms that are involved in neurofeedback.

2.2.1 Cognitive mechanisms underlying neurofeedback
Operant conditioning involves a process of behavior modification whereby the consequences of an action determine the likelihood that the same action will be expressed in the future. Positively reinforced actions will be performed more frequently, whereas negatively reinforced behavior will fade out (Gazzaniga & Heatherton, 2003). Closely related to operant conditioning is Thorndike’s law of effect, stating that any behavior that leads to a satisfying state of affairs is more likely to occur again and behavior that leads to an annoying state of affairs is less likely to occur again (Thorndike, 1933). The principles of operant conditioning are considered to be a major factor in the capacity of neurofeedback to effectuate changes in EEG. During a neurofeedback session, a client is rewarded each time he or she manages to move the bar graph on the computer screen below or above the criterion line. That is, a film clip turns on, music starts playing or a counter starts running. Assuming that these rewards are satisfying to the client, chances increase that the patterns of EEG activity that preceded the reward are generated in the future. Vice-versa, brain activity that produces no rewarding effects will tend to fade away.

In contrast to operant conditioning which is generally considered to be a relatively passive process on which the trainee has little or no direct influence, an active process within neurofeedback treatment is self-regulation, which refers to voluntary control of the EEG signal (Hardt & Kamiya, 1976; Kotchoubey et al., 2002). It has been reported that some clients manage to develop deliberate control over their EEG activity, allowing them to increase or decrease the height of the bar graph in a voluntary manner. Kamiya (1968) was the first to provide evidence for deliberate control over EEG activity. In his study, participants were first trained to recognize the state of alpha and some of them subsequently managed to produce these alpha waves on instruction. Nowadays, the deliberate control over EEG activity is used frequently in clinical settings where patients with neuromuscular impairments or locked-in syndrome use brain computer interfaces to control external devices. Birbaumer and colleagues (1999), for example, showed that paralyzed patients who completely lack muscular control can learn to communicate with their environment by using an electronic spelling device that is controlled by EEG activity. By intentionally activating EEG activity in a specific frequency range, a computer cursor is controlled to point out and select different letters of the alphabet to construct a message.

The functional mechanisms that are used to self-regulate electrical activity of the brain may not be so different from functional mechanisms that we use for controlling our body. A dominant theory in motor control is the Ideomotor Theory (Greenwald, 1970) which states that our actions are primarily controlled at the level of their sensory effects. For instance, when grasping a cup for drinking, the motor system is attempting to match the anticipated visual and tactile consequences of the grasping action with an appropriate motor command. In the development of new movement repertoire, e.g. in case children are learning how to drink from a cup without spilling its contents, internal models that map the relation between sensory consequences and action output need to be formed through experience. The ability to control one’s own brain waves may well operate on similar principles, whereby the client’s brain, over time, establishes the relationship between EEG activity and their sensory consequences, allowing an internal model to form and control the sensory effects that are provided by the neurofeedback. A simple experiment provides a convincing demonstration of this idea. Most people are unable to wiggle their ears but may easily learn to do so when the signal of the muscles controlling their ears is made explicit to them (Bair, 1901). You can try this yourself by putting your fingers behind your ears on the tendons that are controlling their movement. The direct sensory effect will make it much easier to establish control. In a sense, neurofeedback is not different from this example. All it does is make unconscious biological signals explicit to the client so that he or she may learn to control these signals in a deliberate manner.

2.2.2 Neuronal mechanisms underlying neurofeedback
The exact cortical and subcortical mechanisms of the brain supporting neurofeedback training have received little or no attention so far, as have its neural effects. There is one fMRI study that investigated the effects of neurofeedback on neural substrates in children with ADHD (Beauregard & Levesque, 2006). Fifteen children were trained to reduce 4 to 7 Hz power at Cz while enhancing power in the 12 to 15 Hz and 15 to 18 Hz frequency ranges. After neurofeedback training participants showed significant loci
of activation in brain systems mediating selective attention and response inhibition compared to the control group that had no neurofeedback training. The results of this study suggest that neurofeedback has the capacity to functionally normalize brain systems in children with ADHD.

Sterman theorized on possible neuronal mechanisms underlying the effects of neurofeedback targeting SMR (Sterman, 1996; Sterman & Egner, 2006). SMR is a 12 to 15 Hz rhythm that is found maximal over the sensorimotor cortex of the brain. SMR was found positively associated with control over excitation in the thalamocortical somatosensory and somatomotor pathways of the brain (Sterman, 1996; Sterman & Egner, 2006). By repeatedly producing increased amounts of SMR, postsynaptic cells may become more sensitive and consequently the probability of future activation of these cells may be increased. By increasing thresholds for excitation, neurofeedback may have beneficial effects on severity and frequency of seizures in clients with epilepsy. In ADHD, similarly increased thresholds for excitation are believed to be responsible for reductions in cortical and thalamocortical hyper-excitability and accompanying reductions in impulsive tendencies.

The aim of neurofeedback treatment in children and adolescents with ASD has been on normalizing abnormalities in EEG power spectra (Jarusiewicz, 2002; Scolnick, 2005; Sichel et al., 1995), connectivity (Cohen & Padolsky, 2007), and the mirror neuron system (Pineda et al., 2008), because EEG studies in individuals with ASD have revealed abnormal patterns of EEG activity in each of these three domains. With respect to EEG power spectra, increased delta and theta power in frontal and central regions of the brain were reported (Chan, Sze, & Cheung, 2007; Murias, Webb, Greenson, & Dawson, 2007; Pop-Jordanova, Zorcec, Demerdzicheva, & Gucev, 2010). In addition, decreased alpha power was reported (Chan et al., 2007; Murias et al., 2007), as well as increased beta (Murias et al., 2007) and gamma power (Orekhova et al., 2007). A second consistent finding of EEG studies concerns abnormal patterns of connectivity in children with ASD as compared to normal controls. That is, over-connectivity was reported within local, short-distance networks of the ASD brain, whereas long-distance brain areas of children with ASD showed under-connectivity (Wass, 2011). Finally, dysfunctions of the mirror neuron system were reflected in the EEGs of children with ASD (Dapretto et al., 2006; Oberman et al., 2005). Mirror neurons are motor neurons that fire when a person watches the actions of others. In children with ASD, mirror neurons are dysfunctional while observing others and attempting to imitate their emotional expressions. Although children with ASD are able to perform such tasks, they show no mirror neuron activity in the inferior frontal gyrus, an area that was inversely related to symptom severity in the social domain (Dapretto et al., 2006; Oberman et al., 2005). Even though neurofeedback usually focuses on one of these three domains, there is no research demonstrating the actual neuronal consequences of these forms of neurofeedback treatment in ASD.
Chapter 3

Neurofeedback Improves Executive Functioning in Children with Autism Spectrum Disorders

Abstract

Seven children diagnosed with autism spectrum disorders (ASD) received a neurofeedback treatment that aimed to improve their level of executive control. Neurofeedback successfully reduced children's heightened theta/beta ratio by inhibiting theta activation and enhancing beta activation over sessions. Following treatment children's executive capacities were found to have improved greatly relative to pre-treatment assessment on a range of executive function tasks. Additional improvements were found in children's social, communicative, and typical behavior, relative to a waiting list control group. These findings suggest that a basic executive function impairment in ASD can be alleviated through specific neurofeedback treatment. Possible neural mechanisms that may underlie neurofeedback mediated improvement in executive functioning in children with ASD are discussed.

3.1 Introduction

Neurofeedback refers to a form of operant conditioning of electrical brain activity, in which desirable brain activity is enhanced and undesirable brain activity is inhibited. Neurofeedback is believed to elicit growth and changes at cellular levels of the brain, which in turn support brain functioning and behavioral cognitive performance (Demos, 2005). In the domain of intervention, neurofeedback training is useful in treatment of different disorders in adults and children. Positive effects of neurofeedback in adults have been found for attention deficit hyperactivity disorder (ADHD) (Kropotov et al., 2005), traumatic brain injury (Thornton, 2000), epilepsy (Sterman, 2000), depression (Hammond, 2003), migraine (Kropp, Siniatchkin, & Gerber, 2002), addiction (Trudeau, 2005), anxiety disorders (Moore, 2000), and general cognitive performance (Vernon et al., 2003).

Less is known about the effects of neurofeedback in children. In children, research on the effects of neurofeedback is mainly carried out in the area of ADHD (Fuchs et al., 2003; Monastra et al., 2005; Vernon, Frick, & Gruzelier, 2004), but positive effects of neurofeedback have also been found for children with migraine (Kropp et al., 2002) and learning disorders (Fernandez et al., 2003; Thornton & Carmody, 2005). ADHD is typically characterized by a heightened ratio between theta (4-8 Hz) and beta (12-21 Hz) activity in the ongoing electroencephalogram (EEG) during rest. Neurofeedback protocols that have aimed at inhibiting theta activity while enhancing beta activity have led to successful alleviation of symptoms associated with ADHD such as deficits in sustained attention, impulsivity, and hyperactivity (reviews in Butnik, 2005; Fox, Tharp, & Fox, 2005).

Several studies suggest that neurofeedback protocols that have been successful for the treatment of ADHD may also be efficacious for treating children with autism related deficits. Sichel, Fehmi, and Goldstein (1995) reported about Frankie, a 8,5 year old boy with a mild form of autism spectrum disorder (ASD) and attention impairments suggesting ADHD. Frankie's 19-channel quantitative EEG (QEEG) demonstrated theta (4-8 Hz) to beta (13-21 Hz) ratios of 3.59 (Cz), 3.40 (C3), 3.03 (C4), 3.98 (Pz), 4.07 (P3), 3.63 (P4), and 3.02 (Fz). After 31 neurofeedback sessions aimed at inhibiting theta (4-8 Hz) and enhancing low beta (12-15 Hz), his mother reported positive changes in all the diagnostic criteria defining ASD in DSM-III-R (e.g. attending and reacting to others, imaginative play, seeking comfort, more talking, and...
Further support for a relation between theta/beta power and ASD was provided by Jarusiewicz (2002) who conducted a group study investigating effects of neurofeedback in 12 children with ASD, compared with matched controls. The main protocol aimed at inhibiting theta (2-7 Hz) and enhancing sensory motor rhythm (SMR) activity (10-13 Hz) over the right motor area. Results indicated a substantial decline in symptoms of ASD (26% as compared to 3% for the controls) as reflected by the Autism Treatment Evaluation Checklist (ATEC). Parent reports furthermore indicated considerable improvements on socialization, vocalization, school work, anxiety, tantrums, and sleep, whereas no or minimal changes were found for the control group.

More recently Scolnik (2005) conducted a neurofeedback study with five children diagnosed with Asperger disorder (a subclass of ASD), each with unique behavioral problems, i.e., poor social skills, lack of empathy, and inflexibility, coupled with abnormal high theta/beta ratios varying from 2.19 to 6.89. Each child’s protocol was determined on the basis of their individual QEEG and consisted of variations on the theme of enhancing 12-15 Hz in the lower beta range while inhibiting slower 4-10 Hz activity in the theta and low alpha band. After 24 sessions of neurofeedback, parents and teachers reported improvements in behavior, i.e., less anxiety, more flexibility, higher self-esteem, more empathy, improvement in frustration tolerance, increased social interaction, and fewer severe mood changes. Furthermore, in two of the five children, theta/beta ratios changed into a positive direction.

The above studies suggest that neurofeedback protocols that inhibit theta and enhance beta and SMR may hold particular value for the treatment of children with ASD. We hypothesize that the reason for the efficacy of neurofeedback protocols that inhibit theta and enhance beta lies primarily in the enhancement of activation in the anterior cingulate cortex (ACC). The ACC is one of the main generators of theta (Meltzer, Negishi, Mayes, & Constable, 2007; Onton, Delorme, & Makeig, 2005; Tsujimoto, Shimazu, & Isomura, 2006) and is well known for its role in regulating cognitive and emotional processes in the brain contributing to cognitive control and executive function (review in Bush, Luu, & Posner, 2000). Neuroimaging studies investigating the neural basis of ADHD and ASD have reported hypo-activation and functional under-connectivity of the ACC (Barkley, 1997). Furthermore, combined EEG-functional magnetic resonance imaging (fMRI) studies have indicated a negative relationship between theta power and blood oxygen level dependent (BOLD) signal in the ACC (Meltzer et al., 2007), in line with the hypothesis that theta activation in children with ASD is associated with under-activation of the ACC (Murius, Webb, Greensen, & Dawson, 2007).

Following the above reasoning we predict that down-regulation of theta activity intend to further our understanding of the possible (neural) mechanisms supporting treatment effects.

In order to optimize the neurofeedback treatment protocol for children with ASD and its rationale, further methodological improvement is necessary in the form of controlled studies, larger sample sizes, a more accurate description of sample characteristics, and collection of follow-up data. Another guiding principle should be the assessment of the clients’ satisfaction with the treatment and procedure to enhance the social validity of the approach. Social validity refers to the use of evaluative feedback from clients to guide program planning and evaluation (Schwartz & Baer, 1991). Social validity may be evaluated at three levels of treatment: goals, procedures, and outcomes (Wolf, 1978). In the current study we included the above guidelines and evaluative measures (cf. Heinrich, Gevensleben, & Strehl, 2007) to further validate the use of neurofeedback treatment for children with ASD.

In addition to the practical evaluation of neurofeedback treatment for children with ASD, the current study aims to contribute to understanding the cognitive and neural mechanisms that underlie neurofeedback related improvements in children with ASD. We hypothesize that the reason for the efficacy of neurofeedback protocols that inhibit theta and enhance beta lies primarily in the enhancement of activation in the anterior cingulate cortex (ACC). The ACC is one of the main generators of theta (Meltzer, Negishi, Mayes, & Constable, 2007; Onton, Delorme, & Makeig, 2005; Tsujimoto, Shimazu, & Isomura, 2006) and is well known for its role in regulating cognitive and emotional processes in the brain contributing to cognitive control and executive function (review in Bush, Luu, & Posner, 2000). Neuroimaging studies investigating the neural basis of ADHD and ASD have reported hypo-activation and functional under-connectivity of the ACC (Barkley, 1997). Furthermore, combined EEG-functional magnetic resonance imaging (fMRI) studies have indicated a negative relationship between theta power and blood oxygen level dependent (BOLD) signal in the ACC (Meltzer et al., 2007), in line with the hypothesis that theta activation in children with ASD is associated with under-activation of the ACC (Murius, Webb, Greensen, & Dawson, 2007).
should enhance activation of the ACC and executive control mechanisms of the brain, which should lead to more efficient behavior of children with ASD on tasks requiring executive function. To investigate the hypothesized relationship between theta and executive function, a group of children diagnosed with ASD were selected for neurofeedback training that inhibited theta activity while enhancing low beta activity, in accordance with the standard ADHD treatment protocol. A waiting list control group, also diagnosed with ASD, served as a baseline to determine treatment effects of neurofeedback on children's social, executive, and neurophysiological levels of functioning.

3.2 Method

3.2.1 Participants
Fourteen children with ASD (12 males; 2 females) with a mean age of 10.1 years (range 8 to 12 years) were recruited by an advertisement in a magazine for parents of children with ASD. Inclusion criteria were an IQ-score of 70 and above and the presence of ASD as diagnosed by a child psychiatrist or health care psychologist. All participants had the diagnosis pervasive developmental disorder – not otherwise specified (PDD-NOS). Each diagnosis was confirmed by a clinical psychologist and by results on the Children's Communication Checklist (CCC-2). Excluded were children using medication, children with a history of severe brain injury, and children with co-morbidity such as ADHD and epilepsy. The seven children who applied first were assigned to the intervention group. The control group included seven children who were recruited out of a larger group of children who applied later and were selected to match children of the intervention group on age, sex, and intelligence scores. Table 1 represents the demographic characteristics of the intervention and the control group. There were no significant differences between both groups with respect to the variables sex, mean age, total IQ, verbal IQ, and performal IQ. Children in the control group were invited for neurofeedback training after finishing the present study.

3.2.2 Procedure
A non-randomized pretest-posttest control group design with individual matching was used with follow-up measurements after three months. During a baseline period, all participants were pre-tested on QEEG and a range of executive functions tasks, and parents completed a communication checklist (CCC-2). After 40 sessions of neurofeedback, or comparable time interval for the waiting list control group, QEEG, executive functions skills, and communicative abilities were re-collected. During follow-up three months after ending neurofeedback sessions, again, QEEG, executive functions skills and communicative abilities were measured together with a questionnaire (Auto-R) to estimate behavioral improvements in children. For the intervention group, the follow-up measurement furthermore included a social validity questionnaire. The research design was authorized by an ethics committee for behavioral sciences.

An interview was conducted with the parents prior to the neurofeedback treatment to survey the anamneses of the child, family history, and current problems of the participant. Procedures and possible side effects were explained to all participants. All participants signed an informed consent. Pre and post-treatment measures took two hours for each participant to complete. Tasks for executive functioning were given to all participants in a fixed order, with the first five tasks before QEEG assessment and the rest after QEEG assessment. The CCC-2, the adapted Auto-R, and the social validity questionnaire were filled out by the parents at home.

Table 1.
Demographic characteristics of the Intervention Group (IG) and the Control Group (CG).

<table>
<thead>
<tr>
<th>Variable</th>
<th>IG (n=7)</th>
<th>CG (n=7)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>6/1</td>
<td>6/1</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>9.63 (1.53)</td>
<td>10.64 (1.41)</td>
<td>.220</td>
</tr>
<tr>
<td>Mean total IQ</td>
<td>92.50 (16.05)</td>
<td>93.83 (13.67)</td>
<td>.891</td>
</tr>
<tr>
<td>Mean verbal IQ</td>
<td>97.80 (18.38)</td>
<td>95.40 (18.15)</td>
<td>.841</td>
</tr>
<tr>
<td>Mean performal IQ</td>
<td>99.60 (25.77)</td>
<td>93.40 (9.71)</td>
<td>.628</td>
</tr>
</tbody>
</table>

Note. Standard deviations are in parentheses. 1Age range IG: 8-12, CG: 9-12, 2Total IQ range IG: 73-111, CG: 82-119, 3Verbal IQ range IG: 77-119, CG: 78-125, 4Performal IQ range IG: 73-134, CG: 81-108.
3.2.3 QEEG measurement
Children's QEEG was recorded and digitized with a TruScan 32 Acquisition EEG System (Deymed Diagnostic, USA). Data were acquired using a stretchable electrode cap embedded with 19 sensors at scalp locations Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2, according to the International 10/20 System (Jasper, 1958). A ground electrode was placed between Fp2 and F8 and two ear clips were used as reference electrodes (A1 and A2). Impedance was kept below 5 kΩ, with a maximum difference of 1 kΩ between electrodes. Data were collected for three minutes in eyes opened and eyes closed conditions.

3.2.4 Neurofeedback training
A portable NeXus-4 amplifier and recording system (Mindmedia, the Netherlands) was used for neurofeedback training and concurrent data collection. Ag/AgCl disposable snap-on sensors (MedCaT, the Netherlands) were applied to the patients' scalp at the locations C3 and C4.

Each participant in the intervention group visited a private practice twice a week until 40 sessions were completed. Training was carried out by a state licensed psychotherapist with extensive training in neurofeedback. During each session a protocol was carried out, which consisted of a baseline of three minutes, i.e., no feedback, followed by seven three-minute intervals of neurofeedback. Neurofeedback intervals were separated by one-minute rest intervals, in which the participant was instructed to sit still and relax, without receiving feedback. Neurofeedback training followed a standard ADHD training protocol (Heinrich et al., 2007 for review) aimed at reducing theta activity (4-7 Hz) while increasing activity in the low beta band (12-15 Hz) at C4 (reference at A1). The EEG recorded at location C4 was fed back to the patient in visual form. Theta and beta activity were visualized in separate bar graphs on the computer screen and participants were instructed to "try to move down the theta activity below the criterion line on the computer screen and to move up the beta activity above the criterion line, using the feedback to guide you". During intervals when specified amplitude conditions were met, subjects were rewarded by the continuation of a short movie that was selected to fit each child's individual interest and age. All movies were presented with audio. When subjects failed to maintain power within the required range, the movie and music would stop playing. Individual criteria were set to allow each participant to reach the reward.

3.2.5 Executive function tasks
According to Smidts (2003), executive functions are typically divided into separate subdomains, each including one or more executive function tasks.

**Attentional control**
Attentional control encompasses selective attention, visual as well as auditory, and response inhibition. Visual selective attention was measured by the Continuous Performance Test (CPT), a subtest of the neurocognitive test battery CNS Vital Signs (CNSVS). In the CPT, the participant has to respond to one particular character on the computer screen while ignoring other characters during five minutes. The score for visual selective attention is based on the amount of errors of the CPT (range 0 – 200). Selective attention for auditory stimuli was measured by the Test of Sustained Selected Attention (TOSSA; Kovács, 2005c). In the TOSSA, participants have to respond to sets of 3 beeps while ignoring sets of 2 or 4 beeps. Beeps are presented during eight minutes with variable speed. The test score reflects the percentage of good answers, calculated by dividing the number of hits by the total amount of items, times 100. Response inhibition is divided in a verbal and a motor variant. Verbal response inhibition was assessed by the Stroop test (Stroop, 1935). In this test, participants have to read aloud as soon as possible A) 100 words (green, red, yellow, and blue), B) the color of 100 colored rectangles, and C) the color of the ink of 100 written incongruent color names. The goal in part C is to pronounce the name of the color of the ink, while ignoring reading the word. The score on this test is represented by the interferential time (time C minus time B). Motor response inhibition was assessed with the response inhibition score (RIS; range 0 – 100) of the TOSSA, based on the number of commission errors.

**Cognitive flexibility**
Cognitive flexibility covers verbal memory and visual memory, set-shifting, concept generation, and feedback utilization. Verbal memory and visual memory were
assessed by the Verbal Memory Test (VBM) and the Visual Memory Test (VIM) of the CNSVS, respectively. In the VBM and the VIM, participants have to memorize words \((n=15, \text{VBM})\) and geometric figures \((n=15, \text{VIM})\) and later recognize them in a series of distracters \((n=15 \text{ for both tests})\). The sum of correct responses (maximum \(= \text{60}\)) was calculated to get a final score for verbal memory (maximum \(= \text{60}\)) and a final score for visual memory (maximum \(= \text{60}\)). Set-shifting was examined by the Trail Making Test (TMT; Reitan, 1956). In the TMT, participants have to switch between the numerical mode and the alphabetic mode by connecting 26 numbers and characters in the 1-A-2-B-3-C – order. A score on the TMT is comprised of the total time needed to finish the test, translated into an age related \(t\)-score (range \(20 – 75\)). Concept generation and feedback utilization were examined by the Milwaukee Card Sorting Test (MCST; Kovács, 2005a), a computerized version of the Wisconsin Card Sorting Test. The participant has to generate and apply a non-spoken rule for sorting cards \((n=60)\), based on feedback (e.g. ‘good’ or ‘fault’). These card sorting principles can be either color, shape or number and change after every 10 correct answers. An indicator for cognitive flexibility is the number of categories (range \(0 – 6\)) a child creates with 60 cards.

**Goal setting**

Goal setting was assessed by the Tower of London (TOL; Kovács, 2005b). Participants have to copy a construction of blocks and bars by moving three prearranged different colored blocks along three bars of different lengths. The score on the TOL is a percentage calculated by dividing the participants’ score by the maximum score, times 100.

**Speed and efficiency**

Speed and efficiency is measured by the Symbol Digit Coding (SDC) of the CNSVS. Participants have to code as many symbols as possible within two minutes, according to a set of eight symbol–digit pairings that are displayed continuously for reference on screen. A score for speed and efficiency is calculated by the number of correct responses minus the number of errors on the SDC.

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### 3.2.6 Questionnaires

**Children’s Communication Checklist**

The Children’s Communication Checklist (CCC-2; Geurts, 2007) was used to assess improvement in children’s language structure, pragmatics, and social interaction. Language structure includes the subscales speech production, syntax, semantics, and coherence. The domain of pragmatics consists of the subscales inappropriate initiation, stereotyped conversation, use of context, and non-verbal communication. The domain of social interaction includes the subscales social relations and interests. Response categories for each question are ‘never or less than once a week’, ‘at least once a week’, ‘once or twice a day’ or ‘more than twice a day or always’. An age-related standard score was calculated for each subscale and for the composed scales general communication (sum of scores on language structure and pragmatics) and pragmatics.

**Auto-R**

An adapted version of the Auto-R (Berckelaer-Onnes & Hoekman, 1991) was used to study improvement of children in the intervention group on social interaction, communication, and restricted, repetitive, and stereotyped patterns of behavior, interests, and activities. Eleven items of the Auto-R that were considered not relevant for the present study and five items that did not fall into the categories social interaction, communication or restricted, repetitive, and stereotyped patterns of behavior, interests, and activities, were excluded from the list. The adapted questionnaire contained 33 items, subdivided into the scales Social interaction \((n=10)\), Communication \((n=8)\), and Behavior \((n=15)\). Items on the questionnaire were rated on a 5-point scale, with 1 point indicating low progression and 5 points indicating strong progression. Mean scores were calculated for the subscales Social interaction, Communication, and Behavior and for the complete questionnaire.

**Social validity**

Social validity was assessed by a self-constructed anonymous 5-point scale questionnaire with 15 items about the Goals of treatment \((n=4)\), Treatment procedures \((n=8)\), and Outcomes \((n=3)\) (Wölf, 1978). All items were scored, with 1 point indicating low
satisfaction and 5 points indicating high satisfaction. Sum scores were calculated for each subscale to evaluate the acceptability of the neurofeedback treatment. Three open response questions were added to assess whether parents had any remarks, whether they had suggestions to improve neurofeedback treatment, and whether they would recommend neurofeedback treatment to others.

### 3.2.7 Data analysis

#### QEEG

Eye blinks and other artifacts were manually removed from the raw EEG data by an independent EEG specialist and statistician, who was blind to the subject’s classification (i.e., intervention group vs. control group) and the type of the EEG file (i.e., pre vs. post training). The raw data were processed with fast Fourier transformation to determine the magnitude of each frequency band in microvolt. Separate power measures were calculated for delta (1-4 Hz), theta (4-8 Hz), low beta (12-15 Hz), beta 2 (15-18 Hz), beta 3 (18-25 Hz), and high beta (25-30 Hz). EEG data of all individuals were compared with the Neuroguide (Thatcher et al., 2003) database, which provides reliable descriptors of normative brain electrical activity (John et al., 1988). Linked ears montages were used. Data from all 19 electrode sites were used for analysis. The split-half reliability and test-retest reliability of the artifact free data of all subjects were above .95 (p < .05). Absolute power (the amount of energy in μV²), relative power (the percentage of power in a frequency band relative to the total power contained by all other frequency bands), and coherence were calculated for each participant, frequency band, and individual electrode lead. All power and coherence values were subsequently transformed into Z-scores, reflecting deviancy from the normative database (Hughes & John, 1999). A 2 (Time: time1 vs. time2) x 2 (Group: intervention vs. control) repeated measures MANOVA was performed to look for treatment effects in the intervention group relative to the control group.

#### Session data

Eye blinks and other artifacts were manually removed from the raw EEG data of 40 sessions, collected at C3 and C4 during training intervals. The raw data were fast Fourier transformed (FFT) to determine the power of each frequency. Separate power measures were calculated for delta (1.5-3.5 Hz), theta (4-8 Hz), alpha (8-12 Hz), low beta (12-15 Hz), beta 2 (13-21 Hz), and high beta (22-30 Hz). Power values of each frequency band were log-transformed. A 2 (Time: first sessions vs. last sessions) x 2 (Location: C3 vs. C4) repeated measures MANOVA was conducted to compare power during the first 20 sessions with the final 20 sessions. Furthermore, the efficacy of neurofeedback over sessions per frequency band was estimated for each individual subject by calculating a linear regression line and Spearman regression coefficient fitting the progression of power values over sessions.

#### Executive function tasks

Results of a one-sample Kolmogorov-Smirnov test showed that data of each variable did not deviate significantly from normality. A MANOVA was conducted to test differences in executive functions for the intervention group and the control group at time1. Neurofeedback related changes in executive functions were verified by performing a 2 (Time: first sessions vs. last sessions) x 2 (Group: intervention vs. control) repeated measures MANOVA.

#### Questionnaires

Results of a one-sample Kolmogorov-Smirnov test showed that data of each variable of the CCC-2 did not deviate significantly from normality. MANOVA was conducted to test for differences on the CCC-2 between the intervention group and the control group at time1. Neurofeedback related changes on the CCC-2 were verified by performing a 2 (Time: time1 vs. time2) x 2 (Group: intervention vs. control) repeated measures MANOVA. In order to assess whether the intervention group decreased in ASD symptoms more than the control group, a comparison between scores on the adapted Auti-R of the intervention group and the control group was made using a MANOVA with between-subjects factor Group. The social validity of the neurofeedback treatment was evaluated via the sum scores of the subscales Goals, Procedures, and Outcomes, and open response questions.
3.3 Results

3.3.1 Session data

At the individual level, Spearman’s correlation coefficients showed a significant reduction of theta power (4-7 Hz) over 40 sessions of neurofeedback in five participants at C4, \( r = -.596 \) to \(-.718, p < .05\), and in the same five participants at C3, \( r = -.496 \) to \(-.771, p < .05\). Two participants did not show significant reduction of theta power at C4, \( r = .035, p = .411; r = .056, p = .359\), and C3, \( r = .453, p = .018; r = .135, p = .170\). Results of theta reduction at C3 and C4 for all participants can be found in Figure 1.

Low beta power (12-15 Hz) increased significantly over time for five participants at C4, \( r = .218 \) to \(.410, p < .05\), and for six participants at C3, \( r = .253 \) to \(.529, p < .05\). Two participants did not show significant increase of low beta power at C4, \( r = .079, p = .311; r = -.145, p = .173\), and one participant did not show significant increase at C3, \( r = .051, p = .372\) (see Figure 2).

Besides changes in theta and low beta power, changes in delta power (1.5-3.5 Hz) were found as well. Delta power decreased significantly in five participants at C4, \( r = -.550 \) to \(-.605, p < .01\), \( r = -.466 \) to \(-.549, p < .01\), and \( r = -.552 \) to \(-.562, p < .01\) (see Figure 3).

Figure 1.
Average theta (4-7 Hz) power during neurofeedback sessions recorded over C3 (left graph) and C4 (right graph) indicating the reduction in theta power over consecutive sessions. Regression lines reflect the slope of theta reduction over time for each individual client, with * < .05 and ** < .01.

Figure 2.
Average low beta (12-15 Hz) power during neurofeedback sessions recorded over C3 (left graph) and C4 (right graph) indicating the increase in low beta power over consecutive sessions. Regression lines reflect the slope of beta enhancement over time for each individual client, with * < .05 and ** < .01.

Figure 3.
Average delta (1.3-3.5 Hz) power during neurofeedback sessions recorded over C3 (left graph) and C4 (right graph) indicating the reduction in delta power over consecutive sessions. Regression lines reflect the slope of delta reduction over time for each individual client, with * < .05 and ** < .01.
showed significant reduction of theta power (4-7 Hz), \( F(1,6)=11.419, p<.05 \) and significant increase of low beta (12-15 Hz), \( F(1,6)=21.922, p<.05 \), at C3 and C4 over 40 sessions of neurofeedback. Besides power changes in theta and low beta, a significant decrease of delta power (1.5-3.5 Hz) over time was found as well, \( F(1,6)=6.982, p<.05, \eta^2=.538 \). For alpha power (8-12 Hz), beta2 power (13-21 Hz), and high beta power (22-30 Hz), no significant effects of time were found.

Decrease of delta power was significantly correlated with decrease in theta power, \( r=-.449 \), and in five participants at C3, \( r=-.291 \), \( p<.05 \). No increase in delta power was found in two participants at C4, \( r=.177, p=.125, r=.356, \) and at C3, \( r=.098, p=.263; r=.243, p=.054 \). Results can be found in Figure 3. In alpha power (8-12 Hz), beta2 power (13-21 Hz), and high beta power (22-30 Hz), no unanimous patterns of change were found.

Analysis at group level further supported the correlation results. A 2 (Time: first sessions vs. last sessions) x 2 (Location: C3 vs. C4) repeated measures MANOVA showed significant reduction of theta power (4-7 Hz), \( F(1,6)=11.419, p<.05, \eta^2=.656 \), and significant increase of low beta (12-15 Hz), \( F(1,6)=21.922, p<.01, \eta^2=.785 \), at C3 and C4 over 40 sessions of neurofeedback. Besides power changes in theta and low beta, a significant decrease of delta power (1.5-3.5 Hz) over time was found as well, \( F(1,6)=6.982, p<.05, \eta^2=.538 \). For alpha power (8-12 Hz), beta2 power (13-21 Hz), and high beta power (22-30 Hz), no significant effects of time were found.

Decrease of delta power was significantly correlated with decrease in theta power, \( r=.667, p<.01 \), and with increase in low beta power, \( r=-.695, p<.01 \). The correlation between decrease in theta power and increase in low beta power was highly significant, \( r=-.811, p<.001 \).

### 3.3.2 QEEG
The absolute and relative power of each frequency band for all 19 channels for the intervention group and the control group were compared using MANOVA. In order to claim a treatment effect, we need the interaction between Time (time1 vs. time2) and Group (intervention vs. control) to be significant. The repeated measures MANOVA suggested no significant multivariate interaction between Time and Group in the target frequency bands, i.e., absolute, \( F(1,12)=2.382, p=.149, \eta^2=.166 \), or relative theta power, \( F(1,12)=.986, p=.340, \eta^2=.076 \), and absolute, \( F(1,12)=.018, p=.897, \eta^2=.001 \), or relative low beta power, \( F(1,12)=.614, p=.449, \eta^2=.049 \). Univariate results of absolute and relative theta and low beta power in 19 separate electrodes revealed no significant interaction effects either, \( F\)-values=.000 to 3.977, \( p'>.05 \). A similar 2 (Time: time1 vs. time2) x 2 (Group: intervention vs. control) repeated measures MANOVA for the other frequency bands, i.e., delta, alpha, beta2, beta3 and high beta revealed no significant multivariate effects for absolute or relative power, \( F\)-values=.000 to 1.820, \( p'>.05 \).

For the analysis of coherence, a 2 (Time: time1 vs. time2) x 2 (Group: intervention vs. control) repeated measures MANOVA was performed. Univariate results revealed a significant reduction of hypo connectivity in theta power at time2, \( F\)-values up to 17.572, \( p<.05 \), especially between frontal and central/temporal electrodes. However, since this reduction was found in both the intervention and the control group, no significant interaction effects were found, \( F\)-values=.000 to 2.914, \( p'>.05 \).

### 3.3.3 Executive function tasks
A MANOVA was conducted to test the hypothesis that participants in the intervention group would display the same scores as participants in the control group at time1. No statistical significant differences between intervention and control group were found on tests for executive functioning at time1, \( F(1,12)=1.066, p=.577, \eta^2=.082 \).

To analyze whether children in the intervention group scored significantly higher on tests for executive functioning at time2 compared to the matched control group, a 2 (Time: time1 vs. time2) X 2 (Group: intervention vs. control) repeated measures MANOVA was performed.

#### Attentional control
Subjects’ capacity for attentional control was tested using separate measures targeting children’s attentional capacity in the visual and auditory domains and their ability to inhibit verbal and manual response tendencies. Table 2 reports the behavioral results of all executive function tests gathered for both groups at time1 and time2. No significant interaction between Time and Group was found for measures of visual selective attention, \( F(1,11)=.047, p=.832, \eta^2=.004 \). Both groups made very little errors in detecting a target letter in a continuous stream of distractors, leaving little or no room for improvement at time2 (values for visual selective attention in Table 2 represent the amount of errors found with 200 items). However, a significant Time x Group interaction effect was found for measures of auditory selective attention, \( F(1,11)=8.437, p=.014, \eta^2=.434 \). Children in the intervention group showed a considerable improvement in their ability to correctly detect auditory targets in the TOSSA, from 48% to 62% correct responses after neurofeedback training, as compared to the control group who showed minimal improvement from 68% to 69% correctly detected targets. In addition, a significant interaction between Time and Group was found for children’s capacity to inhibit verbal
responses, \( F(1,11)=4.890, p=.049, \eta^2=.308 \). Interference effects of written names were strongly reduced from 68 seconds before to 30 seconds after neurofeedback training for the intervention group. The control group also showed a difference between interference effects at time1 and time2 (66 seconds and 50 seconds respectively) but this reduction was about half the size of the effect found with the intervention group. Consistent with the increased ability to inhibit verbal responses, children of the intervention group were also better able to inhibit impulsive tendencies in responding on the TOSSA, suggesting improved inhibition capacity after neurofeedback training (78% correctly inhibited before training vs. 90% after neurofeedback training). Only minimal improvements in impulse control were found for the control group (89% correct inhibitions at time1 followed by 91% correct inhibitions at time2), resulting in a significant Time x Group interaction, \( F(1,11)=5.064, p=.046, \eta^2=.315 \).

### Cognitive flexibility

Children's cognitive flexibility was investigated using measures of visual and verbal memory, set-shifting, and concept generation. Neurofeedback training did not influence children's capacity to memorize and recognize words, \( F(1,11)=.021, p=.889, \eta^2=.002 \), and geometric shapes, \( F(1,11)=.004, p=.952, \eta^2=.000 \). Both groups showed a minimal non-significant reduction of performance from time1 to time2 (see Table 2), on verbal memory, \( F(1,11)=0.355, p=.563, \eta^2=.031 \), and visual memory, \( F(1,11)=0.138, p=.717, \eta^2=.012 \). However, children's set-shifting ability as indexed by the TMT did show a significant Time x Group interaction, \( F(1,11)=5.602, p=.037, \eta^2=.337 \), reflecting improved cognitive flexibility after neurofeedback treatment. For the intervention group, \( t \)-scores improved from 30 (time1) to 47 (time2), whereas only a small improvement was found for the control group with \( t \)-scores improving from 30 (time1) to 34 (time2). Also concept generation and use of feedback, as measured by the MCST, were found to improve significantly for the intervention group as compared to the control group, \( F(1,11)=5.081, p=.046, \eta^2=.316 \). After neurofeedback, children with ASD discovered an average of 5 (out of 6) card sorting rules, whereas before training they only reached an average of 2.5. In contrast, the performance of the control group was comparable at time1 (3.5 rules) and time2 (3.8 rules).

### Goal Setting

Analysis of children's goal setting capacity as assessed by the TOL showed a significant interaction between Time and Group, \( F(1,11)=7.198, p=.021, \eta^2=.396 \), reflecting a clear improvement in complex sequential problems after neurofeedback training, as compared to the control children. At time1, children from both groups reached an average performance of 55 (range 0-138). However, whereas children of the control group showed little improvement (57 at time2), children of the intervention group drastically improved their capacity score to 76 at time2.

### Speed and efficiency

Children's combined score for speed and efficiency on the SDC indicated a stronger improvement for the intervention group than for the control group (see Table 2), but the required interaction between Group and Time was not found significant, \( F(1,11)=.397, p=.542, \eta^2=.035 \).
A 2 (Time: time2 vs. follow-up) x 2 (Group: intervention vs. control) repeated measures MANOVA indicated no significant differences between post treatment and 3-month follow-up measurements of children’s executive functioning at time3, \( F(1,11)=.987, p= .602, \eta^2=.832 \).

### 3.3.4 Questionnaires

**CCC-2**

The CCC-2 measured parents’ ratings of their children’s communication skills for different aspects (subscales) of communication. A MANOVA was conducted in order to test the hypothesis that participants in the intervention group would display the same scores on the CCC-2 questionnaire as participants in the control group at time1. No statistically significant differences between intervention and control group were found on the CCC-2 questionnaire collected at time1, \( F(1,12)=54.149, p= .106, \eta^2= .998 \).

To analyze whether children in the intervention group scored significantly higher on the CCC-2 at time2 compared to the matched control group, a 2 (Time: time1 vs. time2) x 2 (Group: intervention vs. control) repeated measures MANOVA was performed. Separate analysis of the communication subscales of the CCC-2 showed a significant Time x Group interaction effect for non-verbal communication, \( F(1,12)=5.505, p= .037, \eta^2=.314 \), reflecting an improvement in non-verbal communication for the intervention group, relative to the control group. For none of the other subscales the interaction between Time and Group was found significant, all \( p’s>.05 \). In Table 3 the average ratings of children’s communication skills are reported for sub- and composed scales of the CCC-2 for the control group and the intervention group at time1 and time2. Lower values in Table 3 reflect better communication skills. Analysis of the two composed scales, general communication and pragmatics, revealed a significant interaction effect between Time and Group for general communication, \( F(1,12)=5.379, p= .039, \eta^2=.310 \), but not for pragmatics, \( F(1,12)=.036, p= .852, \eta^2=.003 \). Parents of children in the intervention group regarded their children’s communication skills as more advanced after neurofeedback training than before, whereas no such difference was found for the control group.

<table>
<thead>
<tr>
<th>Time</th>
<th>M (SD)</th>
<th>M (SD)</th>
<th>M (SD)</th>
<th>M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General communication</strong></td>
<td>115.14 (10.45)</td>
<td>115.86 (9.42)</td>
<td>101.29 (12.09)</td>
<td>114.29 (16.45)</td>
</tr>
<tr>
<td><strong>Pragmatics</strong></td>
<td>60.57 (7.00)</td>
<td>60.71 (7.25)</td>
<td>54.14 (5.579)</td>
<td>65.86 (20.84)</td>
</tr>
<tr>
<td><strong>Speech production</strong></td>
<td>12.86 (2.54)</td>
<td>12.14 (3.63)</td>
<td>10.86 (2.96)</td>
<td>11.43 (4.08)</td>
</tr>
<tr>
<td><strong>Syntax</strong></td>
<td>12.71 (1.89)</td>
<td>14.43 (1.40)</td>
<td>11.29 (2.69)</td>
<td>14.71 (1.89)</td>
</tr>
<tr>
<td><strong>Semantics</strong></td>
<td>12.29 (2.29)</td>
<td>13.14 (1.57)</td>
<td>12.00 (2.08)</td>
<td>13.43 (1.40)</td>
</tr>
<tr>
<td><strong>Coherence</strong></td>
<td>15.43 (1.81)</td>
<td>15.43 (1.51)</td>
<td>14.28 (1.50)</td>
<td>14.14 (3.58)</td>
</tr>
<tr>
<td><strong>Inappropriate initialization</strong></td>
<td>14.29 (1.89)</td>
<td>13.57 (2.76)</td>
<td>13.86 (1.57)</td>
<td>14.57 (2.57)</td>
</tr>
<tr>
<td><strong>Stereotyped conversation</strong></td>
<td>15.14 (2.27)</td>
<td>15.57 (1.40)</td>
<td>13.57 (1.81)</td>
<td>14.43 (3.64)</td>
</tr>
<tr>
<td><strong>Context use</strong></td>
<td>15.14 (1.77)</td>
<td>16.71 (1.89)</td>
<td>13.71 (1.80)</td>
<td>16.14 (2.54)</td>
</tr>
<tr>
<td><strong>Non-verbal communication</strong></td>
<td>15.86 (2.34)</td>
<td>14.86 (2.85)</td>
<td>13.71 (2.50)</td>
<td>15.57 (2.76)</td>
</tr>
<tr>
<td><strong>Social relations</strong></td>
<td>15.57 (1.90)</td>
<td>14.42 (2.63)</td>
<td>14.57 (2.07)</td>
<td>14.57 (2.44)</td>
</tr>
<tr>
<td><strong>Interests</strong></td>
<td>13.57 (1.90)</td>
<td>14.00 (2.16)</td>
<td>12.14 (3.67)</td>
<td>14.14 (2.04)</td>
</tr>
</tbody>
</table>

Note. M= Mean, SD= Standard deviation.

### Table 3.

Test results of the CCC-2 for the intervention group (IG) and the control group (CG) at time1 and time2.

The Auti-R measured parents’ evaluation of children’s improvements on social interaction, communication, and typical behavior. Table 4 shows the average improvement for the intervention and control group for each subscale of the Auti-R. Following treatment, parents’ ratings suggested improvements for children in the intervention group on social interaction, communication, and typical behavior as compared to children in the control group. A MANOVA with between subjects factor Group was used to analyze the results of the three subscales of the adapted Auti-R. Results indicated a significant increase in desired behavior after neurofeedback training for the intervention group in comparison with the control group. Children’s
social interaction ability was valued to be improved following treatment, as compared to the control group, $F(1,12)=17.775$, $p=.001$, $\eta^2=.618$. Children’s communication ability was assessed to be enhanced in comparison to the assessment of children in the control group, $F(1,12)=29.054$, $p=.000$, $\eta^2=.725$. Furthermore, typical autistic behavior was found to be attenuated as compared to the assessment of children in the control group, $F(1,12)=7.782$, $p=.018$, $\eta^2=.414$.

Table 4.
Means and standard deviations of the subscales of the adapted Auti-R for the intervention group (IG) and the control group (CG).

<table>
<thead>
<tr>
<th>Subscale</th>
<th>IG (M, SD)</th>
<th>CG (M, SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social interaction</td>
<td>36.50 (3.51)</td>
<td>30.71 (.92)</td>
</tr>
<tr>
<td>Communication</td>
<td>29.00 (1.79)</td>
<td>24.14 (.64)</td>
</tr>
<tr>
<td>Typical behavior</td>
<td>48.33 (3.44)</td>
<td>44.14 (1.06)</td>
</tr>
<tr>
<td>Total</td>
<td>113.83 (7.17)</td>
<td>99.00 (1.95)</td>
</tr>
</tbody>
</table>

Note. M= Mean, SD= Standard deviation.

3.4 Discussion

The present study evaluated the effects of a specific ADHD neurofeedback training protocol for treatment of children diagnosed with ASD. Reduction of theta power was hypothesized to improve children’s executive capacities by enhancing activation of the ACC, which is one of the main generators of theta activation over central areas. Consistent with our prediction, children of the intervention group made large improvements in performance on a range of executive function tasks after neurofeedback training, whereas no such effects were found for a matched control group. These findings reinforce existing neurobiological views on ASD that suggested abnormal functioning of the ACC. Furthermore our findings provide further evidence in support of the view that neurofeedback may hold particular value for treatment of children with ASD which might be comparable with the effects found with ADHD.

At a neurophysiological level, neurofeedback training successfully reduced theta power (4-7 Hz) and significantly increased low beta power (12-15 Hz) in all but two of seven participants in the intervention group. Interestingly, and consistent with our hypothesis that neurofeedback protocols that target children’s theta/beta ratio mainly work because they reduce theta power, attenuation of theta power was found more reliable than enhancement of beta power over sessions. Children’s individual Spearman correlation coefficients reflected significant reductions of theta in five participants showing consistent effects over both hemispheres at C4 (average $r=.68$) and C3 (average $r=.64$), and enhancement of beta in five participants at C4 (average $r=.30$) and C3 (average $r=.38$). Furthermore, consistent decreases in delta power (1.5-3.5 Hz) were found for 5 participants at C4 (average $r=.55$) and at C3 (average $r=.45$). The gradual reduction in delta power probably co-occurred in conjunction with the reduction in theta power, which is further supported by the strong correlation between power reductions of both frequencies over time ($r=.67$).
Considering the consistent suppression of theta and delta frequencies and enhancement of low beta activation over time across sessions, one could imagine structural changes in QEEG to develop between pre- and post-test recordings. However, no significant changes were found in the QEEG of the intervention group as compared with QEEG data of the control group. Our findings are in line with results of Kropotov and colleagues (2005) who found no notable changes in QEEG power spectra of children with ADHD after neurofeedback training, although neurofeedback was found to affect the amplitude of event-related potential (ERP) components.

Coben and Padolsky (2007) found changes in children's QEEG coherence after neurofeedback training reflecting a decrease in cerebral hyper-connectivity in 76% of all children of the intervention group. QEEG coherence values were only available for the intervention group, not for the control group. In the present study, changes in connectivity were found for both the intervention and the control group. These findings suggest a test-retest effect between pre- and post-test EEG assessment which could reflect differences in vigilance or arousal between the two assessments. That is, young children may be more alert and attentive during their first EEG assessment as compared to the second time. This different mental state may be responsible for the observed differences in QEEG between the pre- and post-test in both groups. Another explanation for the absence of differences in QEEG might be the small sample size that was used in the present study.

At a cognitive level, neurofeedback training was hypothesized to improve the executive functions of children with ASD, comparable with the success of the protocol in the treatment of ADHD (Butnik, 2005). Results indicated significant improvement in attentional control, cognitive flexibility, and goal setting for children in the intervention group when compared to children in the control group. These results are important because they reflect a serious cognitive improvement in the intervention group that cannot be reduced to differences in perceived well-being by parents. Instead, these findings indicate that neurofeedback training was associated with a clear improvement in cognitive functioning on tasks requiring executive control. Improvements were found for the majority of tasks taxing executive control, with strong improvements on sustained auditory selective attention (30% more correct responses), inhibition of verbal responses (55% reduction in response interference time), inhibition of motor responses (15% reduction of commission errors), set shifting (57% reduction of time needed to switch between the numerical and alphabetical mode), concept generation (50% increase in the number of card sorting categories created), and planning ability (37% increase in performance on the Tower of London task). Symbol digit coding was found improved (20% more accurate) for the treatment group, but the difference with the improvement of the control group (7%) was not significant. No noteworthy improvements were found on tasks taxing verbal and visual memory, and sustained visual attention. Most children showed to be already highly efficient on these tasks before the start of the neurofeedback treatment at time1, leaving little room for further improvement. Coben and Padolsky (2007) evaluated executive functioning of children with ASD after neurofeedback training using a questionnaire completed by parents and teachers. In agreement with the present results a significant improvement on measures of executive functions was reported. The present experimental findings further extend these previous results by showing enhanced performance on a range of cognitive tasks requiring executive control. Whereas the appraisal of a child's level of executive functioning might be influenced by wishful thinking or social expectation, such factors can not explain a 40% average increase in cognitive performance. The fact that similar improvements were found over a range of different executive tasks further strengthens the conclusion that neurofeedback substantially enhanced the executive capacity of children with ASD. These results are furthermore in line with recent models that suggest a single genetic factor to underlie most executive functions (Friedman, Miyake, Young, DeFries, Corley, & Hewitt, 2008).

We hypothesized that the elevated theta power that characterizes children with ASD is functionally related to their executive impairment. EEG and magnetoencephalographic (MEG) studies have localized frontal theta activation to the rostral ACC (Gevins, Smith, & McEvoy, 1997; Ishii et al., 1999) and studies combining EEG and fMRI have consistently found correlations between theta power and BOLD signal in rostral ACC (Meltzer et al., 2007; Pizzagalli, Oakes, & Davidson, 2003; Sammer et al., 2007). Interestingly, ACC activation and theta power appear to be inversely related. High-functioning individuals with ASD show hypoactivation and reduced connectivity of the ACC (Cherkassky et al., 2006; Kana, Keller, Minshew, & Just, 2007) whereas EEG measures consistently indicate elevated levels of theta power over medial frontal areas in ASD (e.g. Murias et al., 2007). Meltzer and colleagues (2007) found increasing working memory load to be associated with enhancements of
EEG theta power which correlated negatively with BOLD signal in a network of areas including the rostral ACC (Meltzer et al., 2007). Similar findings were reported by Sammer and colleagues (2007) using mental arithmetic-induced workload and Kana and colleagues (2007) using a response inhibition paradigm. Interestingly, deactivation of the ACC during cognitive demanding tasks is often found in association with deactivations of other (medial) areas, such as the precuneus, which together have been labeled the default mode network (DMN) reflecting its high default metabolism during rest (Gusnard & Raichle, 2001). Much interest has developed in understanding the function of the DMN and several interesting views have been formulated which appear to converge on the idea that the DMN is involved in self-referential processing (Northoff et al., 2006) and understanding others’ intentions through mental simulation (Uddin, Iacoboni, Lange, & Keenan, 2007). These findings may have implications for understanding social impairments in ASD. However, for the present discussion it is first important to note that the rostral ACC is not directly involved in executing cognitive control (Rushworth, Walton, Kennerley, & Bannerman, 2004), but that its activation is inversely related to other areas that are activated during cognitive tasks, such as the lateral prefrontal cortex (Greicius, Krasnow, Reiss, & Menon, 2003). Following this suggestion, Fox and colleagues (2005) discovered strong spontaneous anticorrelations between a “task-negative” DMN and an opposing “task-positive” attentional network, in a resting state. Kelly, Uddin, Biswal, Castellanos, and Milham (2008) furthermore found differences in individual attentional capacity to depend on the strength of the negative correlation between the two opposing networks, with a reduced antiphase relation resulting in more variable behavioral performance. In addition, a recent fMRI study by Weissman, Roberts, Visscher, and Woldorff (2006) indicated that a failure to suppress the DMN may result in lapses of attention. Uddin, Kelly, Biswal, Castellanos, and Milham (2009) yield further support for this view by indicating that the balance between the two networks is primarily controlled by the DMN.

Importantly, these findings provide a possible mechanism through which we can understand the relation between theta power, ACC activation, and executive function. The enhancement of theta that is consistently found during cognitive effortful tasks, such as use of working memory (Jensen & Tesche, 2002), mental arithmetic (Mizuhara, Wang, Kobayashi, & Yamaguchi, 2004), error monitoring (Luu, Tucker, & Makeig, 2004), and sentence comprehension (Bastiaansen, van Berkum, & Hagoort, 2002), probably reflects deactivation of the rostral ACC / DMN, to allow activation in (task-positive) areas supporting the processing of external goals (cf. Fransson, 2005). Consistent with the hypothesis that the executive problems of children with ASD may originate from a defective DMN, Kennedy, Redcay, and Courchesne (2006) recently found that subjects with ASD, as compared with controls, did not deactivate their DMN during a range of cognitive and emotional Stroop tasks. Inability to deactivate or modulate activation of the DMN might thus impair the engagement of task-positive areas exerting cognitive control.

So far we mainly focused on theta and its possible contribution to improvements in executive control. However, in addition to theta reduction the neurofeedback protocol also operated to enhance beta activation, which might also have contributed to the success of the treatment. Interestingly, whereas theta activation is negatively related to activation in medial frontal areas, beta power appears to be positively related to activation in those same areas, as is indicated by recent EFG-EEG studies (Laufs et al., 2003; Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007) and intracerebral recordings studying the neural origins of the beta rhythm (Bočková, Chládek, Jurák, Halánek, & Rektor, 2007). That is, comparable with the effect of theta, enhancing beta should also increase activation in the DMN. In other words, the effects of reducing theta and at the same time enhancing beta power may actually work together in parallel to increase activation of hypoactive areas of the DMN in children with ASD.2

Interestingly, the hypothesis that ASD is primarily characterized by underactivation of the DMN may explain both executive dysfunctioning and social deficits that are typical of ASD. As was indicated earlier, parts of the DMN are known to be involved in self-referential processes and internal models of the self (reviews in Northoff & Bermpohl, 2004; Northoff et al., 2006). Importantly, the capacity to mentalize about others’ intentions and their internal states is thought to rely for a large part on our ability to simulate others’ thoughts and feelings via the self. That is, we can understand what others might be feeling, thinking or aiming for, by putting ourselves into their shoes, i.e., by imagining what we would feel, think or do in their situation.

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1 As a side-note, however, bear in mind that both theta and beta rhythms are not the sole property of the DMN areas or its associated function. Both theta and beta rhythms have been found in association with other areas and in support of different cognitive functions (e.g. Mantini et al., 2007).
In other words, impairments of the DMN supporting self-referential thought could well be held responsible for a reduced ability to represent intentions and mental states of others, which in turn would result in various social impairments. Consistent with this perspective, several studies have indicated similar activations of DMN areas in conditions that required subjects to either think about themselves or think about close others (see review in Mitchell, Macrae, & Banaji, 2006; Moriguchi et al., 2006; Seger, Stone, & Keenan, 2004; Ochsner et al., 2005; Uddin et al., 2007). Furthermore, studies investigating structural abnormalities in brains of children with ASD have been identified to overlap with areas that are known to support theory of mind tasks and social cognition (Abell et al., 1999; Barnea-Goraly et al., 2004; Haznedar et al., 2000).

In line with the above suggestion that neurofeedback enhancement of DMN activation may both reduce ASD executive dysfunctions and at the same time improve children's social and communicative abilities, a significant improvement in general communication was found for children in the treatment group (14%), but not for children in the control group (-7%) on the CCC-2. This result was furthermore supported by the estimated improvement of children in the treatment group on levels of social interaction (16%), communication (17%), and typical behavior (9%) as measured by the Auti-R. These findings are in line with previous studies that reported significant reductions in ASD symptoms (Cohen & Padolsky, 2007; Jarusiewicz, 2002) and improvements in behavior on several social and cognitive factors (Scolnick, 2004; Sichel et al., 1995) following neurofeedback training inhibiting theta activation.

Although the present findings are encouraging, studies with improved methodology regarding the effectiveness of neurofeedback training for children with PDD-NOS and other types of ASD are needed. This study used the same training protocol for each participant, but evidence is now growing for the use of an individualized protocol based on the individual EEG. We intend to incorporate protocols based on individualized EEGs in future research. The most important methodological improvement would be to control for direct, unintentional effects of neurofeedback training, such as providing extra time and attention to participants in the intervention group twice a week and learning them to handle an attention-demanding task like neurofeedback (Heinrich et al., 2007). We also expect indirect influence of neurofeedback training on children in the intervention group via their parents. Parents have brief talks or conversations with the neurofeedback trainer the minutes before and after neurofeedback sessions and during evaluations and they get advice, encouragement, support, and compliments. These occasions raise expectations of improvement in parents, act upon parents’ answers on behavior questionnaires, and change the parents’ approach to their children. A solution for this problem would be randomized double blind studies with random feedback for the control group. However, the use of such a placebo condition raises ethical questions and therefore does not seem feasible. Instead of placebo feedback, neurofeedback training could be compared with established interventions like medication and behavior therapy (Heinrich et al., 2007), like Fuchs and colleagues (2003) did in ADHD. However, in the case of ASD it does not seem easy to create such a design. Comparison with medication is not attainable, since no appropriate medication is available for children with ASD (Buitelaar & Willemsen-Swinkels, 2000). Comparison with an intervention like behavior therapy seems almost impossible, since time and intensity of the neurofeedback training and the time-consuming and more intensive behavior therapy should be kept constant (Matson & Smith, 2008).

In conclusion, application of a typical ADHD neurofeedback protocol to a group of children diagnosed with ASD was found to be highly effective. Neurofeedback treatment resulted in clear improvements in children's executive functioning as reflected in a wide range of executive function tasks. These findings suggest a relationship between enhanced theta/beta ratios in children with ASD and hypoactivation of the ACC as a possible neural origin of this impairment.

Acknowledgements

We thank all the families who participated in the study. We also thank Erwin Hartsuiker (MindMedia, the Netherlands) for his share in the availability of neurofeedback equipment.
Chapter 4

Long-Term Effects of Neurofeedback Treatment in Autism

Abstract

Previously we demonstrated significant improvement of executive functions and social behavior in children with autism spectrum disorders (ASD) treated with 40 sessions of neurofeedback in a nonrandomized waiting list control group design. In this paper we extend these findings by reporting the long-term results of neurofeedback treatment in the same group of children with ASD after 12 months. The present study indicates maintenance of improvement of executive functions and social behavior after 12 months in comparison with the immediate outcomes. Neurofeedback mediated suppression of theta power is supposed to promote more flexible functioning of the brain by enhancing activation in the medial prefrontal cortex and improving flexibility of activation in the default mode network supporting the improvement of executive functions and social behavior in children with ASD.

4.1 Introduction

In the evaluation of any treatment, it is extremely important to gather information about the long-lasting effects of treatment by collecting follow-up data. Follow-up research aims to measure effects of treatment over time to determine if the treatment has resulted in a structural improvement or if clients relapsed to pre-treatment levels. The importance of follow-up data for the evaluation of neurofeedback has been noted repeatedly. Heinrich, Gevensleben, and Strehl (2007), for example, suggested investigation of clinical outcomes, spectral EEG analysis, and neuromodulatory skills using at least a 6-month follow-up interval. Despite many recommendations, the use of follow-up in evaluating neurofeedback as a treatment for several disorders has been used only in a few studies. In ADHD, the population in which most of the neurofeedback research has been performed, follow-up data were only collected by Tansey (1993) in a case study and by Lubar (2003) in a retrospective study of 52 patients who ended neurofeedback treatment 1 to 10 years before. Recently, follow-up data after 6 months were reported by Leins and colleagues (2007).

In a recent study, we reported the results of neurofeedback treatment in children with autism spectrum disorders (ASD) as compared to a waiting list control group (Kouijzer, de Moor, Gerrits, Congedo, & van Schie, 2009b). Treatment consisted of 40 sessions of neurofeedback and included inhibition of theta activity (4-7 Hz) and enhancing low beta activity (12-15 Hz) over the right hemisphere. It was hypothesised that this induced change in EEG power enhanced activation of the anterior cingulate cortex (ACC) that has been found to be underactivated in clients with ASD (Cherkassky, Kana, Keller, & Just, 2006) and improved executive functioning and social behavior. Session data gathered during neurofeedback treatment revealed a clear and consistent linear decrease in theta power and an increase in low beta power over 40 sessions. On tasks taxing executive functioning, significant improvement in the treatment group was found for attention control, cognitive flexibility, and planning in comparison to the waiting list control group. Analysis of the CCC-2 and Auti-R questionnaires measuring social behavior of children with ASD revealed significant improvements in general communication and in non-verbal communication for children in the treatment group, but not for the waiting list control group. Furthermore, parents of children in the treatment group reported more improvement compared to parents of children in the control group on levels of social interaction, communication, and...
typical behavior. These parents also reported to be highly satisfied with the results. A follow-up after three months revealed maintenance of the described outcomes on both executive functioning and social behavior. See Kouijzer and colleagues (2009b) for detailed explanation of the improvement in executive functioning and for an explanation of the tasks that were used.

The present study investigates maintained or increased performance in executive functioning and social behavior by comparing 12 months follow-up data (follow-up) with data gathered before (pre-assessment) and immediately after treatment (post-assessment). Maintenance of benefits of neurofeedback treatment would be demonstrated if, firstly, no significant decrease in performance is found between follow-up and post-assessment. Second, a comparison between follow-up and pre-assessment was made in order to confirm the significant effects of neurofeedback treatment in children with ASD in line with Kouijzer and colleagues (2009b). No significant changes were expected in QEEG, since no significant differences between pre- and post-assessment were found in our earlier study.

4.2 Method

4.2.1 Participants

Participants of the present study were the same as in our earlier study (Kouijzer et al., 2009b), i.e., fourteen children (12 males; 2 females) with a mean age of 10.1 years (range 8 to 12 years). All children had an IQ-score of 70 and above and a diagnosis of ASD (subtype pervasive developmental disorder – not otherwise specified, PDD-NOS), according to the criteria of DSM-IV conferred by a child psychiatrist or licensed psychologist. Each diagnosis was confirmed by a clinical psychologist and by results on the CCC-2 questionnaire. None of the children used medication, had a history of severe brain injury or had co-morbid diagnoses such as ADHD and epilepsy. The seven children who applied first were assigned to the intervention group. The control group included seven children who were recruited out of a larger group of children who applied later and were selected to match children of the intervention group on age, sex, and intelligence scores. There were no significant differences between both groups with respect to the variables sex, mean age, total IQ, verbal IQ, and performal IQ. Most participants in the control group subscribed for neurofeedback treatment after ending participation in the waiting list control group.

4.2.2 Materials and procedure

Assessment of all participants during follow-up followed the same procedure and used the same materials, questionnaires, and tasks as in pre- and post-assessment. All participants performed tasks to assess four sub domains of executive functioning, i.e., attentional control, cognitive flexibility, goal setting, and speed and efficiency (Smidts, 2003). Parents of all children filled out two questionnaires about social interaction, communication, and typical behavior (CCC-2 and Auti-R). A detailed explanation of tasks and questionnaires can be found in Kouijzer and colleagues (2009b).

4.3 Results

4.3.1 Executive functioning

For the comparison of results on executive functioning tasks between post-assessment and follow-up, a repeated measures MANOVA with within-subject factor Time was performed. Table 1 reports means and standard deviations of all executive function tasks. Higher scores reflect better executive functioning, except on tasks evaluating visual selective attention and inhibition of verbal responses. On these tasks, lower scores indicate better results.

When post-assessment and follow-up data were compared, a significant improvement in auditory selective attention, $F(1,6)=16.248, p<.010, \eta^2=.765$, between post-assessment and follow-up was found, indicating continuation of improvement of selective attention after 12 months. Furthermore, a marginal significant improvement was found for inhibition of motor responses, $F(1,6)=4.560, p=.086, \eta^2=.477$. Non-significant improvement was found for inhibition of verbal responses, $F(1,6)=.479, p=.520, \eta^2=.087$, verbal memory, $F(1,6)=2.791, p=.156, \eta^2=.358$, concept generation, $F(1,6)=1.52, p=.713, \eta^2=.039$, and speed and efficiency, $F(1,6)=.572, p=.483, \eta^2=.103$. No significant decrease of performance was found between post-assessment and follow-up data on any aspect of executive functioning.

To compare follow-up data with pre-assessment data, a repeated measures MANOVA with within-subject factor Time was conducted. Results confirmed the significant improvement of the treatment group for the same variables that were found improved in the previous comparison between pre- and post-assessments, i.e., sustained auditory selective attention, $F(1,6)=39.201, p<.01, \eta^2=.887$, inhibition
4.3.2 Behavior

For the comparison of communication skills assessed by the CCC-2 questionnaire between post-assessment and follow-up, a repeated measures MANOVA with within-subject factor Time was conducted. In Table 2 the average ratings of children’s communication skills are reported for sub- and composed scales of the CCC-2. Lower values reflect better communication skills.

Subscales that significantly improved previously in the comparison between pre- and post-assessment data maintained at the same level when post-assessment and follow-up were compared, i.e., general communication, \( F(1,6)=.016, p=.904, \eta^2=.003 \), and non-verbal communication, \( F(1,6)=.578, p=.476, \eta^2=.088 \). Subscales that were not significant in the previous analysis did not show significant changes either, \( F\) values of .000 to 3.111, \( p\)'s>.05, \( \eta^2\)'s=.000 to .341. This finding confirmed the hypothesis that behavioral improvement after neurofeedback treatment was continued after 12 months. Next, follow-up data was compared with pre-assessment data. Similar to the previous analysis, a repeated measures MANOVA with within-subject factor Time showed significant improvement for the treatment group for non-verbal communication, \( F(1,6)=7.125, p<.05, \eta^2=.543 \), but no longer for general communication, \( F(1,6)=2.745, p=.149, \eta^2=.314 \). Consistent with the comparison between pre- and post-assessment data, none of the remaining scales showed a significant difference between pre-assessment and follow-up data.

Results of the Auti-R questionnaire were analyzed by comparing post-assessment

| Note. Decrease in scores indicates improvement. For other scales, increase in scores indicates improvement. |  

Table 1.
Means and standard deviations on tasks for executive functions at pre-assessment, post-assessment, and follow-up.

<table>
<thead>
<tr>
<th>Subtasks</th>
<th>Pre-assessment</th>
<th>Post-assessment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attentional control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual selective attention (^1)</td>
<td>4.33 (2.81)</td>
<td>4.17 (4.26)</td>
<td>4.71 (1.89)</td>
</tr>
<tr>
<td>Auditory selective attention</td>
<td>47.87 (14.21)</td>
<td>62.40 (14.18)</td>
<td>75.27 (13.79)</td>
</tr>
<tr>
<td>Inhibition of verbal responses (^1)</td>
<td>68.17 (18.87)</td>
<td>30.00 (12.12)</td>
<td>26.50 (11.11)</td>
</tr>
<tr>
<td>Inhibition of motor responses</td>
<td>78.50 (13.16)</td>
<td>89.93 (9.20)</td>
<td>95.90 (4.13)</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal memory</td>
<td>53.33 (3.62)</td>
<td>52.17 (4.07)</td>
<td>56.29 (2.14)</td>
</tr>
<tr>
<td>Visual memory</td>
<td>46.00 (3.74)</td>
<td>45.00 (4.34)</td>
<td>43.14 (4.10)</td>
</tr>
<tr>
<td>Shifting</td>
<td>30.00 (15.68)</td>
<td>47.00 (13.27)</td>
<td>47.86 (10.11)</td>
</tr>
<tr>
<td>Concept generation</td>
<td>2.55 (1.48)</td>
<td>4.96 (4.5)</td>
<td>5.06 (3.9)</td>
</tr>
<tr>
<td>Goal setting</td>
<td>55.45 (9.07)</td>
<td>75.85 (9.17)</td>
<td>72.83 (5.46)</td>
</tr>
<tr>
<td>Speed and efficiency</td>
<td>34.33 (7.06)</td>
<td>41.33 (5.13)</td>
<td>43.67 (10.86)</td>
</tr>
</tbody>
</table>

Table 2.
Means and standard deviations on the CCC-2 at pre-assessment, post-assessment, and follow-up.

<table>
<thead>
<tr>
<th>Subtasks</th>
<th>Pre-assessment</th>
<th>Post-assessment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>General communication</td>
<td>115.14 (10.45)</td>
<td>101.29 (12.09)</td>
<td>101.83 (16.34)</td>
</tr>
<tr>
<td>Pragmatics</td>
<td>60.57 (7.00)</td>
<td>54.14 (5.579)</td>
<td>53.00 (7.48)</td>
</tr>
<tr>
<td>Speech production</td>
<td>12.86 (2.54)</td>
<td>10.86 (2.96)</td>
<td>11.71 (3.50)</td>
</tr>
<tr>
<td>Syntax</td>
<td>12.71 (1.89)</td>
<td>11.29 (2.69)</td>
<td>11.28 (3.45)</td>
</tr>
<tr>
<td>Semantics</td>
<td>12.29 (2.29)</td>
<td>12.00 (2.08)</td>
<td>11.43 (2.64)</td>
</tr>
<tr>
<td>Coherence</td>
<td>15.43 (1.81)</td>
<td>14.28 (1.50)</td>
<td>13.29 (4.57)</td>
</tr>
<tr>
<td>Inappropriate initialization</td>
<td>14.29 (1.89)</td>
<td>13.86 (1.57)</td>
<td>11.86 (3.76)</td>
</tr>
<tr>
<td>Stereotyped conversation</td>
<td>15.14 (2.27)</td>
<td>13.57 (1.81)</td>
<td>13.14 (1.95)</td>
</tr>
<tr>
<td>Context use</td>
<td>15.14 (1.77)</td>
<td>13.71 (1.80)</td>
<td>13.83 (2.14)</td>
</tr>
<tr>
<td>Non-verbal communication</td>
<td>15.86 (2.34)</td>
<td>13.71 (2.50)</td>
<td>13.00 (3.41)</td>
</tr>
<tr>
<td>Social relations</td>
<td>15.57 (1.90)</td>
<td>14.57 (2.07)</td>
<td>13.86 (3.76)</td>
</tr>
<tr>
<td>Interests</td>
<td>13.57 (1.90)</td>
<td>12.14 (3.67)</td>
<td>12.57 (3.31)</td>
</tr>
</tbody>
</table>

Note. Decrease in scores indicates improvement.
and follow-up data in a paired sample t-test for each of the scales on social interaction, communication, and typical behavior and for the complete questionnaire. Mean scores of each scale can be found in Table 3. Higher scores indicate better results. Post-assessment results already revealed increases of the treatment group on all scales of the questionnaire, i.e., social interaction, communication, and typical behavior. The comparison between post-assessment and follow-up data revealed no significant differences, $t$-scores $\approx -1.23$ to $1.647$, $p$'s $>.05$, indicating maintenance of the results after 12 months.

**Table 3.**
Means and standard deviations on the Auti-R at post-assessment and follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Post-assessment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>113.83 (7.17)</td>
<td>109.67 (9.63)</td>
</tr>
<tr>
<td>Social interaction</td>
<td>36.50 (3.51)</td>
<td>35.00 (5.62)</td>
</tr>
<tr>
<td>Communication</td>
<td>29.00 (1.79)</td>
<td>29.17 (3.43)</td>
</tr>
<tr>
<td>Typical behavior</td>
<td>48.33 (3.44)</td>
<td>45.50 (2.17)</td>
</tr>
</tbody>
</table>

### 4.4 Discussion

In our previous paper (Kouijzer et al., 2009b), the results of 40 sessions of neurofeedback treatment in seven children with ASD as compared to a waiting list control group were described. Treatment comprised inhibition of theta activity (4-7 Hz) and enhancement of low beta activity (12-15 Hz) over the right hemisphere. Session data gathered during neurofeedback treatment revealed a clear and consistent linear decrease in theta power and an increase in low beta power over 40 sessions. It was hypothesized that this induced change in EEG power enhances activation of the ACC and improves executive functioning and social behavior of children with ASD. Pre- and post-assessment revealed significant improvement in the treatment group for attention control, cognitive flexibility, and planning in comparison with the waiting list control group. Analysis of the CCC-2 and Auti-R questionnaires revealed significant improvement in social interaction, verbal and non-verbal communication skills, and typical behavior.

The present paper describes 12 month follow-up data that were compared with pre- and post-assessment data. First, analysis of follow-up data concerning executive functions revealed that effects that were found immediately after treatment were maintained or increased 12 months after ending neurofeedback. Second, follow-up data assessing social behavior revealed that children's immediate improvement on social interaction skills, communicative abilities, and typical behavior were maintained as well. Improvement in communication skills were long-lasting as measured by the Auti-R questionnaire and partly sustained according to the CCC-2 questionnaire. It can be concluded that neurofeedback resulted in long-lasting improvement in executive functions and social behavior of children with ASD.

In line with our previous paper we suggest one particular mechanism to underlie the effects of neurofeedback on both executive functions and social behavior levels. This network comprises the default mode network (DMN) including the ACC. The ACC is one of the main generators of theta activity in the brain (Meltzer, Negishi, Mayes, & Constable, 2007; Onton, Delorme, & Makeig, 2005; Tsujimoto, Shimazu, & Isomura, 2006) and is well known for its role in regulating cognitive and emotional processes contributing to cognitive control and executive function (review in Bush, Luu, & Posner, 2000). As part of the DMN, the ACC is characterized by a high default metabolism during rest and inversely related to other areas that are activated during cognitive tasks. Kennedy, Redcay, and Courchesne (2006) found that subjects with ASD, as compared to controls, did not deactivate their ACC in order to allow activation of other task relevant brain areas. By learning to reduce theta activity in the ACC by neurofeedback, structural hypo-activation of the ACC in children with ASD might have increased towards normal levels to allow functional activations and deactivations of the ACC in line with cognitive and executive demands. This increased flexibility of the DMN might allow other brain areas supporting cognitive functions to activate more effectively during cognitive tasks and therefore improve performance.

In contrast to the attenuation of activation in the DMN during tasks requiring cognitive control, the DMN is typically found to be activated during tasks requiring Theory of Mind (ToM). ToM is the ability to ascribe mental states, such as desires, beliefs, feelings, and intentions, to oneself and to other people (Baron-Cohen, 2002). Carlson, Moses, and Breton (2002) found ToM performance and executive functions to be closely interwoven in terms of developmental timetable (substantial growth in the preschool period), brain region (prefrontal cortex), and affected appearance in clients.
with ASD. Because of this close relation between development and manifestation of ToM and executive functions, improved flexibility of the ACC of individuals with ASD might support both executive functions and ToM performance. Where executive functions demand a decrease of ACC activation, optimal performance of ToM tasks requires activation in this area (Kennedy, Redcay, & Courchesne, 2006). Analysis of the present study cautiously confirms this hypothesis by revealing significant improvement in executive functions, social interaction, and communication skills for participants who received neurofeedback treatment.

The hypothesis that neurofeedback increases flexibility of the brain is supported by the results of the comparison between pre- and post-assessment of QEEG data in the previous study. QEEG data of participants in the treatment and the control group were not significantly different (Kouijzer et al., 2009b), in contrast to the session data of the treatment group that showed a clear decrease of theta power and an increase in low beta power. A possible explanation for this apparently paradoxical finding is that neurofeedback allows the brain to function in a more flexible way and enables the brain to switch between different cognitive states more easily. The QEEGs used for this study were recorded during rest and therefore do not demonstrate changes in flexibility of the brain. Session data, however, were gathered during neurofeedback sessions when participants had a clear task to fulfill. A hypothesis to be tested in future research is the effect of neurofeedback on QEEGs collected during the performance of cognitive tasks, where theta activity has to be modulated.

The present study revealed that in addition to the immediate effects of inhibiting theta power in combination with rewarding low beta power over the right hemisphere of the brain, neurofeedback improved executive functions and social performance over a prolonged period of time. Considering the above explanation, these results confirm the hypothesis that enhancement of activation in the ACC may have helped children with ASD to improve executive functions and social behavior structurally and long-lasting.

Acknowledgements
The present study is based on an earlier study that demonstrated the effects of neurofeedback treatment in children with an autism spectrum disorder. We thank all the participants of that study for their co-operation in collecting follow-up data 12 months after they ended the neurofeedback track.

Chapter 5
Neurofeedback Treatment in Autism. Preliminary Findings in Behavioral, Cognitive, and Neurophysiological Functioning

Abstract
Effects of neurofeedback treatment were investigated in children with autism spectrum disorders (ASD). Sixty percent of the participants in the treatment group successfully reduced excessive theta power during neurofeedback treatment. Reduction of theta power was confirmed by pre- and post-QEEG measures. Parents of participants in the neurofeedback treatment group reported significant improvements in reciprocal social interactions and communication skills, relative to the parents of the control group. Set-shifting skills improved following neurofeedback treatment relative to the control group. The reduction of theta power is assumed to reflect modulation of activity in the anterior cingulate cortex (ACC), which is known to be involved in social and executive dysfunctions in autism.

5.1 Introduction

Autism spectrum disorders (ASD) have been defined as developmental disorders characterized by abnormalities in social interaction, communication skills, and behavioral flexibility (American Psychiatric Association, 2000). Although no evidence-based cure exists for ASD, psychosocial and pharmacologic interventions can improve the quality of life of children with ASD and their families. Psychosocial interventions in ASD include behavioral therapy, social skills training, and parental interventions. In general, psychosocial interventions appear to have limited effect sizes and maintenance of results over time. Recent research suggests that of all psychosocial interventions, intensive one-to-one behavioral therapy of at least 20 h per week at an early age is most effective (Van Engeland & Buitelaar, 2008). Pharmacologic interventions such as atypical antipsychotics, serotonin reuptake inhibitors, and stimulants do no affect the core symptoms of ASD, but may be components of a comprehensive treatment program in temporarily reducing additional problem behavior. Both psychosocial and pharmacologic interventions provide no curative solution for the treatment of ASD, but might offer benefits for relieving ASD symptoms.

A relatively new form of treatment for ASD is neurofeedback. The goal of neurofeedback is to influence or change abnormal oscillatory activity by making clients aware of this activity and rewarding the inhibition or enhancement of desired oscillatory activity. In 2002, Jarusiewicz started research on the effects of neurofeedback in children with ASD. She found a 26% decline in symptoms of ASD as reported by parents of 12 children with ASD after inhibiting theta power and enhancing low beta power, compared to a 3% decline in a matched waiting list control group. Coben and Padolsky (2007) extended this research by comparing the outcomes of neurofeedback training in a treatment (n=37) and control group (n=12) on neuropsychological tests, behavior ratings, and neurophysiological measures. They showed improvement on all outcome measures for the treatment group but not for the control group. In our own study (Kouijzer, de Moor, Gerrits, Congedo, & van Schie, 2009b) we evaluated neurofeedback treatment in seven children with ASD compared to a waiting list control group (n=7) and found positive effects of inhibiting theta power and enhancing low beta power on behavioral, cognitive, and neurophysiological outcome measures. These results were maintained after one year, as was found in a follow-up study (Kouijzer, de Moor, Gerrits, Buitelaar, & van Schie, 2009a). Compared to common psychosocial and
pharmacological interventions, neurofeedback may be at an advantage with respect to shortened treatment duration, the absence of side effects, and long-term maintenance of treatment results. These advantages suggest that neurofeedback may be a promising tool for the treatment of children with ASD.

To further establish neurofeedback as an efficacious and specific treatment for children with ASD, the current study implemented several methodological improvements (cf. Heinrich, Gevensleben, & Strehl, 2007; Kouijzer et al., 2009b; LaVaque et al., 2002). First, our previous study reported positive results for children with pervasive developmental disorders – not otherwise specified (PDD-NOS), a relatively mild form of ASD. However, neurofeedback might also benefit children with more severe subtypes of ASD. The present study investigated neurofeedback treatment in children from the full autistic spectrum. Second, in contrast to the fixed treatment protocol that was used in our first study (Kouijzer et al., 2009b), i.e., decrease of 4-7 Hz power and increase of 12-15 Hz power at location C4, frequency bands and electrode placement for treatment in this study were adjusted to the individual quantitative electroencephalogram (QEEG) of each participant, which is referred to as individualized or QEEG-guided neurofeedback (Coben & Padolsky, 2007; Heinrich et al., 2007; Walker & Kozlowski, 2005). Third, our first study reported consistent changes in theta and low beta power over subsequent neurofeedback sessions, but no transfer of these changes in theta and low beta power to QEEG as measured during rest. In the present study, we extended analysis at the neurophysiological level by investigating transfer effects of neurofeedback on QEEG data during a variety of rest and task conditions. Fourth, evaluation of the procedure of the previous study revealed that the investment of time and energy of parents and children to visit the neurofeedback practice twice a week was extensive. In the present study, feasibility of neurofeedback treatment was increased by implementing neurofeedback treatment in the school programs of the participants. Finally, effects on behavior in our previous study were evaluated only by parents. However, behavior of children with ASD often is expressed differently across different contexts and improvement in behavior might vary across contexts as well. This study assessed behavioral effects of neurofeedback both at home and at school by enclosing parent and teacher questionnaires.

This paper describes and discusses the results of individualized neurofeedback in children with ASD by comparing treatment and control groups before and after treatment. Participants were randomly divided into the treatment or control group. Six months after treatment ended there was a follow-up for both treatment and control group. The present study has three aims. First, the effects of neurofeedback treatment on social behavior were investigated. We evaluated social interactions, communication skills, and stereotyped and repetitive behavior in the neurofeedback treatment and control group with behavior questionnaires filled out by parents and teachers. Second, the effects of neurofeedback treatment on executive functioning, i.e., attentional control, cognitive flexibility, goal setting, and speed and efficiency, were investigated using a range of neuropsychological tasks. Finally, the effects of neurofeedback treatment on brain activity were examined by investigating session data that were gathered during neurofeedback treatment and pre- and post-measures of QEEG.

5.2 Method

5.2.1 Participants
A total of 400 school files of two special education schools were screened to select participants for the present study. Inclusion criteria were an age between 8 and 12 years, an IQ-score of 80 and above, and the presence of autism, Asperger disorder or PDD-NOS according to the DSM-IV criteria as clinically diagnosed by a certified child psychiatrist or health care psychologist. Excluded were children using medication, children with a history of severe brain injury, and children with co-morbidity such as ADHD and epilepsy. Twenty children (17 males; 3 females) with a mean age of 9.3 years and a diagnosis of ASD were selected. Diagnoses were confirmed by an independent child psychiatrist who studied the files of the selected participants. Parents of all selected children signed informed consent. The protocol of the study was approved by the local medical ethics committee. Participants were randomly appointed to the neurofeedback treatment and the control group, although this resulted in uneven balanced diagnoses over groups. However, Social Communication Questionnaire (SCQ) data filled out by parents indicated that there were no initial differences in social interaction, communication, and limited and stereotyped behavior, F(1,18)=1.517, p=.251, ηp²=.302, between groups. An overview of the demographic characteristics of the treatment and the control group is given in Table 1.
5.2.2 Neurofeedback training

Neurofeedback shows the participant's real time oscillatory brain activity on a computer screen and uses the principles of operant conditioning to influence or change this activity. During typical neurofeedback training, an electrode located at the scalp of the participant measures EEG activity. This signal is amplified and filtered and subsequently visualized on a computer screen via a bar graph, reflecting the amplitude of the particular frequency that is used for training. That is, the larger the amplitudes of the selected brain frequencies are, the higher the bar graph on the computer screen will be. While observing the amplitude of their own brain waves, the participant is instructed to “try to move down (or up) the brain activity using the feedback to guide you”. A criterion line is shown together with the bar graph reflecting a concrete goal during training, e.g. participants try to keep the bar graph beneath the criterion line. Visual and audio rewards fitting the participant’s individual age and interest are provided when the participant meets the criteria set by the criterion line. At first, changes in brain activity are short and mainly accidentally, but after more training changes become more enduring and controlled.

The procedure within each of the 40 neurofeedback sessions comprised seven three-minute intervals of active neurofeedback training separated by one-minute rest intervals. During active training intervals, participants watched the computer screen while being motivated by the therapist to actively work on changes in the bar graph, i.e., their brain activity. Within each active training interval, criterion line placement was adapted to the participant’s ability to be rewarded 50-80% of the time. Figure 1 illustrates the neurofeedback setting that was used in this study.

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Treatment group (n=10)</th>
<th>Control group (n=10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>9 / 1</td>
<td>8 / 2</td>
<td>-</td>
</tr>
<tr>
<td>Mean age in years</td>
<td>9.43 (1.44)</td>
<td>9.14 (1.34)</td>
<td>.646</td>
</tr>
<tr>
<td>Diagnosis (Autism/ Asperger/ PDD-NOS)</td>
<td>6 / 0 / 4</td>
<td>2 / 4 / 4</td>
<td>-</td>
</tr>
<tr>
<td>SCQ total score</td>
<td>14.20 (6.56)</td>
<td>16.67 (3.97)</td>
<td>.251</td>
</tr>
</tbody>
</table>

Note: Standard deviations are in parentheses.

5.2.3 Social behavior

Three questionnaires evaluating social interactions, communication skills, and stereotyped and repetitive behavior were filled out by parents and teachers, i.e., the
Social Communication Questionnaire (SCQ), the Social Responsiveness Scale (SRS), and the Children's Communication Checklist (CCC-2).

**SCQ**
The version 'Current situation' of the SCQ (Rutter, Bailey, & Lord, 2003; translated into Dutch by Warreyn, Raymaekers, & Roeyers, 2004) generates a total score and sub scores for social interaction, communication, and limited and stereotyped behavior based on behavior of the last three months. An example of a question is 'Did he or she use your hand as a tool as it was part of his or her own body?' and response categories are 'yes' and 'no'. This questionnaire is based on items of the Autism Diagnostic Interview – Revised (ADI-R). The primary dependent measure for social behavior was the SCQ Total scale based on parent ratings.

**SRS**
The SRS (Constantino, 2002; translated into Dutch by Roeyers, Thys, & Schittekatte, 2009) investigates whether 65 examples of behavior are 'not true', 'sometimes true', 'often true' or 'always true' during the last six months. An example of an item is 'His or her facial expressions correspond with his or her verbal expressions'. A total score and sub scores for Social awareness, Social cognition, Social communication, Social motivation, and Autistic mannerisms are calculated.

**CCC-2**
The CCC-2 (Bishop, 2003; translated into Dutch by Geurts, 2007) assesses improvement in children's language structure, pragmatics, and social interaction. Language structure includes the subscales speech production, syntax, semantics, and coherence. Pragmatics consists of the subscales inappropirate initiation, stereotyped conversation, use of context, and non-verbal communication. Social interaction includes the subscales social relations and interests. An example of an item is 'Does not look at the person to whom he or she is talking' and response categories for each question are 'never or less than once a week', 'at least once a week, but not every day', 'once or twice a day', and 'more than twice a day or always'. An age-related standard score was calculated for each subscale, for pragmatics, and for the total score comprising language structure and pragmatics.

**5.2.4 Executive functions**
According to Anderson (2002), executive functions are typically divided into separate sub domains, i.e., attentional control, cognitive flexibility, goal setting, and speed and efficiency. Each domain is represented by one or more executive function tasks. Selection of the tasks in this study was based on outcomes of our previous study (Kouijzer et al., 2009b).

**Attentional control**
Attentional control encompasses selective attention and response inhibition. Selective attention was measured by the Test of Sustained Selective Attention (TOSSA; Kovács, 2005c). In the TOSSA, participants have to respond to sets of 3 beeps while ignoring sets of 2 or 4 beeps. Beeps are presented during eight minutes at variable speed. The test score reflects the percentage of correct answers, calculated by dividing the number of hits by the total amount of items, times 100. Response inhibition is divided in a verbal and a motor variant. Verbal response inhibition was assessed by the Stroop test (Stroop, 1935). In this test, participants have to read aloud as soon as possible A) 100 words (green, red, yellow, and blue), B) the color of 100 colored rectangles, and C) the color of the ink of 100 written incongruent color names. The goal in part C is to pronounce the name of the color of the ink, while ignoring reading the word. The score on this test is the inferential time (time C minus time B) and represents the primary dependent measure of executive functioning in the present study. Motor response inhibition was assessed with the response inhibition score (RIS; range 0 – 100) of the TOSSA, based on the number of commission errors.

**Cognitive flexibility**
Cognitive flexibility covers set-shifting and concept generation. Set-shifting was examined by the Trail Making Test (TMT; Reitan, 1936). Participants have to A) connect 26 numbers, B) connect 26 characters, and C) switch between the numerical mode and the alphabetic mode by connecting 26 numbers and characters in the 1-A-2-B-3-C – order. A score on the TMT is calculated by subtracting the time needed to finish part C and the time needed to finish part B in seconds. Concept generation was examined by the Milwaukee Card Sorting Test (MCST; Kovács, 2005a), a computerized version of the Wisconsin Card Sorting Test. The participant has to generate and apply a non-
spoken rule for sorting cards (n=60), based on feedback (e.g. ‘good’ or ‘fault’). These card sorting principles can be either color, shape or number and change after every 10 correct answers. An indicator for cognitive flexibility is the percentage (0-100%) of cases in which a participant gives the right answer.

**Goal setting**
Goal setting was assessed by the Tower of London (TOL; Kovács, 2005b). Participants have to copy a construction of blocks and bars by moving three prearranged different colored blocks along three bars of different lengths. The score on the TOL is a percentage calculated by dividing the participants’ score by the maximum score, times 100.

**Speed and efficiency**
Speed and efficiency was assessed by a computerized Stroop task that shows 90 words (red, blue or green) on a computer screen for two seconds, written with either congruent or incongruent color of ink. In case of corresponding ink color and word, participants push the left mouse button, in case of non-corresponding ink color and word, participant push the right mouse button. Reaction times in seconds for incongruent items were used for analysis.

### 5.2.5 Neurophysiological measures

**Session data**
During all neurofeedback sessions, training equipment recorded oscillatory activity at the location where the electrode was attached. Ground and reference electrodes were attached to the mastoids. Training equipment included a portable Nexus-4 amplifier and recording system (Mindmedia, the Netherlands). Ag/AgCl disposable snap-on sensors (MedCaT, the Netherlands) were used.

**QEEG**
A QEEG is an assessment tool to determine individual differences in EEG oscillations along different frequency bands. A Mitsar EEG 201 System (Mitsar Medical Diagnostic Equipment, Russia) was used for recording and digitizing EEG. Data were acquired using a stretchable electrode cap containing 19 sensors at scalp locations Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2, according to the International 10/20 System (Jasper, 1958). Two ear clips were used as reference electrodes. Impedance was kept below 5 kΩ, with a maximum difference of 1 kΩ between electrodes. Data were collected for three minutes in rest and task conditions. Rest conditions involved eyes opened and eyes closed conditions in which participants were instructed to sit quietly and relax, either with their eyes opened or closed, for three minutes. Task conditions involved a Stroop task as described under Executive functions, Speed and efficiency and a Movement task in which participants had to open and close their fist while watching their own movement. The Stroop task was included to investigate levels of theta activation during cognitively demanding conditions, considering the possibility that effects of neurofeedback training may become apparent during the actual conditions that require modulation of these components (i.e., Stroop performance is known to modulate theta power; Hanslmayr et al., 2008). The Movement task was included because children with ASD may experience less agency over their movements resulting in difficulty in anticipating the consequences of their actions (Schmitz, Martineau, Barthélémy, & Assaiante, 2003). Impairments in agency may be reflected in theta activation accompanying deactivation of cortical midline structures in association with agency loss (Scheeringa et al., 2008; Spengler, Von Cramon, & Brass, 2009). QEEG data were collected during all four conditions before (Time1) and after treatment (Time2).

**5.2.6 Procedure**
The study started with a baseline assessment (Time1) including a series of behavioral questionnaires completed by parents and teachers, a range of executive functions tasks, and QEEG recording. Participants were then randomly divided into treatment and control group. Individualized neurofeedback treatment protocols were developed for participants of the treatment group as described under Neurofeedback training. Shortly after, participants of the treatment group started neurofeedback training twice a week at their own schools and during school hours. After 40 sessions of neurofeedback (Time2) and a comparable time interval for the control group, data on social behavior, executive functions, and QEEG were re-collected. Six months after ending all neurofeedback sessions (Time3), the same measures were collected again in a follow-up. Teachers did not fill out behavioral questionnaires at Time3, because the
summer holidays were in between Time2 and Time3 and pupils changed classes after the summer holidays.

5.2.7 Data analysis

Social behavior
Results of a one-sample Kolmogorov-Smirnov test showed that questionnaire data did not deviate significantly from normality. Besides, MANOVA demonstrated that treatment and control group showed no differences at any questionnaire scale at Time1, $F(1,18)=3.334$, $p=.409$, $\eta^2=.983$. All outcome measures were analyzed with Time x Group repeated measures MANOVA. Follow-up data were analyzed by Time (Time2 vs Time3) x Group and Time (Time1 vs Time3) x Group repeated measures MANOVA.

Executive functions
Results of a one-sample Kolmogorov-Smirnov test showed that data concerning attentional control, cognitive flexibility, goal setting, and speed and efficiency did not deviate significantly from normality. Besides, MANOVA demonstrated that treatment and control group showed no differences at any test for executive functions at Time1, $F(1,18)=.907$, $p=.544$, $\eta^2=.397$. All outcome measures were verified by Time x Group repeated measures MANOVAs. Follow-up data were analyzed by Time (Time2 vs Time3) x Group and Time (Time1 vs Time3) x Group repeated measures MANOVAs.

Session data
EEG data of all participants were recorded during 40 neurofeedback sessions at the scalp location where the electrode was placed for training. Eye blinks and other artifacts were manually removed. Data from a consecutive period of training at one scalp location and within the same frequency band were used for analysis. For each participant, Spearman's correlation coefficients were calculated for the relation between EEG power and Time, i.e., the number of completed sessions.

QEEG
Eye blinks and other artifacts were manually removed from the raw EEG data, based on a screening of electrodes Fp1 and Fp2 for eye blinks, electrodes F7 and F8 for horizontal eye movement, and the full EEG for head movement and muscular interference. The artifacted raw data of 15 electrodes (F3, Fz, F4, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2) were processed with fast Fourier transformations. Grand averages were calculated in each of four conditions (eyes opened, eyes closed, Stroop, movement) to determine individual location and frequency with maximum theta power. Data were analyzed in a Condition x Time x Group repeated measures MANOVA.

Correlation analysis between social behavior, executive functions, and neurophysiological data
Spearman's correlation coefficients between behavior, executive functions, and neurophysiological data in the treatment group were calculated using improvement scores of each level. The primary dependent measures for behavior (SCQ Total score) and executive functioning (Stroop interferential time) and theta power in QEEGs were used for calculating improvement scores by subtracting Time2 and Time1 scores. Improvement in session data was represented by the correlation coefficient between EEG power and Time.

5.3 Results

5.3.1 Social behavior

Parent informant
Three aspects of social behavior, i.e., social interactions, communication, and stereotyped and repetitive behavior, were compared before (Time1) and after treatment (Time2) for treatment and control group. Analysis of the primary dependent measure of social behavior, i.e., the SCQ Total score, with a Time (2) x Group (2) repeated measures MANOVA revealed a significant interaction effect, $F(1,18)=9.874$, $p<.01$, $\eta^2=.367$. Subsequent analyses revealed a main effect of Time indicating improvement in social behavior for the treatment group, $F(1,9)=24.962$, $p<.001$, $\eta^2=.735$, but not for the control group, $F(1,9)=.497$, $p=.501$, $\eta^2=.058$. Other questionnaires were analyzed with a Time (2) x Group (2) x Questionnaire (2) repeated measures MANOVA revealing a significant three-way interaction, $F(1,18)=6.276$, $p<.05$, $\eta^2=.287$.
ηr² = .270. Subsequent analyses revealed a main effect of Time indicating improvement in social behavior for the treatment group, F(1,9) = 10.628, p < .01, ηr² = .541, but not for the control group, F(1,9) = .007, p = .936, ηr² = .001. Table 2 shows means and standard deviations of all questionnaire's total and sub scale scores of treatment and control group and corresponding p-values of univariate Time (2) x Group (2) interactions. Lower mean scores indicate less problematic behavior.

**Teacher informant**

Analysis of the SCQ Total score, with a Time (2) x Group (2) repeated measures MANOVA revealed no significant interaction effect, F(1,18) = .341, p = .566, ηr² = .019. The other questionnaires were analyzed with a Time (2) x Group (2) x Questionnaire (2) repeated measures MANOVA and revealed no significant differences between treatment and control group, F(1,18) = .292, p = .597, ηr² = .042. Means, standard deviations, and corresponding p-values can be found in Table 3, with lower scores indicating less problematic behavior.

### 5.3.2 Executive functions

Tasks taxing attentional control, cognitive flexibility, goal setting, and speed and efficiency before (Time1) and after treatment (Time2) were compared for treatment and control group using Time (2) x Group (2) repeated measures MANOVAs. Means, standard deviations, and p-values of Time x Group interactions can be found in Table 4. Higher scores indicate improvement of executive functions, except for inhibition of verbal responses, shifting, and speed and efficiency. Analysis of the primary dependent measure of executive functioning, i.e., the Stroop interferential time, with a Time (2) x Group (2) repeated measures MANOVA revealed no significant interaction effect, F(1,18) = 1.454, p = .243, ηr² = .075. The other measures of cognitive performance were analyzed with a Time (2) x Group (2) x Executive function (6) repeated measures MANOVA revealing a significant three-way interaction, F(1,18) = 3.735, p < .05, ηr² = .633. Further analysis revealed a significant Time x Group interaction for set-shifting, F(1,18) = 4.652, p < .05, ηr² = .205. Subsequent analysis revealed a main effect of Time for the treatment group indicating significant improvement, F(1,18) = 3.555, p < .05, ηr² = .221, but not for the control group, F(1,18) = .454, p = .502, ηr² = .045. No significant effects were found for other domains of executive functioning, p's > .05.
5.3.3 Session data

Table 3.

Means and standard deviations of SCQ, SRS, and CCC-2 questionnaires and corresponding subscales filled out by teachers for the treatment and the control group and p-values of Time x Group interactions.

Table 4.

Means and standard deviations of treatment and control group on tests for executive functions and p-values of Time x Group interactions.
Cz. Data in the 4 to 6 Hz band at Cz were therefore averaged for further analysis. Table 5 shows means and standard deviations of averaged 4 to 6 Hz power at Cz of participants that reduced theta power in session data and of the control group in each condition.

Time1 and Time2 theta power in each condition were compared for participants that successfully reduced theta power during neurofeedback sessions and for the control group. Repeated measures MANOVA revealed a significant Time x Group x Condition interaction, $F(1,14)=3.763, p<.05, \eta^2=.653$. Further analysis showed decreases in theta power reflected by significant Time x Group interactions for the conditions eyes closed, $F(1,14)=4.883, p<.05, \eta^2=.259$, and movement, $F(1,14)=7.856, p<.05, \eta^2=.359$. Separate analysis of the two groups, however, revealed no main effects of Time for the condition eyes closed for the treatment group, $F(1,5)=3.116, p=.138, \eta^2=.384$, or for the control group, $F(1,9)=1.340, p=.277, \eta^2=.130$, suggesting that opposite directionality of effects in both groups contributed to the interaction. In the condition movement there was an effect of Time for the treatment group, $r=857$, $r=-.412^*$, $r=-.684^{**}, r=-.214, r=-.387^*$, $r=-.770^{**}, r=-.842^{**}, r=-.339, r=-.713^{**}$.

$F(1,5)=4.791, p<.05, \eta^2=.620$, but not for the control group, $F(1,9)=2.433, p=.153, \eta^2=.213$. The interaction between Time and Group for the condition eyes opened was not significant, $F(1,14)=1.828, p=.153, \eta^2=.115$. No pre-post differences in theta power were found in the Stroop condition, $F(1,14)=.018, p=.896, \eta^2=.001$.

5.3.5 Correlation analysis for social behavior, executive functions, and neurophysiological data

Correlation analyses were conducted to find relations between changes in behavior, executive functions, and neurophysiological data within the treatment group. Spearman's correlation analyses showed a positive correlation between improvement on the primary outcome measure for social behavior (SCQ) and improvement on the primary outcome measure for executive functions (Stroop), $r=.701, p<.05$ (see Figure 3). No such significant correlation was found for the control group, $r=.328, p=.389$. Average decreases in QEEG theta power correlated significantly with decreases in theta power in the session data that were shown by 60% percent of the participants, $r=.943, p<.01$ (see Figure 4).

5.3.6 Follow-up data

Social behavior was evaluated by parents six months after treatment ended (Time3) to investigate maintenance of effects. Comparing Time2 and Time3 data with repeated measures MANOVA revealed no significant Time x Group x Questionnaire interaction.

**Table 5.**

Means and standard deviations of the average of 4, 5, and 6 Hz power at Cz for treatment and control group before (Time1) and after treatment (Time2).

<table>
<thead>
<tr>
<th></th>
<th>Treatment group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time1</td>
<td>Time2</td>
</tr>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>Eyes closed</td>
<td>6.071 (3.357)</td>
<td>4.921 (1.972)</td>
</tr>
<tr>
<td>Eyes open</td>
<td>4.584 (1.835)</td>
<td>4.087 (1.155)</td>
</tr>
<tr>
<td>Stroop</td>
<td>5.476 (2.746)</td>
<td>5.125 (1.663)</td>
</tr>
<tr>
<td>Movement</td>
<td>4.810 (1.533)</td>
<td>3.547 (1.517)</td>
</tr>
</tbody>
</table>

Note. M= Mean, SD= Standard deviation.
F(1,18)=1.099, \ p=0.820, \ \eta^2 = 0.180, nor an effect of Time, F(1,18)=.306, \ p=0.820, \ \eta^2 = 0.058, suggesting maintenance of post-treatment levels six months after treatment ended. The comparison between Time1 and Time3 with repeated measures MANOVA revealed a significant Time x Group interaction, F(1,18)=4.871, \ p<0.05, \ \eta^2 = 0.223. Separate analysis of treatment and control group revealed significant improvement for the treatment group, F(1,9)=8.988, \ p<0.05, \ \eta^2 = 0.794, but not for the control group, F(1,9)=0.306, \ p=0.820, \ \eta^2 = 0.058. Within the treatment group, improvement was found on all questionnaires, e.g. the SCQ, F(1,9)=22.043, \ p<0.05, \ \eta^2 = 0.710, the SRS, F(1,9)=6.355, \ p<0.05, \ \eta^2 = 0.414, and the CCC, F(1,9)=7.892, \ p<0.05, \ \eta^2 = 0.467.

Follow-up data (Time3) on executive functions was compared with Time2 data by Time x Group x Executive function repeated measures MANOVA and revealed no significant interaction, F(1,18)=.186, \ p=0.671, \ \eta^2 = 0.010, suggesting maintenance of post-treatment levels six months after treatment ended. The comparison between Time1 and Time3 with Time x Group x Executive function repeated measures MANOVA revealed a marginal interaction effect, F(1,18)=2.513, \ p=0.077, \ \eta^2 = 0.594.

Further analysis revealed a significant Time x Group interaction for set-shifting, F(1,18)=5.499, \ p<0.05, \ \eta^2 = 0.234. Subsequent analysis revealed a main effect of Time for the treatment group, F(1,18)=17.249, \ p<0.05, \ \eta^2 = 0.976, indicating significant improvement six months after treatment ended compared to baseline, whereas no such effect was found for the control group, F(1,18)=2.302, \ p=0.265, \ \eta^2 = 0.843.

5.4 Discussion
The present study was successful in generating effects of neurofeedback training at
behavioral, cognitive, and neurophysiological outcome measures in a group of children with ASD as compared to a control group who received no training.

5.4.1 Behavioral outcome measures
Parents of children in the treatment group reported improvement on questionnaire subscales measuring reciprocal social interactions and verbal and non-verbal communication skills, compared to parents of children in the control group who indicated little or no improvement. This result is in line with studies of Jarusiewicz (2002), Coben and Padolsky (2007), and Pineda and colleagues (2008), who found improvement in social behavioral and communication skills after neurofeedback training as well. Jarusiewicz (2002), for example, found improvement in social interactions and communication measured with Autism Treatment Evaluation Checklist (ATEC) subscales such as ‘sociability’ and ‘speech, language, and communication’ in the treatment group, but not in the control group. In our previous study (Kouijzer et al., 2009b), significant improvements in social interactions, communication, and stereotyped and repetitive behavior were reported by parents of the neurofeedback treatment group. These results were maintained for at least one year (Kouijzer et al., 2009a). In the present study, follow-up measures after six months indicated maintenance of the results as well.

The positive effects of neurofeedback on reciprocal social interactions and communication skills reported by parents were not observed by teachers. There might be several reasons why this was not the case. First, agreements on the rating of behavioral traits between different informants, i.e., parents and teachers, are often only moderate (Achenbach, McConaughy, & Howell, 1987; Ronald, Happé, & Plomin, 2008) and might explain different outcomes on parent and teacher questionnaires in the present study. Second, from behavioral analyses we know that context characteristics may influence behavior (Achenbach et al., 1987). That is, because the child’s home and classroom provide largely different contexts, this might have affected the behavior of the children and subsequent estimations of parents and teachers. Finally, children with ASD may not automatically transfer newly acquired skills from one situation, for example at home, to other situations, for example the school. This generativity problem, which is often seen in ASD (Hill, 2004), may have enhanced the variation of the behavior of children with ASD across contexts.

5.4.2 Cognitive outcome measures
At the cognitive level, executive function tasks before and after neurofeedback treatment revealed improvement on set-shifting for the treatment group as compared to the control group that improved less. Additionally, there was a positive correlation between cognitive and behavioral task improvement: the more participants improved on the primary outcome measure for executive functioning, i.e., the Stroop task, the more improvement in behavior parents reported on the primary outcome measure for behavior, i.e., the SCQ questionnaire. Follow-up measures revealed that improvement in set-shifting was maintained for at least six months after neurofeedback treatment ended. Similar results were found in our previous study (Kouijzer et al., 2009b) where improvements on several executive function tasks including set-shifting were found after neurofeedback treatment. These results were maintained for at least one year.

5.4.3 Neurophysiological outcome measures
In addition to improvement at behavioral and cognitive levels, neurophysiological changes were found both during and after neurofeedback treatment, i.e., in EEG activity. Sixty percent of the participants in the present study succeeded to linearly decrease excessive theta activity over fronto-central scalp locations during neurofeedback training. Similar percentages were reported in previous studies (65%; Kouijzer et al., 2009b, 60-70%; Monastra et al., 2005). Furthermore, neurofeedback treatment was found to have an effect on theta power in participants’ QEEG that was recorded during post-treatment measures, in particular in the conditions eyes closed and movement, whereas no effects were found in the control group. No differences between groups were found for the Stroop task and the eyes opened condition. Interestingly, decreases of theta power in session data and in QEEG were highly correlated, suggesting that the treatment induced reduction in theta power was sustained after neurofeedback treatment ended. It is however unclear at this point why reductions in theta activation were found selectively during eyes closed and movement conditions and not during eyes opened and the Stroop task.

Results of the present study indicate that children with ASD were able to reduce slow wave brain activity and that neurofeedback caused changes in QEEG and improvement in set-shifting, reciprocal social interactions, and communication skills. It is interesting to speculate about the possible neurophysiological mechanisms.
underlying these outcomes. Neurofeedback treatment aimed at decreasing theta power, which is known to be generated in the medial prefrontal brain regions including the anterior cingulate cortex (ACC; Tsuijimoto, Shimazu, & Isomura, 2006). The medial prefrontal cortex (MPFC) has been associated with executive functions and social cognitive ability and is likely involved in executive dysfunctioning and behavioral disturbances in ASD (Bush, Luu, & Posner, 2000; Di Martino et al., 2009; Henderson et al., 2006; Mundy, 2003; Ohnishi et al., 2000). Ohnishi and colleagues (2000), for example, found that abnormal ACC activity was related to behavioral symptoms measured with the Childhood Autism Rating Scale (CARS).

Medial frontal theta power is inversely related to activation of medial prefrontal areas. The reduction of excessive theta power by neurofeedback in the present study thus might have enhanced activation of the MPFC and may thus have contributed to positive changes in set-shifting, reciprocal social interactions, and communication skills. Activation of the ACC by neurofeedback treatment was already demonstrated by Levesque, Beauregard, and Mensour (2006) who showed significant activation of the right ACC during a Stroop task in subjects with ADHD after 40 neurofeedback sessions inhibiting theta power (4-7 Hz) and enhancing SMR (12-15 Hz) and beta power (15-18 Hz).

Parts of the ACC belong to the default mode network (DMN), which is found activated mainly during rest and tasks requiring self-reflection (Northoff et al., 2006; Raichle et al., 2001). The rostral ACC and posterior cingulate cortices are mainly found to activate during rest and self-reflective, social tasks, whereas the dorsal ACC typically deactivates in these conditions (Di Martino et al., 2009; Kennedy & Courchesne, 2008; Raichle et al., 2001; Scheeringa et al., 2008). In reverse, the dorsal ACC becomes activated during cognitive demanding tasks, whereas the rostral ACC and posterior cingulate cortices will deactivate (Bush, Luu, & Posner, 2000; Raichle et al., 2001). In children with ASD, both dorsal and rostral ACC and posterior cingulate cortices were found to be functionally and structurally abnormal (Cherkassky, Kana, Keller, & Just 2006; Di Martino et al., 2009; Kennedy & Courchesne, 2008). A recent meta study of Di Martino and colleagues (2009), for example, reported hypoactivation of the dorsal and perigenual ACC during cognitive and social tasks respectively.

It is presently unclear which cortical structures were influenced by the current neurofeedback treatment. In both our previous and present studies, effects in theta power were most clearly visible at the central scalp location Cz. Luu and Tucker (2001) suggest that different parts of the ACC may contribute to theta activity at Cz. One explanation might be that neurofeedback treatment targeted dorsal ACC activity. This would mean that the neurofeedback treatment directly enhanced activation of areas in the ACC supporting executive functions, which may have contributed to the improvement in set-shifting that was found. Set-shifting refers to the ability to reflect on more than one set of rules and to shift rapidly between different actions or thoughts in reaction to changes in the context (Hill, 2004). Dealing with changes in schedules and procedures in daily life requires set-shifting and is crucial in showing socially adjusted behavior (Anderson, 2002). Set-shifting might be a basic skill for a variety of daily pursuits, such as reciprocal social interactions and communication skills. The improvements in set-shifting skills that were found in the present study might arise from enhancing activation in the dorsal ACC and may have contributed indirectly to the improvements in reciprocal social interactions and communication skills that were observed by parents. Another possibility is that neurofeedback treatment affected theta power in the rostral ACC and the posterior cingulate cortex. Enhancing activation in the rostral ACC and the posterior cingulate cortex would be expected to support social interactions and self-reflection, which could underlie the reported improvements in subjects’ reciprocal social interactions and communication skills indicated by parents. Furthermore, enhancing participants’ ability to modulate activity in rostral ACC and posterior parts of the DMN might positively affect operation of these areas. That is, during cognitive tasks, enhanced activation of the dorsal ACC is typically supported by lowering activation in the DMN. The clear correlation between improvement in behavior measured with the SCQ and improvement on the cognitive Stroop task supports the hypothesized relation between social and executive functions of the ACC.

Interestingly, compared to other studies that found theta power maximal at electrode site Fz (Ishii et al., 1999; Meltzer et al., 2007; Onton, Delorme, & Makeig, 2005), the current study found maximal effects of theta power at Cz. The most likely explanation is that our study included children who typically show enhanced theta power more posterior than adults (Yordanova & Kolev, 1997). Future research should clarify the involvement of the rostral and dorsal ACC and posterior cingulate cortices in neurofeedback treatment to further elaborate the neurophysiological basics underlying the efficacy of neurofeedback treatment.
5.4.4 Limitations
Randomized, controlled research should disentangle specific and unspecific effects of neurofeedback treatment (Heinrich et al., 2007). Although participants in the present study were randomly appointed to treatment and control conditions, we can not exclude effects of parents’ expectations on the questionnaire data. Nevertheless, a positive correlation between behavioral improvements as indicated by parents and improvements on a non-biased executive functioning task suggests that parents’ evaluations were in line with the more objective measures of cognitive performance. Besides expectations of parents, teachers filling out behavioral questionnaires before and after treatment could have been influenced by expectations similarly to parents, especially because treatment was carried out at school and during their classes. However, no effects were found in the teacher questionnaires.

In addition to expectation biases, results at behavioral, cognitive, and neurophysiological levels could be biased by differences in attention that were provided to both groups. Providing high amounts of time and attention to a group of participants might have positively affected these participants, rather than the treatment was truly effective. Providing an attention placebo to the control group would control for possible attention differences between groups and thereby helps to disentangle specific and unspecific effects of neurofeedback treatment.

5.4.5 Recommendations
Intervention programs should control for unspecific effects that might affect the outcomes of the study by carefully designing adequate research designs. As was mentioned earlier, parents’ expectations of the treatment and the provision of time and attention to the treatment group could have influenced the data. Future research should disentangle these biases.

As indicated by Heinrich and colleagues (2007), investigating the optimal neurofeedback protocol for each participant is necessary in further developing neurofeedback as an intervention for children with ASD. First, attention has to be paid to the frequency of training. In both our previous and present studies, neurofeedback sessions were successfully conducted twice a week until 40 sessions were completed. Whether this is the optimal composition of a neurofeedback treatment for children with ASD, however, is unknown. Second, procedures for determining scalp locations for electrode placement and frequency bands to be used for training have to be investigated. Autism has been referred to as a spectrum disorder ranging from a relatively mild to severe disorder and encompasses a broad range of symptoms. Therefore, it has been recommended to adapt interventions for children with ASD to the individual needs of each participant (Howlin, 1998). In contrast to our previous study (Kouijzer et al., 2009b) where one single treatment protocol was applied to all participants, i.e., inhibition of 4-7 Hz and stimulation of 12-15 Hz at C4, frequency bands and scalp locations in the present study were based on outcomes of individual QEEG comparisons with a normative database and therefore optimally adapted to each participant. In all cases, treatment protocols comprised the inhibition of a frequency range within the theta band between 3 and 8 Hz. Scalp locations varied between Cz, F2, and F4. Both neurofeedback treatments using fixed (Kouijzer et al., 2009b) and individualized treatment protocols thus appeared to be successful. The added value of individualized neurofeedback over fixed treatment protocols should be studied more directly in a single study.

5.4.6 Conclusion
Children with ASD who participated in the present study were able to reduce excessive theta power by neurofeedback, as was demonstrated by 60% of the participants. QEEG measures indicated significant decreases of theta power over medial frontal brain regions, suggesting a structural enhancement of activation of the ACC. Furthermore, reciprocal social interactions, communication skills, and set-shifting skills improved after neurofeedback treatment. Although there were biases in the study design concerning parents’ expectations and time and attention provided to both groups, these results suggest that neurofeedback treatment has the potential to become an important and prominent intervention for children with ASD.

Acknowledgements
We thank the boards of directors and all staff members of PI-school Entréa and Maashorst for offering the possibility to accomplish this research project. In particular we thank drs. Helen Coumans for her help as a neurofeedback therapist in this study. We also thank all the children that participated in the study and their parents. Finally, we thank MindMedia for their share in the availability of neurofeedback equipment.
Chapter 6

Is EEG-biofeedback an Effective Treatment For Autism? A Randomized Controlled Trial

Abstract

EEG-biofeedback has been reported to reduce symptoms of autism in several studies. However, these studies did not control for unspecific effects of EEG-biofeedback, such as treatment expectancy, implicit attention training, and one-to-one contact with the therapist. To overcome these methodological shortcomings, this study evaluated the effects of EEG-biofeedback in autism in a randomized pretest-posttest control group design with blinded active comparator and six months follow-up. Thirty-eight participants were randomly allocated to the EEG-biofeedback, skin conductance (SC)-biofeedback or waiting list group. EEG- and SC-biofeedback sessions were similar and participants were blinded to the type of feedback they received. Assessments pre-treatment, post-treatment, and after six months included parent and teacher ratings of autistic symptoms, executive function tasks, and EEG recordings. Fifty-four percent of the participants responded to EEG-biofeedback by significantly reducing delta and/or theta power during EEG-biofeedback sessions. No clinical effects were observed in these responders, but they showed significant improvement in cognitive flexibility as compared to EEG-non responders and participants of SC-biofeedback and waiting list groups. EEG-biofeedback is an applicable tool to change EEG activity of children with autism. Improvement in cognitive flexibility is observed after successful EEG-biofeedback. Further large scale clinical trials with EEG-biofeedback in autism seem to be warranted.

This chapter is based on: Kouijzer, M.E.J., van Schie, H.T., Gerrits, B.J.L., Buitelaar, J.K., & de Moor, J.M.H (under review). Is EEG-biofeedback an Effective Treatment For Autism? A Randomized Controlled Trial.
Chapter 6 Is EEG-biofeedback an Effective Treatment For Autism?

6.1 Introduction

Autism spectrum disorders (ASD) are characterized by qualitative abnormalities in social behavior and communication skills and restricted, repetitive, and stereotyped patterns of behavior, interests, and activities. Currently, no curative treatment of ASD is available, though many behavioral training programs exist to change abnormal behavior, such as programs based on applied behavior analysis (ABA; Peters-Scheffer, Didden, Kozlilius, & Sturkey, 2011). However, such programs do not entirely take away the symptoms of ASD, are expensive and demanding to administer, and take years to complete. Medication may play a role in the management of associated symptoms of ASD, such as irritability, rigidity, hyperactivity, impulsivity, and inattention, but side-effects may compromise therapeutic benefits (King & Bostic, 2006). In the search of alternative treatment options for children with ASD, electroencephalography (EEG)-biofeedback emerged as a promising option.

The rationale of applying EEG-biofeedback to children with ASD is based on findings from EEG studies. These studies have revealed abnormal patterns of EEG activity in individuals with ASD as compared to normal controls, such as increased delta and theta power (Chan, Sze, & Cheung, 2007; Murias, Webb, Greenson, & Dawson, 2007; Pop-Jordanova, Zorcec, Demerdzieva, & Gucev, 2010), decreased alpha power (Chan et al., 2007; Murias et al., 2007), and increased beta (Murias et al., 2007) and gamma power (Orekhova et al., 2007). Another consistent finding concerns local over-connectivity and long-distance under-connectivity in ASD (Wass, 2011). Finally, dysfunctions of the mirror neuron system were reflected in the EEGs of children with ASD (Oberman et al., 2005).

Previous studies that investigated the effects of EEG-biofeedback in children with ASD revealed improvement in social interactions and verbal and non-verbal communication skills after EEG-biofeedback (Coben & Padolsky, 2007; Jarusiewicz, 2002; Kouijzer et al., 2009b; Kouijzer et al., 2010; Scolnick, 2005; Sichel, Fehmi, & Goldstein, 1995; Thompson, Thompson, & Reid, 2010). In addition, executive functions improved after EEG-biofeedback (Coben & Padolsky, 2007; Kouijzer et al., 2009b; Kouijzer et al., 2010). Finally, EEG-biofeedback was found to successfully act upon several EEG frequency bands, such as theta power and low beta power (Scolnick, 2005; Sichel et al., 1995; Kouijzer et al., 2009b).

However, many of the previous studies have methodological shortcomings...
which make it difficult to draw the conclusion that EEG-biofeedback for individuals with ASD is evidence based. That is, the apparent effects of EEG-biofeedback might have been produced by unspecific effects of EEG-biofeedback such as treatment expectancy, implicit training of attention, and intensive one-to-one contact with the therapist (Heinrich, Gevensleben, & Strehl, 2007).

The present study aimed to control for unspecific effects of EEG-biofeedback in ASD. Therefore, a randomized pretest-posttest control group study with blinded active comparator group and six months follow-up was conducted. Participants were randomized over the EEG-biofeedback, skin conductance (SC)-biofeedback, and waiting list group. EEG-biofeedback aimed at normalizing absolute power in the frequency band that shows maximal deviations from normality in the participant’s pre-treatment EEG recording. SC-biofeedback aimed at reducing sweat gland activity, represented by the amount of electrical current the skin allows to pass after a very small electrical current is applied to the skin (Peek, 2003). SC-biofeedback is applied in the treatment of hypertensive patients and aims to relax patients (McGrady & Linden, 2003). In the present study, only minimal effects of SC-biofeedback were expected on symptoms of ASD and executive functions.

We hypothesized that EEG-biofeedback would change EEG activity in the direction of normality over sessions in a substantial subsample of children with ASD, i.e., the EEG-responders, in accordance with earlier research (Kouijzer et al., 2010; Kropotov et al., 2005; Lubar, Swartwood, Swartwood, & O’Donnell, 1995). Secondly, in line with outcomes of previous studies we hypothesized that EEG-responders would reduce in symptoms of ASD as well as improve in executive functions, as compared to non responding participants and participants of the control groups. Finally, we hypothesized to find normalizations in the post-treatment 19-channel EEGs of participants similar to the effects in EEG found during EEG-biofeedback sessions.

6.2 Method

6.2.1 Participants

Thirty-eight children and adolescents with ASD, aged 12 to 18 years (mean age: 15.2 ± 1.5 years) participated in the study. Participants were recruited from a Dutch secondary school for special education. Participants were randomly assigned to the EEG-biofeedback, SC-biofeedback or waiting list group. There were no pre-treatment differences between the groups concerning demographic, clinical, and neuropsychological variables (see Tables 1 and 2).

All participants fulfilled DSM-IV-TR criteria for ASD (American Psychiatric Association, 2000) according to the clinical diagnosis of a certified and independent child psychologist. The diagnosis was confirmed for 35 participants by the results of the Autism Diagnostic Interview revised (ADI-R; Lord, Rutter, & Le, 1994). Diagnoses of three participants were not in accordance with the ADI-R criteria for ASD, but their clinical diagnoses were all convincing. Participants with co-morbid ADHD, epilepsy, or acquired brain injury were excluded from the study. Eight participants used medication, i.e., Risperdal (n=4), Risperdal and Fluoxetine (n=1), Fluvoxamine (n=1), Dipiperone (n=1), and Enalapril (n=1).

The study was approved by the local medical-ethics committee. Written informed consent was obtained from all participants and their parents.

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>Demographic and clinical characteristics of the EEG-biofeedback, SC-biofeedback, and waiting list group.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EEG-group</td>
</tr>
<tr>
<td>n=13</td>
<td>n=12</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>3/10</td>
</tr>
<tr>
<td>Age (years; months)</td>
<td>15.3 ± 1.5</td>
</tr>
<tr>
<td>Medication use (yes/no)</td>
<td>2/11</td>
</tr>
<tr>
<td>IQ</td>
<td>104.1 ± 15.8</td>
</tr>
<tr>
<td>Diagnosis (autism/ Asperger/ PDD-NOS)</td>
<td>3/4/6</td>
</tr>
<tr>
<td>ADI reciprocal social interaction</td>
<td>15.8 ± 5.3</td>
</tr>
<tr>
<td>ADI communication</td>
<td>12.6 ± 5.5</td>
</tr>
<tr>
<td>ADI restricted, repetitive and stereotyped behavior</td>
<td>3.9 ± 3.1</td>
</tr>
<tr>
<td>SCQ total score</td>
<td>17.31 ± 6.23</td>
</tr>
<tr>
<td>SCQ reciprocal social interactions</td>
<td>6.54 ± 3.31</td>
</tr>
<tr>
<td>SCQ communication skills</td>
<td>7.38 ± 1.76</td>
</tr>
<tr>
<td>SCQ restricted and stereotyped behavior</td>
<td>2.38 ± 1.85</td>
</tr>
</tbody>
</table>
6.2.2 Design of the study
The set up of EEG- and SC-biofeedback treatment was similar. The only difference was that in the EEG-biofeedback group, feedback was provided on EEG and in the SC-biofeedback group, feedback was provided on SC. Both treatments were introduced as experimental, but promising treatments for children with ASD. Both EEG- and SC-biofeedback treatment included 40 individual sessions that were provided twice a week and at the school of the participants. Pre-treatment assessment took place about one week before the first session. Post-treatment and follow-up assessments were done about one week after the last session and after six months, respectively. Participants, parents, and teachers were blinded for treatment allocation to EEG- or SC-biofeedback groups, but not for the waiting list group.

6.2.3 Design of the biofeedback treatments
A Nexus-4 amplifier and recording system and Ag/AgCl disposable snap-on electrodes were used for EEG- and SC-biofeedback treatment. During EEG- and SC-biofeedback sessions, participants sat in front of a computer screen while EEG and SC were measured concurrently. Each session comprised seven three-minute intervals of EEG- or SC-biofeedback, separated by one-minute rest intervals. The task was to decrease the bar graph on the computer screen. This bar graph represented EEG activity in the EEG-biofeedback group and SC in the SC-biofeedback group. If the bar graph moved below the criterion line, participants were rewarded with a counter and a film clip with sound of interest to the participants. Feedback was provided in 50-80% of the time. SC feedback was derived from electrodes attached to the participants’ index finger of their non-dominant hand. EEG feedback (reference: mastoids, bandwidth: 1-30 Hz, sampling rate: 250 Hz) was calculated from the electrode and frequency band defined by comparing each participant’s pre-treatment EEG recording to a validated normative database (Neuroguide; Thatcher, Walker, Biver, North, & Curtin, 2003).

6.2.4 Symptoms of ASD
Social Communication Questionnaire
The version ‘Current situation’ of the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003; translated into Dutch by Warreyn, Raymaekers, & Roeyers, 2004) is a 40-item questionnaire related to ADI-R criteria for ASD. Response categories are ‘yes’ and ‘no’. Outcome measures are scores for reciprocal social interactions (range 0-15), communication (range 0-13), and limited and stereotyped behavior (range 0-8). The parents’ SCQ total score (range 0-36) constituted the primary outcome measure of the study. Parent and teacher ratings were assessed at two time points: pre- and post-training. Parent ratings were additionally assessed at follow-up after six months.

Clinical Global Impression
The global improvement item of the Clinical Global Impression (CGI) reflects overall symptomatic change as compared to baseline and is measured on a 7-point scale ranging from ‘very much improved’ to ‘very much worse’ (Guy, 1976). The CGI was filled out by the EEG- or SC-biofeedback therapist after the final session.

6.2.5 Treatment expectancy
A 5-item questionnaire was developed by the authors of this study and was based on Borkovec & Nau (1972). Response was given on a 9-point scale ranging from ‘completely negative’ to ‘completely positive’. An example of an item is ‘Do you think biofeedback will reduce your symptoms of ASD?’ Outcome measure was the mean score of all items (range 1-9). This questionnaire was filled out by participants, parents, and teachers before participants were randomly allocated to one of the research groups.

6.2.6 Executive functions
Cognitive flexibility
The Trail Making Test (TMT; Reitan, 1956) was used to measure cognitive flexibility. Participants locate and connect as soon as possible and in the right order 26 numbers (part A), 26 characters (part B), and 26 numbers and characters in the 1-A-2-B-3-C – order (part C). The score for cognitive flexibility is represented by the time in seconds needed to finish part C minus the time in seconds needed to finish part B.

Inhibition
The Stroop task (Stroop, 1935) was used to measure inhibition. Participants read aloud as soon as possible 100 words (part A), the color of 100 colored rectangles (part B),
19-channel EEG data were processed with fast Fourier transformations and averages were calculated per condition, electrode, and frequency band (delta: 1-4 Hz, theta: 4-8 Hz). MANOVA was applied to investigate differences between conditions. Repeated measures MANOVAs with between-subjects factor Group and within-subjects factor Time were applied to investigate differences in treatment expectancy of participants, parents, and teachers.
subjects factors Time and Frequency band were applied for midline electrodes Fz, Cz, and Pz. A significant multivariate Time x Frequency band x Group interaction was required in order to continue with subsequent analyses.

6.3 Results

6.3.1 EEG database comparisons
Comparing the pre-treatment EEG recording of each participant in the EEG-biofeedback group to a normative database revealed maximal deviations from normality at Cz (n=8) or CFz (n=5). These deviations were found in delta and/or theta power (2-9 Hz), resulting in the following frequency bands to be inhibited during EEG-biofeedback treatment: 2-7 Hz (n=4), 3-7 Hz (n=2), 3-9 Hz (n=1), 4-7 Hz (n=4), 5-7 Hz (n=1), and 5-9 Hz (n=1).

6.3.2 EEG- and SC-biofeedback sessions

EEG amplitude
Seven participants of the EEG-biofeedback group showed a negative correlation of delta and/or theta power across sessions, r's -.365 to -.803, p's < .05, and were referred to as EEG-responders. None of the participants in the SC-biofeedback group showed such a correlation. Repeated measures MANOVA showed a marginally significant interaction of delta and/or theta power of EEG- and SC-responders, F(1,13)=4.423, p=.055, ηp²=.254, demonstrating a decrease in delta and/or theta in EEG-responders, F(1,6)=6.584, p=.043, ηp²=.523, but not in SC-responders. No decreases in delta and/or theta were found in EEG- and SC-non responders.

SC amplitude
Eight participants in the SC-biofeedback group showed a negative correlation of SC across sessions, r's -.365 to -.840, p's<.05, and were referred to as SC-responders. Five participants of the EEG-biofeedback group (one EEG-responder, four EEG-non responders) showed such a correlation, r's -.472 to -.741, p's<.05. This was not unexpected, since familiarity with EEG-biofeedback might enhance relaxation and thus decrease SC. Repeated measures MANOVA showed a main effect of Time, F(1,13)=6.332, p=.026, ηp²=.328, suggesting that SC decreased in both EEG- and SC-responders.

Number of sessions
Forty EEG- or SC-biofeedback sessions were not completed by four participants of the EEG-biofeedback group (they completed 34, 33, 29, and 23 sessions) and five participants of the SC-biofeedback group (they completed 38, 35, 32, 31, and 29 sessions), because of frequent school absence due to illness, tiredness or overstimulation during school days.

Blinding
There were no differences between groups regarding the success in blinding. Fifty-eight percent of the participants of both groups thought they had received a combination of EEG- and SC-biofeedback; 33% of the EEG-biofeedback group and 42% of the SC-biofeedback group thought they had received EEG-biofeedback.

6.3.3 Symptoms of ASD

SCQ
Repeated measures MANOVA of both parent and teacher ratings showed no changes in the SCQ total score (primary outcome measure) of EEG-responders as compared to participants of other groups. No effects were found in the SCQ subscales.

CGI
Repeated measures MANOVA showed no global improvement after EEG-biofeedback compared to SC-biofeedback, neither was there a difference between the global improvement of EEG-responders and EEG-non responders.

6.3.4 Treatment expectancy
ANOVA revealed no differences in treatment expectancy between groups, neither was there a difference between responders and non responders. Using treatment expectancy as a covariate in any analysis did not reveal significant effects.

6.3.5 Executive functions
Scores of executive function tasks are summarized in Table 2. Repeated measures
Note. 1 Lower scores indicate improvement; 2 Higher scores indicate improvement.

<table>
<thead>
<tr>
<th></th>
<th>EEG-biofeedback group</th>
<th>SC-biofeedback group</th>
<th>Waiting list controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders</td>
<td>Non responders</td>
<td>Responders</td>
</tr>
<tr>
<td></td>
<td>pre post follow-</td>
<td>pre post follow-</td>
<td>pre post follow-</td>
</tr>
<tr>
<td></td>
<td>up</td>
<td>up</td>
<td>up</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>23.57 ±17.83</td>
<td>40.14 ±15.51</td>
<td>66.04 ±15.24</td>
</tr>
<tr>
<td>Inhibition</td>
<td>14.50 ±14.84</td>
<td>32.67 ±8.94</td>
<td>68.98 ±10.84</td>
</tr>
<tr>
<td>Planning</td>
<td>12.50 ±6.97</td>
<td>29.00 ±13.30</td>
<td>73.56 ±11.06</td>
</tr>
<tr>
<td>Attention</td>
<td>12.46 ±11.37</td>
<td>39.85 ±21.16</td>
<td>70.79 ±13.59</td>
</tr>
<tr>
<td>Working memory</td>
<td>11.57 ±13.58</td>
<td>29.86 ±10.95</td>
<td>69.86 ±12.87</td>
</tr>
<tr>
<td>Inhibition</td>
<td>4.33 ±5.86</td>
<td>22.00 ±9.85</td>
<td>59.67 ±27.20</td>
</tr>
<tr>
<td>Planning</td>
<td>12.84 ±7.74</td>
<td>31.92 ±17.77</td>
<td>84.39 ±13.08</td>
</tr>
<tr>
<td>Attention</td>
<td>10.4 ±13.86</td>
<td>21.80 ±4.87</td>
<td>71.74 ±6.50</td>
</tr>
<tr>
<td>Working memory</td>
<td>11.12 ±7.84</td>
<td>27.87 ±9.64</td>
<td>85.88 ±13.68</td>
</tr>
<tr>
<td>Inhibition</td>
<td>4.33 ±5.86</td>
<td>22.00 ±9.85</td>
<td>59.67 ±27.20</td>
</tr>
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<td>12.84 ±7.74</td>
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<td>Attention</td>
<td>10.4 ±13.86</td>
<td>21.80 ±4.87</td>
<td>71.74 ±6.50</td>
</tr>
<tr>
<td>Working memory</td>
<td>11.12 ±7.84</td>
<td>27.87 ±9.64</td>
<td>85.88 ±13.68</td>
</tr>
<tr>
<td>Inhibition</td>
<td>4.33 ±5.86</td>
<td>22.00 ±9.85</td>
<td>59.67 ±27.20</td>
</tr>
</tbody>
</table>

Table 2. Scores of executive function tasks (mean scores ± standard deviations).

MANOVA showed a Time x Group interaction, $F(12,40)=3.013$, $p=0.004$, $\eta^2=.475$. Subsequent analysis revealed a marginally significant interaction for cognitive flexibility, $F(2,25)=2.665$, $p=0.089$, $\eta^2=.176$, but not for other executive functions. Pairwise group comparisons revealed differences in cognitive flexibility between EEG- and SC-responders, $F(1,13)=12.013$, $p=0.004$, $\eta^2=.480$, EEG-responders and waiting list controls, $F(1,18)=3.313$, $p=0.085$, $\eta^2=.155$, EEG-responders and EEG-non responders, $F(1,17)=7.498$, $p=0.019$, $\eta^2=.405$, and EEG-responders and SC-non responders, $F(1,19)=9.810$, $p=0.012$, $\eta^2=.522$. EEG-responders showed improvement in cognitive flexibility, $F(1,6)=16.346$, $p=0.007$, $\eta^2=.731$, as compared to participants of other groups. After six months, the cognitive flexibility score of EEG-responders was still significantly higher than their score before EEG-biofeedback treatment, $F(1,6)=11.128$, $p=0.016$, $\eta^2=.650$, as compared to participants of other groups.

6.3.6 19-Channel EEG

MANOVA revealed no differences between conditions and thus mean values were calculated over conditions. Repeated measures MANOVA showed a significant Time x Frequency band x Group interaction for electrode Pz, $F(2,19)=3.782$, $p=0.045$, $\eta^2=.279$. Subsequent analyses revealed a marginally significant Time x Group interaction for delta power, $F(2,19)=3.478$, $p=0.052$, $\eta^2=.268$. Pairwise group comparisons revealed differences between EEG- and SC-responders, $F(1,11)=5.611$, $p=0.037$, $\eta^2=.338$, and EEG-responders and EEG-non responders, $F(1,11)=3.828$, $p=0.076$, $\eta^2=.258$, but not between EEG-responders and participants of other groups. EEG-responders showed a reduction of delta power, $F(1,6)=8.971$, $p=0.024$, $\eta^2=.599$, as compared to participants of other groups. No effects were found in the theta band or in other electrodes. After six months, the reduction in delta power of EEG-responders was not maintained.

6.4 Discussion

The present study showed that EEG-biofeedback resulted in a negative correlation of delta and/or theta power across sessions in 54% of the participants, i.e., EEG-responders. These EEG-responders improved in cognitive flexibility, as compared to EEG-non responders and participants in the SC-biofeedback and waiting list groups. Importantly, the improvement in cognitive flexibility was found sustained after six months, implicating a long lasting effect of the treatment. Furthermore, a temporary reduction of
delta power was found in the 19-channel EEGs of EEG-responders, as compared to other participants. Finally, no improvement in symptoms of ASD was reported by parents or teachers of EEG-responders, as compared to other participants.

The improvement in cognitive flexibility we found after EEG-biofeedback is consistent with the results of previous studies that also found improved cognitive flexibility after EEG-biofeedback (Cohen & Padolsky, 2007; Kouijzer et al., 2009b; Kouijzer et al., 2010). Improvement in cognitive flexibility seems to be a specific consequence of the successful application of EEG-biofeedback and can not be explained by implicit attention training, intensive one-to-one contact with the therapist during EEG-biofeedback or treatment expectancy. That is, no improvement in cognitive flexibility was found in EEG-non responders and in participants of the SC-biofeedback group, who had similar quantities of attention training, one-to-one contact with the therapist, and expectancies of the treatment.

Cognitive flexibility in the present study was measured with the TMT, in which participants had to locate and connect as quickly as possible and in the right order 26 numbers (part A), 26 characters (part B), and 26 numbers and characters in the 1-A-2-B-3- C -order (part C). In a study investigating the construct validity of the TMT (Sanchez-Cubillo et al., 2009), it was concluded that this task primarily reflects task switching abilities. Task switching, or cognitive flexibility, is defined as the ability to shift to a different thought or action according to situational changes (Hill, 2004). In the TMT, cognitive flexibility is defined as the additional time needed to shift between numbers and characters (part C) compared to the time needed to connect characters only (part B). EEG-responders showed a 49% reduction of time needed to complete part C as compared to part B. Six months after EEG-biofeedback ended the improvement in TMT performance increased even further to 88%. These percentages are in accordance with previous studies that showed similar improvement in TMT performance following EEG-biofeedback, i.e., 57% (Kouijzer et al., 2009b) and 43% (Kouijzer et al., 2010). Follow-up studies after six and twelve months showed further increases of TMT performance to 79% (Kouijzer et al., 2010) and 60% (Kouijzer et al., 2009a) respectively. Multiple studies thus suggest substantial improvement in cognitive flexibility as measured with the TMT following EEG-biofeedback.

Deficient cognitive flexibility is found as one of the characteristic deficits in ASD (e.g. Hughes, Russell, & Robbins, 1994). Children and adolescents with ASD often lack the ability to adapt to continuously changing social situations, which makes it hard to adjust their behavior to varying circumstances. As a result, children and adolescents with ASD often become distressed in changing situations and insist on sameness. Deficient cognitive flexibility is furthermore associated with a lack of improvement in social adaptive functioning following treatment (Berger, Aerts, van Spaendonck, Cools, & Teunisse, 2003). Hence, the positive effect of EEG-biofeedback on cognitive flexibility could be of great importance to the lives of children and adolescents with ASD. For instance, they might be better able to deal with changing situations at home and in school and their abilities to improve in social adaptive functioning might improve after EEG-biofeedback. It would be of great interest to include measures of cognitive flexibility in real life situations in future studies to determine whether EEG-biofeedback results in better coping with situational changes and improved social adaptive functioning.

In contrast to the large effect of EEG-biofeedback on cognitive flexibility, no effects were found on the clinical symptoms of ASD. This finding contradicts previous studies that did find reductions in sociability problems and communication deficits after EEG-biofeedback (Cohen & Padolsky, 2007; Jarusiewicz, 2002; Kouijzer et al., 2010). The absence of reductions in ASD symptoms in the present study provides some support for the suggestion that previous findings of parental report may have been confounded by unspecific effects of EEG-biofeedback. At the same time, however, we need to be careful in drawing firm conclusions considering that the EEG- and SC-biofeedback groups showed no improvement over the waiting list group. That is, if it would really be the case that unspecific effects of EEG-biofeedback would be responsible for reductions in ASD symptoms, one would have expected a significant difference between the treatment and waiting list group.

There may be alternative reasons for the difference in outcomes in symptoms of ASD between the present and previous studies, such as differences in sample characteristics. The samples of participants with ASD of present and previous studies were different with respect to age and co morbidity. Participants of the present study were 12 to 18 years old, whereas most other studies included younger participants. Older children and adolescents may be less sensitive to changes in behavior, or alternatively, parents of older children and adolescents may have less notion of their children's behavior throughout the day. Furthermore, the participants in the present study had no co morbid ADHD diagnoses, whereas previous studies might have included participants with ASD and ADHD.
Perhaps participants with both ASD and ADHD react differently to EEG-biofeedback than participants with only ASD. Alternatively, the effects of EEG-biofeedback might be less noticeable in participants with only ASD. This idea is supported by recent studies indicating substantial improvements in impulsive and hyperactive behavior in ADHD following EEG-biofeedback (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009). Future studies investigating the behavioral effects of EEG-biofeedback in individuals with ASD with or without ADHD may further explicate this possibility.

In conclusion, the present study demonstrated that EEG-biofeedback resulted in reduced delta and/or theta power in 54% of the children and adolescents with ASD. These EEG-responders showed long-term improvement in cognitive flexibility. An outstanding challenge for future research in this domain is to investigate the effects of EEG-biofeedback on cognitive flexibility in real life situations. Another issue is that no significant reductions in symptoms of ASD were observed by the parents and teachers. Such improvements in real life situations or observable reductions in symptoms of ASD might be important criteria for children and adolescents with ASD and their parents in opting for EEG-biofeedback. As such, the results of the present study are inconclusive with respect to the application of EEG-biofeedback in children and adolescents with ASD. Nevertheless, the study provides further incentive and direction to future research investigating EEG-biofeedback as an efficacious treatment for children and adolescents with ASD.

Acknowledgements
We would like to thank the board of VSO Mariëndaal, Arnhem, the students that participated in the study, and the EEG- and SC-biofeedback therapists who assisted us. We offer thanks to Fonds NutsOhra, who financially supported this research project. We thank MindMedia for sharing in the availability of biofeedback equipment and BrainClinics Nijmegen for providing us with biofeedback supplies.

Chapter 7
General discussion

The main aim of the research reported in this dissertation was to investigate the efficacy of neurofeedback treatment for children and adolescents with autism spectrum disorders (ASD). In three consecutive studies, we focused on the effects of neurofeedback on clinical symptoms of ASD, executive functions, and EEG activity. In the following section I will first summarize the results of the studies described in this dissertation. Subsequently I will discuss two clear effects we found neurofeedback to have on children and adolescents with ASD and the relations between these effects. After that, I will describe the results of the presented studies that are less obvious. Next, I will address the feasibility of a randomized controlled trial with skin conductance (SC)-biofeedback as a blinded control condition. Finally, I will address the status of neurofeedback as a treatment for ASD and provide suggestions for future research.

7.1 Overview of the results
In the first pilot study we explored the effects of neurofeedback in children with ASD (chapter three). Seven 8 to 12 year old children with pervasive developmental disorder not otherwise specified (PDD-NOS) received 40 neurofeedback sessions in which theta power was inhibited and sensorimotor rhythm (SMR) was enhanced. During these neurofeedback sessions, five out of seven children showed decreased
theta and increased SMR. Compared to seven matched controls, children who had neurofeedback showed improvement in social interactions, communication skills, and typical behavior, as reflected by behavior questionnaires filled out by parents. Furthermore they improved in inhibition, cognitive flexibility, planning, and attention skills, as measured by executive functioning tasks. The long term effects of neurofeedback were investigated in a follow-up study (chapter four). Twelve months after neurofeedback training ended, the participants of the neurofeedback group had maintained their improved levels of behavioral and cognitive performance.

In a second study, we further investigated the effects of neurofeedback in children with ASD in a randomized controlled design with six months follow-up (chapter five). Twenty children with ASD aged 8 to 12 were randomly assigned to a neurofeedback or waiting list group. During 40 neurofeedback sessions that aimed to inhibit theta power, six out of ten children showed reduced levels of theta power. These theta reductions were also seen in post treatment 19-channel EEG recordings relative to pre treatment recordings. No changes in EEG activity were found in the waiting list group. After neurofeedback training, parents indicated improvement in reciprocal social interactions and communication skills on behavior questionnaires measuring symptoms of ASD, relative to parents of children in the waiting list group. Furthermore, children in the neurofeedback group improved on a neuropsychological task measuring cognitive flexibility as compared to children in the waiting list group. The differences in social interactions, communication skills, and cognitive flexibility between the neurofeedback and the waiting list group were still present after six months, suggesting maintenance of the effects of neurofeedback treatment.

In the final study, we investigated the effects of neurofeedback in children and adolescents with ASD in a randomized controlled design with blinded active comparator and six months follow-up (chapter six). Thirty-eight children and adolescents with ASD aged 12 to 18 were randomly assigned to one of three experimental groups: EEG-biofeedback (or neurofeedback), skin conductance (SC)-biofeedback or waiting list. Participants of the EEG-biofeedback group received neurofeedback treatment that aimed to reduce delta and/or theta power; participants of the SC-biofeedback group received SC-biofeedback treatment that aimed to reduce SC. Neurofeedback and SC-biofeedback treatment were similar and participants were blinded to the type of treatment they received. Delta and/or theta power were reduced during neurofeedback sessions in seven out of 13 participants of the EEG-biofeedback group, i.e., the responders to neurofeedback. These responders improved in cognitive flexibility, as compared to non responders and participants of other groups. Six months after the last neurofeedback session, responders to neurofeedback had maintained an improved level of cognitive flexibility as compared to other participants. In the 19-channel EEGs of responders to neurofeedback, a temporary reduction of delta power was found post treatment, whereas no such reduction was found in other participants. Parent and teacher ratings indicated no effects on clinical symptoms of ASD after neurofeedback treatment.

7.2 Altered EEG activity and improved cognitive flexibility after neurofeedback

Two main conclusions can be drawn from the research presented in this dissertation: 1) neurofeedback can be used to alter EEG activity in a substantial part of children and adolescents with ASD and 2) neurofeedback results in improved cognitive flexibility in participants whose delta and/or theta power is reduced during neurofeedback sessions. The first conclusion confirms the main assumption of neurofeedback that abnormal patterns of EEG activity can be altered by neurofeedback. In the three studies that are presented here, 70% (chapter three), 60% (chapter five), and 54% (chapter six) of the children and adolescents with ASD showed reduced delta and/or theta power during 40 consecutive neurofeedback sessions. In other words: they responded to neurofeedback treatment at the level of EEG.

The second conclusion points to the fact that responders to neurofeedback improved in cognitive flexibility in all three studies1. This finding is important, since children and adolescents with ASD often display impairments in cognitive flexibility (Hughes, Russell, & Robbins, 1994). As a result, they are often distressed in changing situations and they insist on sameness. Deficient cognitive flexibility was also considered as a factor that prevents individuals with ASD from improving in social adaptive functioning following treatment (Berger, Aerts, van Spaendonck, Cools, & Teunisse, 2003). Hence, improvement in cognitive flexibility following neurofeedback may be of great importance to children and adolescents with ASD if it would allow

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1 Although not reported in chapter three and five of this dissertation, the improvement in cognitive flexibility was only found for responders to neurofeedback and not for non responders.
them to deal with changing situations better or offer them a chance to improve their social adaptive functioning.

7.3 Relation between altered EEG activity and improved cognitive flexibility: two explanations

How to explain the relation between the two main findings of these studies, i.e., altered EEG activity and improved cognitive flexibility? The most obvious explanation is that altered EEG activity, i.e., decreased delta and/or theta power, elicited improvement in cognitive flexibility. This explanation is in line with the idea that correcting abnormal EEG patterns through neurofeedback results in symptom reduction and other positive changes (e.g., Demos, 2005). Interestingly, a post-hoc analysis including the responders of all three studies revealed a significant negative correlation between decreased delta and/or theta power during neurofeedback sessions and improvement in cognitive flexibility, \( r = -0.47, p = 0.01 \) (see Figure 1). This correlation suggests that participants who show a large decrease in delta and/or theta power during neurofeedback treatment show most improvement in cognitive flexibility.

In relation to this explanation, previous studies have reported a negative relation between decreases in delta and theta power and activation in the default mode network (DMN) of the brain (Scheeringa et al., 2008; Meltzer, Negishi, Mayes, & Constable, 2007). An interesting possibility that was suggested in chapter three of this dissertation is that enhanced activation in the DMN is responsible for the improved cognitive flexibility of children and adolescents with ASD. Influencing excessive delta and theta activation in individuals with ASD towards a normal range via neurofeedback may have allowed participants more room in varying delta and theta activation in accordance with task requirement demanding a flexible allocation of attention\(^2\). As such the presented findings provide a confirmation of the in chapter three proposed functional involvement of theta power in relation to the DMN and its contribution to cognitive flexibility (chapter three).

An alternative explanation for the relation between altered EEG activity and improved cognitive flexibility is that a third factor has caused both effects. Such a factor might be dealing with alternating time periods with and without rewards during neurofeedback sessions. That is, participants were rewarded with a film clip and sound that started to play each time the amplitude of the EEG signal was below a predetermined threshold. The rewards were interrupted if the amplitude exceeded the threshold. As a consequence, participants had to switch numerous times between time periods with and without rewards. One possibility is that the alternating onset/offset of the film clip and sound provided an additional training of cognitive flexibility, which in turn might have resulted in improved cognitive flexibility skills. In line with the idea of Eling and Maes (2009) that EEG activity only changes as a result of behavioral changes, decreased delta and/or theta power may actually be another result of flexibility training. The fact that participants of the SC-biofeedback group did not improve in cognitive flexibility (chapter six) might be a consequence of the fewer opportunities to train flexibility skills in these participants as compared to participants of the neurofeedback group. That is, SC is a much slower signal compared to EEG and thus the time periods

\(^2\) That is, effective allocation of externally directed attention is found to be supported by de-activations in the DMN (Kelly et al., 2008; Weissman et al., 2006).

![Figure 1](image_url)

**Figure 1.**

The correlation between decreased delta and/or theta power (the correlation coefficient of session x delta/theta power) and improved cognitive flexibility (pre- minus post-treatment assessment) of the responders of three studies.
with and without rewards of participants in the SC group alternated less frequently than in the neurofeedback group. The exact relation between decreased delta and/or theta power and improved cognitive flexibility cannot be investigated in the data of the presented studies and calls for future research investigating these hypotheses.

### 7.4 Inconclusive effects of neurofeedback on clinical symptoms of ASD

Neurofeedback treatment was associated with a reduction in clinical symptoms of ASD in two of the studies described in this dissertation (chapter three and five) and in several previous studies (Cohen & Padolsky, 2007; Jarusiewicz, 2002; Sichel, Fehmi, & Goldstein, 1995), but not in the final study of this dissertation (chapter six). Currently, we can not explain why the effects of neurofeedback on clinical symptoms of ASD are inconsistent, but there were some differences between the studies that might have played a role. These differences concern the age of participants of the studies, their type of behavioral problems, and the control for unspecific effects.

The age of participants in the study where neurofeedback did not result in less symptoms of ASD was 12 to 18 years, whereas in most of the earlier studies participants were 8 to 12 years old. Perhaps 12 to 18 year olds are less capable of reducing symptoms of ASD as compared to younger children with ASD, or alternatively, parents of older children and adolescents may have less notion of their children’s behavior throughout the day.

Secondly, participants of the study where no reductions in symptoms of ASD were found were recruited from a special education school that only allowed students with mainly internalizing behavior problems, such as anxiety and shyness. Previous studies did not specify the behavior problems of participants and probably included participants with externalizing behavior problems as well. Children and adolescents with ASD and internalizing behavior problems might react differently to neurofeedback treatment as compared to children and adolescents with ASD and externalizing behavior. This idea is supported by recent studies indicating substantial improvements in impulsive and hyperactive behavior of children with ADHD following EEG-biofeedback (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009).

Finally, only the study where no reductions of symptoms of ASD were found following neurofeedback controlled for unspecific effects (chapter six). Unspecific effects are positive effects that are caused by other factors than the treatment of interest. In the case of neurofeedback, implicit attention training and intensive one-to-one contact with the therapist might have been such factors. That is, participants might be positively affected just by being involved in a treatment that requires paying sustained attention to a computer screen (Geversleben et al., 2009; Heinrich, Geversleben, & Strehl, 2007). Furthermore, participants might be positively influenced by the intensive one-to-one contact with the neurofeedback therapist, who provides attention, warmth, empathy, and acceptance. However, if reductions of symptoms of ASD would have been caused by such unspecific factors of neurofeedback, participants in both the EEG- and SC-biofeedback conditions should have outperformed participants of the waiting list group who did not receive attention training and one-to-one contact with the therapist. However, this was not the case. Future studies should always control for unspecific effects of neurofeedback. In addition, the role of age and type of behavioral problems of participants should be studied in future studies in order to examine the effects of neurofeedback in these specific groups.

### 7.5 Non responders to neurofeedback

The responses rate of children and adolescents with ASD to neurofeedback in the presented studies varied from 54 to 70%. Although these response rates are comparable to the response rates of children with ASD to medication, i.e., 48 to 69% (Buitelaar & Willemsen-Swinkels, 2000; McCracken et al., 2002; Research Units on Pediatric Psychopharmacology, 2005), there is still a significant percentage of children with ASD who do not respond to neurofeedback. It would be of great advantage for clients who consider starting with neurofeedback if they would know who has a reasonable chance of responding to neurofeedback and who not.

In order to identify variables that may distinguish responders from non responders to neurofeedback, I have looked at effects of age, intelligence scores, diagnosis, cognitive skills such as attention and cognitive flexibility, severity of symptoms of ASD, and EEG characteristics such as delta and theta power. None of these factors was found to be predictive with regard to the identification of responders to neurofeedback. Furthermore, when thinking back to the neurofeedback sessions of responders and non responders, it was also not possible to separate responders from non responders on the basis of their motivation, preference for certain types of reward.

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3 Data not reported in this dissertation.
or sensitivity to rewards. Finally, also the training progress in terms of altered EEG amplitude after ten sessions did not have any predictive value. The fact that responders to neurofeedback can not be identified at this time calls for future research in order to investigate who responds to neurofeedback and who does not.

7.6 The feasibility of a randomized controlled design
The research presented in this dissertation demonstrates that a randomized controlled design with SC-biofeedback as a control condition and with blinding of participants can be used to investigate the effects of neurofeedback in children and adolescents with ASD. SC-biofeedback appeared to be an adequate control condition. That is, children and adolescents with ASD were able to decrease SC over time, i.e., in 40 sessions, and they could be challenged by using arousing film clips once they learned that calming down and relaxing is effective in decreasing SC.

The outcomes of this dissertation call for a large scale research project to further investigate the effects of neurofeedback treatment in a larger sample of children and adolescents with ASD. Such a study could include, for example, 160 participants aged 8 to 12 years with either ASD (n=80) or ASD and comorbid ADHD (n=80). Ideally, these participants would be randomized over two experimental conditions: neurofeedback and SC-biofeedback, with both the therapists and the participants blinded for treatment allocation to either condition. EEG and SC signals should be similarly smoothed in order to prevent differences in the frequency of onset/offset of rewarding stimuli. The effects of neurofeedback treatment should be examined by taking clinical measures of symptoms of ASD as well as the use of executive function tasks. In addition, real life measures of clinical improvement should be included, such as behavioral observations in home and class situations. This research design should allow more decisive conclusions regarding the effects of neurofeedback treatment in children with ASD and in children with ASD and comorbid ADHD in both laboratory and clinical settings.

7.7 The status of neurofeedback as a treatment for ASD and future research
In the introduction of this dissertation, I described the controversial status of neurofeedback as a treatment for children and adolescents with ASD and I emphasized the urgent need for scientific research investigating the efficacy of neurofeedback for individuals with ASD. After conducting three consecutive studies, part of the controversy surrounding neurofeedback can be taken away. Importantly, the outcomes of the studies in this dissertation support the scientific basis for the application of neurofeedback in children and adolescents with ASD. Neurofeedback is clearly a technique that can be used to alter abnormal patterns of EEG activity in a substantial part of children and adolescents with ASD. Furthermore, neurofeedback can be applied to enhance cognitive performance of children and adolescents with ASD. A substantial part of the controversy, however, continues to exist. That is, the effects of neurofeedback on the clinical symptoms of ASD remain unclear at this time, which has major implications for the decision concerning the application of neurofeedback in clinical practice. Would anyone start neurofeedback training if only his or her brain activity and performance on tasks measuring cognitive flexibility would change?

Future research is required to further investigate the clinical effects of neurofeedback for children and adolescents with ASD. If it could be demonstrated decisively that neurofeedback reduces clinical symptoms of ASD, this would drastically improve the usefulness of neurofeedback for children and adolescents with ASD. The same goes for the effects of neurofeedback on cognitive flexibility in daily life. If future research could demonstrate that cognitive flexibility in daily life improves after neurofeedback training, the treatment would be far more interesting for children and adolescents with ASD. Although the present research answered important research questions concerning the application of neurofeedback for children and adolescents with ASD, there are still some questions that remain to be answered. It is my hope that these issues will be clarified by future studies investigating this new and exciting interdisciplinary field of clinical and scientific research.
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Een autisme spectrum stoornis (ASS) wordt ook wel een pervasieve ontwikkelingsstoornis genoemd. De aanduiding ‘pervasief’ wijst erop dat de stoornis ingrijpend is en tot uiting komt op tal van ontwikkelingsgebieden. De diagnose ASS wordt gesteld op basis van gedragskenmerken. De DSM-IV-TR (APA, 2000) onderscheidt de volgende drie kenmerken: (1) kwalitatieve afwijkingen in sociale interacties, (2) kwalitatieve afwijkingen in communicatievaardigheden, en (3) beperkte en stereotiepe gedragingen, interesses en activiteiten. Er zijn drie subtypen van ASS, elk met eigen diagnostische criteria. Bij het subtype ‘autistische stoornis’ zijn alle genoemde kenmerken aanwezig. Dit subtype wordt gezien als de klassieke en tevens meest ernstige vorm van ASS. Het subtype ‘pervasieve ontwikkelingsstoornis niet anders omschreven’ (PDD-NOS) wordt gezien als mildere vorm van ASS. Kinderen en jongeren met het subtype ‘syndroom van Asperger’ vertonen kwalitatieve afwijkingen in sociale interacties en beperkte en stereotiepe gedragingen, interesses en activiteiten. In tegenstelling tot de andere subtypen van ASS hebben kinderen en jongeren met het syndroom van Asperger zo goed als normale communicatievaardigheden en is er sprake van een normale tot hoge intelligentie. ASS komt voor bij ongeveer 1% van de totale bevolking (Baird et al., 2006; Nederlandse Vereniging voor Autisme, 2011).

Nederlandse samenvatting

Een autisme spectrum stoornis (ASS) wordt ook wel een pervasieve ontwikkelingsstoornis genoemd. De aanduiding ‘pervasief’ wijst erop dat de stoornis ingrijpend is en tot uiting komt op tal van ontwikkelingsgebieden. De diagnose ASS wordt gesteld op basis van gedragskenmerken. De DSM-IV-TR (APA, 2000) onderscheidt de volgende drie kenmerken: (1) kwalitatieve afwijkingen in sociale interacties, (2) kwalitatieve afwijkingen in communicatievaardigheden, en (3) beperkte en stereotiepe gedragingen, interesses en activiteiten. Er zijn drie subtypen van ASS, elk met eigen diagnostische criteria. Bij het subtype ‘autistische stoornis’ zijn alle genoemde kenmerken aanwezig. Dit subtype wordt gezien als de klassieke en tevens meest ernstige vorm van ASS. Het subtype ‘pervasieve ontwikkelingsstoornis niet anders omschreven’ (PDD-NOS) wordt gezien als mildere vorm van ASS. Kinderen en jongeren met het subtype ‘syndroom van Asperger’ vertonen kwalitatieve afwijkingen in sociale interacties en beperkte en stereotiepe gedragingen, interesses en activiteiten. In tegenstelling tot de andere subtypen van ASS hebben kinderen en jongeren met het syndroom van Asperger zo goed als normale communicatievaardigheden en is er sprake van een normale tot hoge intelligentie. ASS komt voor bij ongeveer 1% van de totale bevolking (Baird et al., 2006; Nederlandse Vereniging voor Autisme, 2011).
ASS kan niet worden genezen, maar er bestaan wel gedragsbehandelingen om de symptomen van ASS te verminderen. De enige gedragsbehandeling waarvan men het er over eens is dat deze effectief is bij kinderen met ASS, is gedragsbehandeling op basis van toegepaste gedragsanalyse (Peters-Scheffer, Didden, Korzilius & Sturmey, 2011). Met een dergelijke behandeling kunnen nieuwe vaardigheden worden aangeleerd en ongewenste gedragingen worden afgeleerd door middel van gedragsmodificatietechnieken als positieve bekrachtiging, extinctie en time-out. Daarnaast bestaan er tientallen andere behandelingen voor ASS waarvan beweerd wordt dat deze de symptomen van ASS verminderen, zoals dolfijntherapie, muziektherapie en het gebruik van visolie. Echter, de meeste van deze behandelingen zijn controversieel. Jacobson, Foxx en Mulick (2005) noemen vier redenen waarom een behandeling controversieel te noemen is: (1) de onderliggende rationale is ongegrond, (2) er is geen onomstotelijk bewijs voor de effectiviteit van de behandeling, (3) onderzoek naar de effectiviteit van de behandeling is van onvoldoende kwaliteit of (4) er zijn andere, eenvoudigere verklaringen voor de effecten van de behandeling.

Neurofeedback is een behandeltechniek die mogelijk effectief is in het verminderen van symptomen van ASS. Het doel van neurofeedback is het beïnvloeden van de hersenactiviteit van de cliënt. Deze hersenactiviteit wordt gemeten met behulp van elektroden die op het hoofd van de cliënt worden geplakt en geregistreerd in de vorm van een electroencephalogram (EEG). De mate waarin (een specifiek deel van) de gemeten EEG activiteit aanwezig is, wordt op een computerscherm voor de cliënt zichtbaar gemaakt. Door de cliënt te belonen wanneer hij of zij het gewenste patroon van EEG activiteit laat zien, kan deze leren om de EEG activiteit te veranderen.

De eerste studie (hoofdstuk drie) is een verkennend onderzoek naar de effecten van neurofeedbackbehandeling bij zeven kinderen van 8 tot 12 jaar met PDD-NOS. De kinderen hebben ieder 40 neurofeedbacksessies gehad, waarin theta power werd onderdrukt en het sensomotorische ritme (SMR) werd gestimuleerd. Tijdens deze neurofeedbacksessies was bij vijf van de zeven kinderen een afname in theta power en een toename van SMR te zien. In vergelijking met de zeven kinderen uit de gematchte controlegroep lieten de kinderen die neurofeedbackbehandeling hadden gehad een verbetering zien in sociale interacties, communicatievaardigheden, en stereotiep en repetitief gedrag, zoals gemeten met gedragsvragenlijsten die ingevuld werden door ouders. De kinderen die neurofeedbackbehandeling hadden gehad lieten een verbetering zien in sociale interacties, communicatievaardigheden, en stereotiep en repetitief gedrag, zoals gemeten met gedragsvragenlijsten die ingevuld werden door ouders. Daarnaast lieten de kinderen die neurofeedbackbehandeling hadden gehad een verbetering zien in sociale interacties, communicatievaardigheden, en stereotiep en repetitief gedrag, zoals gemeten met gedragsvragenlijsten die ingevuld werden door ouders. Daarnaast lieten de kinderen die neurofeedbackbehandeling hadden gehad een verbetering zien in sociale interacties, communicatievaardigheden, en stereotiep en repetitief gedrag, zoals gemeten met gedragsvragenlijsten die ingevuld werden door ouders.
verbeterde niveau van functioneren in gedrag en cognitie te hebben behouden.

In een tweede studie (hoofdstuk vijf) zijn de effecten van neurofeedback-behandeling voor kinderen met ASS verder onderzocht in een gerandomiseerd controle design met follow-up onderzoek na zes maanden. Dit design is gekozen om effecten van selectie van de deelnemers te voorkomen. Twintig kinderen met ASS in de leeftijd van 8 tot 12 jaar werden willekeurig verdeeld over een neurofeedback- en wachtlijstgroep. Tijdens 40 neurofeedbacksessies die gericht waren op het onderdrukken van theta power was bij zes van de tien kinderen uit de neurofeedbackgroep een daling in theta power te zien. Deze daling in theta power was ook zichtbaar in de 19-kanaals EEG metingen die na de neurofeedbackbehandeling plaatsvonden, in vergelijking met dezelfde metingen voor de behandeling en bij de wachtlijstgroep. Uit analyses van de gedragsvragenlijsten bleek dat ouders na afloop van de neurofeedbackbehandeling positiever oordeelden over de wederkerige sociale interacties en communicatievaardigheden van hun kind dan voorheen en in vergelijking met de wachtlijstgroep. Kinderen uit de neurofeedbackgroep presteerden na de neurofeedbackbehandeling beter op een taak voor cognitieve flexibiliteit dan daarvoor, in vergelijking met kinderen uit de wachtlijstgroep. Zes maanden later bleken de verschillen in wederkerige sociale interacties, communicatievaardigheden en cognitieve flexibiliteit tussen de neurofeedback- en wachtlijstgroep nog steeds aanwezig te zijn.

In de laatste studie (hoofdstuk zes) zijn de effecten van neurofeedback onderzocht bij kinderen en jongeren met ASS in een gerandomiseerd controle design met een geblindeerde actieve vergelijkingsconditie en follow-up onderzoek na zes maanden. Dit design is gekozen om behalve voor de effecten van selectie van de deelnemers ook te kunnen controleren voor effecten van de verwachtingen van ouders, de training van aandacht tijdens neurofeedback en het intensieve contact tussen cliënt en therapeut tijdens de behandeling. Achttig kinderen en jongeren met ASS in de leeftijd van 12 tot 18 jaar werden willekeurig verdeeld over drie experimentele groepen: neurofeedback, huidgeleidingbiofeedback of wachtlijst. Deelnemers aan de neurofeedbackgroep kregen 40 sessies waarin delta en/of theta power werden onderdrukt; deelnemers aan de huidgeleidingfeedbackgroep kregen 40 sessies waarin het signaal van de huidgeleiding werd onderdrukt. Neurofeedback- en huidgeleidingfeedbackbehandelingen waren vergelijkbaar en de deelnemers wisten niet welke behandeling zij kregen. Uit de resultaten van deze studie bleek dat delta en/of theta power waren gedaald tijdens de neurofeedbacksessies van zeven van de 13 deelnemers uit de neurofeedbackgroep. Deze deelnemers werden EEG-responders genoemd. Deze EEG-responders verbeterden op een taak die cognitieve flexibiliteit meet in vergelijking met EEG-non responders en deelnemers van andere groepen. Zes maanden na de laatste neurofeedbacksessie bleek dat EEG-responders nog steeds beter presteerden op de taak voor cognitieve flexibiliteit dan andere deelnemers. In de 19-kanaals EEG metingen van de EEG-responders werd een verlaging van delta power gezien na de neurofeedbackbehandeling, terwijl dit niet zo was bij EEG-non responders en deelnemers van andere groepen. Zes maanden later was de verlaging van delta power niet meer zichtbaar in het EEG van de EEG-responders. Uit analyses van de gedragsvragenlijsten bleek dat ouders en leerkrachten van deelnemers uit de neurofeedbackgroep geen verandering in ASS symptomen zagen na de neurofeedbackbehandeling.

Conclusies

In dit proefschrift heb ik de effectiviteit van neurofeedbackbehandeling voor kinderen en jongeren met ASS onderzocht. Er zijn twee belangrijke conclusies die op basis van dit onderzoek kunnen worden getrokken: (1) neurofeedback is een techniek die gebruikt kan worden om EEG activiteit te beïnvloeden bij een substantieel deel van de kinderen en jongeren met ASS en (2) neurofeedback leidt tot verbeteringen in cognitieve flexibiliteit bij diegenen bij wie een daling in delta en/of theta power was te zien tijdens de neurofeedbacksessies. Deze conclusies onderschrijven de wetenschappelijke basis voor neurofeedbackbehandeling van kinderen en jongeren met ASS en nemen een deel van de controverse weg rondom de toepassing van neurofeedback voor de behandeling van kinderen en jongeren met ASS. Een substantieel deel van de controverse blijft echter bestaan. De conclusie over de effecten van neurofeedbackbehandeling op de klinische symptomen van ASS is namelijk minder eenduidig. Er zijn studies waarin neurofeedback heeft geleid tot een verminderd of ASS symptomen, maar er is ook een studie waarbij dit niet het geval was. De reden voor deze verschillende bevindingen is tot op heden niet bekend, maar wel erg belangrijk. Wie zou er immers beginnen aan neurofeedback als daarmee alleen zijn of haar hersenactiviteit en prestaties op een taakje voor cognitieve flexibiliteit verbeteren?

Vervolgonderzoek is nodig om uitsluitend te kunnen geven over de effecten van
neurofeedbackbehandeling op de klinische symptomen van ASS. Als aangetoond kan worden dat neurofeedback inderdaad leidt tot een daling van deze symptomen, dan zou de waarde van neurofeedbackbehandeling voor deze doelgroep enorm toenemen. Hetzelfde geldt voor het effect van neurofeedback op cognitieve flexibiliteit in het dagelijks leven van kinderen en jongeren met ASS. Als uit vervolgonderzoek zou blijken dat cognitieve flexibiliteit ook in school- en thuissituaties verbetert door neurofeedback, dan zou neurofeedback van onschatbare waarde kunnen worden voor kinderen en jongeren met ASS.

In dit proefschrift zijn een aantal belangrijke vragen over de toepassing van neurofeedbackbehandeling bij kinderen en jongeren met ASS beantwoord, maar er zijn ook een aantal belangrijke vragen die nog beantwoord zouden moeten worden. Ik hoop dat veel van deze zaken opgehelderd kunnen worden in toekomstig onderzoek op dit fascinerende gebied van klinisch en wetenschappelijk onderzoek.

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**Curriculum Vitae**


Publications


