Pathophysiology of adhd and associated problems—starting points for nf interventi...

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Introduction

Difficulties with Inattention or Hyperactivity and Impulsivity as the core symptoms of Attention deficit Hyperactivity disorder (ADHD) are a frequent psychosocial burden. With an early onset during childhood, ADHD is often persisting throughout life. It is a heterogeneous disorder, and a challenge to treat. In light of this heterogeneity, the most promising treatment approach should be multimodal in nature (Taylor et al., 2004 ; Swanson et al., 2008). Pharmacological interventions particularly with stimulants such as methylphenidate and amphetamine sulfate, as well as non-stimulants like Atomoxetine are highly effective in reducing ADHD symptoms (Banaschewski et al., 2006 ; King et al., 2006), but long-term effectiveness is still questionable (Molina et al., 2009 ; van de Loo-Neus et al., 2011). In addition, side-effects, non-response and prejudice have raised interest in non-pharmacological treatment options (Sonuga-Barke et al., 2013 ; Daley et al., 2014).

Neurofeedback (NF) as a non-pharmacological intervention for ADHD utilizes cognitive-behavioral therapeutic elements to gain access on and practice brain activity (Arns et al., 2014). In an operant learning paradigm, specific neural activity is quantified by means of Electro-Encephalography (EEG) or functional Magnetic Resonance Imaging (fMRI) and fed back in real time with an easily accessible optical or acoustic signal. In general, the participants learn to modulate their brain activity towards an *a priori* specified criterion (standard EEG-based NF protocols require the participants to increase beta (13–20 Hz) and to decrease theta (4–8 Hz) activity, or to train slow cortical

potentials (SCP) in order to modulate cortical excitability); and successful trials are positively reinforced.

Gevensleben et al. provide two different frameworks, how NF may be effective in ADHD (Gevensleben et al., 2014c). On the one hand, following a " conditioning and repairing model", NF may be used to compensate specific neurophysiological deficits present in patients with ADHD, which in turn ameliorates impairments. On the other hand, the " skill-acquisition model" suggests that NF may be used to train and enhance self-regulation skills not necessarily impaired in ADHD, but may in turn, by means of active transfer and supportive coaching, be used to compensate existing deficits.

There are a number of studies indicating potential effectiveness of NF on ADHD symptom severity, but further evidence particularly from randomized controlled trials using more blinded assessments is required (Arns and Strehl, 2013 ; Sonuga-Barke et al., 2013 ; Micoulaud-Franchi et al., 2014). On the other hand, further double-blinding or particularly sham feedback may diminish motivation and the belief in self-efficacy in both participants receiving sham and NF interventions, and may thus question an important precondition for effective trainings (Logemann et al., 2010 ; Gevensleben et al., 2012). Further details about NF interventions can be found in a number of reviews and conceptual papers (Strehl et al., 2006 ; Heinrich et al., 2007 ; Arns et al., 2014 ; Gevensleben et al., 2014b), and recent advances in the field are described in this issue on " NF in ADHD".

The following selective overview describes pathophysiological characteristics of ADHD alongside their potential relevance for NF intervention. First, a brief

overview of the clinical characteristics of ADHD is given. Second, pathophysiological characteristics of ADHD linked with difficulties in cognitive functions and motivation as well as during resting state are described, and third, a number of associated problems such as frequent comorbidities of ADHD with Conduct- and Tic-disorders are presented. Finally, perspectives for NF interventions will be considered within these contexts.

Characteristics of Attention Deficit Hyperactivity Disorder

ADHD is currently considered as a neurodevelopmental disorder. It is characterized by severe and age-inappropriate levels of inattention and hyperactivity/impulsivity that are present in at least two areas of life for over 6 months (WHO, 1993 ; APA, 2013). According to the fifth edition of the Diagnostic and Statistical Manual (DSM-V), subtypes with predominantly Inattentive or Hyperactive/Impulsive characteristics as well as a combined type are distinguished. In any case, the symptoms must already be manifest in childhood (before age of seven following the DSM-IV, and before age of 12 according to the recently revised DSM-V; Kieling et al., 2010), and must not be better explained by other disorders.

ADHD is one of the most frequent problems in psychiatry. The core symptoms of ADHD are present in approximately 5% of children and adolescents, irrespective of cultural background, and with a strong overrepresentation of boys (Polanczyk and Rohde, 2007). In about one or two out of three of children with ADHD, the symptom may persist with clinical significance into adulthood, leading to a slightly lower prevalence of

more than 3% in adults (larger in higher income countries), which makes ADHD a life-long problem for many patients (Fayyad et al., 2007 ; Polanczyk and Rohde, 2007). Childhood ADHD may lead to lower educational, occupational, social and clinical outcomes in adulthood even if it remits early on, and may thus not be considered as a benign disorder (Klein et al., 2012).

ADHD and its Neuronal Background

ADHD is associated with a number of neurophysiological deficits. More recent theoretical approaches integrate clinical symptoms and neuropsychological difficulties within a framework of specific brain dysfunctions: cognitive deficits may emerge from dysfunctions particularly in fronto-striatal or meso-cortical brain networks, while problems with reward processing may be associated with dysfunctions in the mesolimbic dopaminergic system (Sagvolden et al., 2005 ; Sonuga-Barke, 2005). However, deficits in ADHD may already be seen in the resting brain, and a more fundamental neuronal network approach suggests that in ADHD particularly Default-Mode-Network (DMN) activity (usually prominent during rest) may interfere with activity in neuronal networks engaged in task processing, leading to difficulties in state regulation and periodic attentional lapses (Sonuga-Barke and Castellanos, 2007 ; Castellanos and Proal, 2012).

Cognitive Functions

There are a number of cognitive theories that describe impairments in executive functions as a central problem in ADHD (Pennington and Ozonoff, 1996 ; Tannock, 1998 ; Sergeant, 2000 ; Biederman, 2005). Several theoretical accounts propose a “ top-down” executive system responsible for

inhibition, working memory and cognitive flexibility, which is particularly active when more complex demands require adaptation and effortful control (Baddeley and Della Sala, 1996 ; Miller and Cohen, 2001 ; Diamond, 2013). Following Barkley, children with ADHD may show a core deficit in behavioral inhibition, which in turn leads to impairments in working memory, self-regulation, internalization of speech and reconstitution (Barkley, 1997). This account has been put forward in the more recent " multiple pathway" models of ADHD, which emphasize besides cognitive deficits also motivational or reward processing problems (Nigg et al., 2005 ; Sonuga-Barke, 2005).

Cognitive problems in ADHD are reported in numerous studies with different tasks. It was frequently found that children with ADHD display several deficits in tasks that demand executive control, i. e., their reaction-times were slower and more variable, and more errors were made. This has been demonstrated for important aspects of executive functions such as set shifting assessed with the Wisconsin Card-Sorting Task or planning and problem solving as required in the Tower-of-Hanoi paradigms (Barkley et al., 1992 ; Klorman et al., 1999). On the other hand, interference control during Stroop- or Simon tasks yielded mixed or even negative results, particularly when confounders were controlled for (van Mourik et al., 2005 , 2009 ; Albrecht et al., 2008b), but further improvements on how interference liability can be derived from performance data may clarify these findings (Lansbergen et al., 2007 ; Schwartz and Verhaeghen, 2008).

Thus, ADHD may be associated with a number of cognitive deficits, but these may not “ causes” but rather consequences of the disorder, and may not provide causative therapy options: a recent meta-analysis suggests that cognitive trainings (e. g., on working memory) may improve performance and may ameliorate neuropsychological deficits found in ADHD, but direct effects on ADHD symptoms may be limited (Cortese et al., 2015).

Action Monitoring and Response Inhibition

Action monitoring as an important aspect of executive functioning comes into play when task demands raised response conflicts. There is a large body of evidence from electrophysiological studies elucidating some of the implicated mechanisms. For instance, if a task requires responding to a certain stimulus but to withhold the response to another one, the stimulus-locked event-related potentials (ERP) usually shows a fronto-central negativity peaking around 200–400 ms after onset of the stimulus which is larger for the Nogo than for the Go condition, particularly when the Nogo condition is rare. The same effect can be observed when the target is primed with either congruent or incongruent distractors. The so called N2 and the N2-enhancement were originally attributed to (response) inhibition (Kok, 1986 , 1999 ; Falkenstein et al., 1999), but recent studies suggest that it reflects a more general action monitoring or cognitive control process that is also present if no response needs to be inhibited (Nieuwenhuis et al., 2003 ; Donkers and van Boxtel, 2004). Sources of N2 evoked by Go/Nogo- or Flanker-Tasks were found in medial frontal brain regions, namely the ACC (Van Veen and Carter, 2002 ; Nieuwenhuis et al., 2003 ; Bekker et al., 2005).

While several studies using Continous Performance Tests (CPT) or Go-Nogo-tasks in children did not find conflict-specific differences in N2 between ADHD and controls (Overtoom et al., 1998 ; Banaschewski et al., 2004 ; Fallgatter et al., 2004), some studies did, but variations were explained by comorbidity with other externalizing disorders (Lawrence et al., 2005 ; Wiersema et al., 2006) or appeared only with prolonged time-on-task (Yong-Liang et al., 2000). Thus, the detection of action monitoring deficits in ADHD may require tasks that are particularly demanding, e. g., that reveal a substantial number of performance errors, which is usually not realized in the CPT.

This may be achieved with the Flanker Task, requiring response to a central target flanked by either congruent or incongruent flanker stimuli (Eriksen and Eriksen, 1974) which was frequently used in ADHD research (Jonkman et al., 1999 ; Mullane et al., 2009). In a special variant of this task aimed maximizing the congruency effect, lower N2-enhancement and deficits during error processing in children and adults with ADHD, and moreover intermediate effects in first-degree relatives without a diagnosis of ADHD were found, indicating that action monitoring may be an important feature on the developmental pathway from genetical and environmental liability to ADHD (Albrecht et al., 2008a ; McLoughlin et al., 2009).

Studies on brain activity more specifically related to response inhibition revealed mixed results, which may be explained by heterogeniety of the methods used. Studies with the Stop-Task, requiring a frequent and consequently predominant response which should be withold if a Stop-signal

is presented, indicated that particularly the right inferior frontal gyrus is implicated in successful stopping of an ongoing response (Aron et al., 2003 ; Hughes et al., 2013). Several EEG and fMRI studies suggest impairments in Stop-Task performance and stop-signal related brain activity in ADHD (Brandeis et al., 1998 ; Pliszka et al., 2000 ; Albrecht et al., 2005 ; Rubia et al., 2008), but there are also some negative findings in treatment-naive children (Pliszka et al., 2006). Response inhibition problems in the Stop-Task may be significant in ADHD across the lifespan, and its specificity is particularly clear in adults with ADHD (Lijffijt et al., 2005).

Importantly, activity in the medial prefrontal cortex related to cognitive control (particularly the N2) and error processing (error negativity) may operate with theta (or maybe even lower delta) frequency (Yordanova et al., 2004 ; Cavanagh et al., 2012 ; Zavala et al., 2014).

Perspectives for NF. A number of recent studies with healthy adults indicate that NF training of frontal midline theta activity may improve attention and executive functions like working memory and cognitive flexibility (Wang and Hsieh, 2013 ; Enriquez-Geppert et al., 2014), and may lead to morphological changes in the cingulate cortex (Enriquez-Geppert et al., 2013). An application in ADHD may thus ameliorate cognitive deficits accordingly, but empirical evidence for improvement in executive functioning following NF in ADHD is weak (Vollebregt et al., 2014), and requires better controlled studies with sufficiently sized samples before definitive conclusions can be drawn.

A promising approach may be NF from dedicated brain regions that show diminished functional activity in ADHD. A recent study reported in this issue using near infrared spectroscopy (NIRS) NF of brain activity in the bilateral prefrontal cortex (implicated in executive functions and response inhibition) showed effectiveness in behavioral symptom ratings and executive functions, but may require fewer sessions than EEG or EMG NF (Marx et al., 2015). Activity in the ACC may be directly trained by tomographic NF (Bauer and Pllana, 2014). In a more recent study using tomographic NF from Theta/Beta or SCP activity localized in the ACC, Liechti et al. (2012) reported clinical improvement as well as resting EEG normalization in participants, but it remains open whether these improvements were (region-) specific for tomographic NF training (Liechti et al., 2012).

Preparation

Preparation for an upcoming event may be of great importance not only for specialists like flight controller, carefully watching their radar equipment for cues indicating critical situations that demand intervention. Almost half a century ago, it was found by Walter et al. that cues (predicting a consecutive imperative stimulus requiring a response) evoke a centrally negative SCP that terminates with the presentation of the next stimulus (contingent negative variation, CNV; Walter et al., 1964). Originally interpreted as “ sensorimotor association and expectancy”, neuronal networks generating the CNV may be active if more general preparation for an upcoming event is required (Macar and Vidal, 2003).

Neurophysiological studies suggested that the CNV is generated in thalamo-cortical structures including the dorsal anterior cingulate cortex (ACC), frontal cortex, thalamus and midbrain dopaminergic nuclei (Gómez et al., 2003 ; Fan et al., 2007 ; Lütcke et al., 2008). Patients suffering from Parkinson's disease that goes along with neuronal cell death in these nuclei showed specific reductions in Cue- (or warning stimulus) CNV amplitude (Pulvermüller et al., 1996 ; Ikeda et al., 1997 ; Gerschlager et al., 1999) as well as deficits in performance and slow wave activity during a temporal anticipation paradigm (Praamstra and Pope, 2007). This confirms the role of midbrain dopaminergic neurons in anticipation, time estimation or temporal memory (Suri and Schultz, 2001 ; Macar and Vidal, 2003).

Dopaminergic deficits may also explain anticipation and preparation problems in patients with ADHD, which showed reduced activation in brain regions implicated in CNV generation (Rubia et al., 1999 ; Smith et al., 2008). In line with these considerations, CNV is probably reduced in ADHD (van Leeuwen et al., 1998 ; Hennighausen et al., 2000 ; Perchet et al., 2001 ; Banaschewski et al., 2003a , 2008) and may represent a persistent deficit in patients with ADHD throughout life (McLoughlin et al., 2010 ; Doehnert et al., 2013). Moreover, diminished Cue-CNV may be familially-driven in children and adults with ADHD (McLoughlin et al., 2011 ; Albrecht et al., 2013) and may be related to polymorphisms of the dopamine receptor D4 gene (Albrecht et al., 2014). It is further subject to dopaminergic manipulations used for treatment of ADHD, as performance and CNV amplitude may be enhanced by methylphenidate (Linssen et al., 2011 ; Kratz et al., 2012).

Perspectives for NF. Many psychiatric or neurologic disorders are associated with preparation problems or related difficulties NF training of SCP may be a direct compensatory approach, as it relies on phasic modulation of SCPs and probably consequent cortical excitability (Rockstroh et al., 1984 ; Mayer et al., 2013 ; Gevensleben et al., 2014b).

Change in CNV-activity after SCP training is often replicated in NF-ADHD research (Gevensleben et al., 2012), but the relation to task performance appear rather complex and requires further investigation (Gevensleben et al., 2014a).

Reward Processing

Deficient reward processing is a central aspect of several theories on ADHD. A model proposed by Sagvolden and colleagues claims that rewards have a shorter-term impact on learning and behavior in ADHD, e. g., characterized by a steeper gradient between the delay of a reinforcer and its effect on the probability that the reinforced action will be repeated (Sagvolden et al., 1998). Such a steeper delay of reinforcement gradient may be a consequence of lower tonic levels of dopaminergic activity in the mesolimbic system including the ventral tegmentum and the nucleus accumbens, while attention and response organization problems may originate from hypofunctioning of the mesocortical system also including the ventral tegmentum with projections to the prefrontal cortex (Sagvolden et al., 2005). Another model by Tripp and Wickens argues that phasic dopaminergic activity in the striatum related to cues indicating reinforcement may be impaired in ADHD (Tripp and Wickens, 2008).

A recent review by Plichta and Scheres summarizes consistent evidence from functional imaging studies on reward anticipation in ADHD: particularly the areas in the ventral striatum including nucleus caudatus, nucleus accumbens and the putamen show lower activation during reward anticipation in ADHD than controls, which may be rather related to hyperactive-impulsive symptom severity but perhaps not inattention (Plichta and Scheres, 2014).

Perspectives for NF. Immediate performance feedback may be beneficial for patients having problems with motivation or reinforcement anticipation. This would suggest that NF would be particularly applicable to such patients, but it may further modified to train brain activity associated with delayed reinforcement. As such, NF intervention may also help acquiring self-regulation skills useful for compensating motivational deficits and delay aversion in structured and potentially unattractive and boring situations.

Resting State Brain Activity

Brain activity at rest, recorded when individuals are awake, relaxed and not engaged in any particular task, is characterized by complex oscillations that may reflect important features of arousal and attention that may change with development. Important aspects of resting state brain activity can be obtained using recordings of the EEG (Banaschewski and Brandeis, 2007 ; Rothenberger, 2009). The resting EEG of a time interval can be decomposed by means of a Fourier-Transformation in frequency and power. Cross-sectional developmental studies suggest that from childhood to adolescence and early adulthood a decrease in power of slow Delta (1. 3–3. 5 Hz) and Theta (3. 5–7. 5 Hz), but at the same time an increase in faster Alpha (7. 5–

12. 5 Hz) and Beta (12. 5 − ~25 Hz) activity emerges (Matousek and Petersen, 1973 ; John et al., 1982).

Earlier studies suggest that children with learning disabilities (Harmony et al., 1995), dyslexia (Klimesch et al., 2001) and ADHD (Bresnahan et al., 1999) may be characterized by lower power in the faster Alpha and Beta frequency bands, and in case of ADHD also potentially increased Theta activity (Barry et al., 2003). This view has been challenged by recent studies that did not replicate increased theta or theta/beta ratios in ADHD under resting conditions (Barry and Clarke, 2013 ; Liechti et al., 2013), albeit reduced relative beta power may be characteristic for a subgroup of children and adults with ADHD inattentive subtype (Buyck and Wiersema, 2014). A recent meta-analysis concludes that Theta/Beta-Ratio may not be a reliable diagnostic parameter in ADHD (Arns et al., 2013). However, there is some evidence that aberrances in EEG-frequency bands exist during task processing (El-Sayed et al., 2002). In a recent trial, Heinrich et al. found higher theta and alpha activity during an attentive state in children with ADHD, most pronounced in the upper theta/lower alpha range (5, 5–10, 5 Hz; Heinrich et al., 2014). Taken together, elevated power in lower frequency bands during rest may not be generally associated with ADHD, but there is some evidence that abnormalities of brain activity oscillations at least during task processing (in the “ active brain”) might be part of the problem in children with ADHD.

Another view on resting state activity comes from a network perspective. MRI studies during rest (when participants were awake and rested quietly

with eyes closed) revealed coherent activity fluctuations with low frequency (<0. 1 Hz; Biswal et al., 1995) in a neuronal network including the medial prefrontal cortex, posterior cingulate cortex, precuneus and lateral parietal cortex (Gusnard et al., 2001a , b). This DMN activity is associated with a rather introspective and self-referential state (Gusnard et al., 2001a), which is attenuated during task performance when specific " task-positive" networks take over Fox et al., 2005 ; Fransson (2006) . However, DMN activity may come back into play before performance errors or prolonged reaction times, possibly indicating attentional lapses (Weissman et al., 2006 ; Li et al., 2007 ; Eichele et al., 2008).

Misguided DMN activity may be important in several mental disorders (Broyd et al., 2009), and problems in ADHD may be particularly associated with attentional lapses due to DMN interference with activity in task-positive networks (Sonuga-Barke and Castellanos, 2007 ; Castellanos and Proal, 2012). Recent studies in adults with ADHD suggest lower anti-correlation between the posterior cingulate/precuneus (as an important part of the DMN) and the ACC often implicated in cognitive control and preparation (Castellanos et al., 2008 ; Uddin et al., 2008).

The association between DMN and electrical brain activity appears rather complex (Mantini et al., 2007) and may be unstable over time (Meyer et al., 2013). However, there are reports that very low frequency electrical brain activity (<1. 5 Hz) may be altered in children and adults with ADHD, and particularly adults with higher ADHD symptom ratings show diminished

deactivation in DMN regions during a flanker-task (Helps et al., 2010 ; Broyd et al., 2011).

Perspectives for NF. The theta/beta ratio during rest may not be generally impaired in patients with ADHD, but there is some evidence that problems may be present during task performance. Since NF targets the “ active brain”, it may act as a potentially ameliorating intervention. Training on theta/beta ratio was successfully applied in a series of intervention studies in ADHD children, but the precise mode of action is still under investigation (Heinrich et al., 2007 ; Gevensleben et al., 2009). NF training targets different variables on the neurophysiological (enhancement of regulation capability of different EEG parameters), neuropsychological (executive functions), and the cognitive-behavioral (e. g., enhanced self-regulation by positive reinforcement of goal-directed behavior) level. Until now, it remains open whether regulation capability on the neurophysiological, the neuropsychological (executive functions), or on the cognitive-behavioral level—targeting an initial deficit or activating compensatory mechanisms—account for NF training effects (Gevensleben et al., 2014b). Most likely, NF outcome in ADHD treatment results from a combination of several of these variables.

Further venues of NF interventions may consider DMN interference by training the interplay between and connectivity within in the DMN and task-relevant networks.

Heterogeniety in ADHD

ADHD is in many ways a heterogeneous disorder. This is reflected in the ADHD subtypes, overrepresentation of boys, and moreover in the fact that various comorbid conditions are not an exception, but the rule in patients with ADHD. For the presentation below, we consider comorbidities with a higher prevalence than the simple product of the prevalence of both disorders involved. As an example, the prevalence of oppositional defiant or conduct disorder (ODD/CD) in ADHD should be equal to the prevalence in the total population—in fact it is at least 20-times higher, and the reasons for this are still under debate. Research indicates that some comorbidities may in fact be a separate clinical entity (potentially like ADHD + ODD/CD, as discussed below), whilst others may in many ways an addition of difficulties present in either disorder (e. g., like ADHD + Tic). In any case, heterogeneity in ADHD may further complicate treatment.

Clinical Heterogeneity—Hyperactive/Impulsive and Inattentive Subtypes

The Diagnostic and Statistical Manual distinguishes Hyperactive/Impulsive (ADHD-H) and Inattention (ADHD-I) symptom clusters in the diagnosis of ADHD (APA, 2013), but it remains controversial whether these form separate clinical entities. On the one hand, developmental studies suggest that children initially diagnosed with ADHD-H may shift to Combined Type (ADHD-C) as attention demands increase in school, whilst diagnoses of attention problems alone may remain stable and form a separate clinical entity (Lahey et al., 2005). Compared to patients with ADHD combined type, children with ADHD-I may be characterized by rather passive social interaction and more associated internalizing problems (Maedgen and

Carlson, 2000). In the resting EEG, children and adults with ADHD-I may show lower power in the beta-band and increased theta/beta ratio (Buyck and Wiersema, 2014), which may have significance for compensatory NF intervention.

However, on the neuropsychological level children with ADHD-I show similar performance problems as ADHD-C in a wide range of demands (Nigg et al., 2002 ; Baeyens et al., 2006), albeit there is some evidence that ADHD-I may show particular preparation problems (Adams et al., 2008).

Perspectives for NF. Empirical evidence suggests that NF unfolds an impact on all three symptom clusters of ADHD (inattention, impulsivity, hyperactivity). In a large multicenter randomized controlled trial of a combination of theta-beta/SCP NF training for children with ADHD, we found comparable effects for symptoms of inattention as well as hyperactivity/impulsivity (Gevensleben et al., 2014b). No differences in efficacy concerning subtypes of ADHD were obtained. This result is supported by meta-analytic data, obtaining large effect sizes for inattention and medium to large effect sizes for hyperactivity/impulsivity symptom ratings (Arns et al., 2014). Latest evidence from a trial encompassing children with comorbidity of Tourette-disorder and ADHD suggested that specificity of outcome of NF training concerning patterns of inattention, hyperactivity and or impulsivity may rely on transfer tasks (homework) in the course of the training (Gevensleben et al., 2014b), which should be considered in the treatment of ADHD subtypes.

Similarities and Differences Between Boys and Girls with ADHD

Although overrepresentation of boys in ADHD is at least 3 to 1 in the population and much higher among clinical referrals (Tannock, 1998 ; APA, 2013), studies explicitly addressing the role of sex on cognitive parameters are rare. In an earlier meta-analysis, Gershon concluded that girls suffering from ADHD were lower-rated on ADHD symptoms and externalizing problems, but they were more impaired than boys on internalizing symptoms. Furthermore, females showed lower " crystallized" cognitive functioning as measured by full scale and verbal IQ, but " fluid" performance IQ did not differ between sexes. Regarding executive functions, girls with ADHD show in many ways similar impairments as boys (Gershon, 2002).

That has been demonstrated with several neuropsychological tests including the Stroop- (deHaas, 1986 ; Rucklidge and Tannock, 2002) and Wisconsin Card Sorting Test (Houghton et al., 1999 ; Seidman et al., 2005) as well as with various versions of the CPT (Breen, 1989 ; Schuerholz et al., 1998 ; Sharp et al., 1999 ; Yang et al., 2004 ; Seidman et al., 2006). An exception may be impulsivity, or consequent problems with response inhibition: a recent meta-analysis on CPT performance by Hasson and Fine indicated that girls may generally show less commission errors than boys, and beyond that case-control differences on impulsivity errors were also lower in girls (Hasson and Fine, 2012).

Studies on brain activity during preparation and response control yielded mixed results. Regarding cognitive control, Liotti et al. (2007) found no sex differences in Stop-Task performance and N2 amplitude (Liotti et al., 2007). This is in line with a more recent study with the Flanker-Task, detecting

independently of sex also problems with N2-enhancement and error processing in nonaffected siblings of patients with ADHD (girls were outnumbered in our ADHD sample, not allowing a direct comparison in patients), albeit girls showed a generally more accurate response style and larger error positivity probably associated with affective error processing (Albrecht et al., 2010). In the CPT on familiarity, girls made less commission errors (particularly in a more demanding CPT with additional incompatible flanker stimuli) at the expense of slower response speed, and they also showed larger Cue-P3, but similar Cue-CNV (Albrecht et al. in preparation).

Taken together, girls with ADHD or nonaffected siblings may show a rather accurate response style and fewer problems with impulsivity, but they may share many problems with executive functions detected in studies mostly on boys. It remains an open question whether impulsivity explains the overrepresentation of boys among patients with ADHD as it may lead to more severe and probably clinically relevant psychosocial impairments.

Perspectives for NF. Since girls with ADHD may show similar impairments as boys, although they may be less impulsive, the current literature suggests that NF interventions need no sex-specific adaptations, but more research is needed before definitive recommendations can be given.

ADHD and Conduct Disorder

Children with conduct problems display a repetitive and persistent pattern of oppositional or dissocial behavior, aggression, or deliquency for more than 6 months that goes beyond childlike mischief or typical problems during puberty. The DSM distinguishes ODD, characterized by “ negativistic, hostile,

and defiant behavior” from CD including aggression, violation of “ the basic rights of others”, and delinquency (APA, 2013). Since ODD and CD often occur interrelated and the former may antecede the latter in child development, both are often considered together as ODD/CD (Loeber et al., 2000).

With a prevalence of approximately 2% in children and adolescents, it is one of the more frequent child psychiatric diagnoses. However, among patients with ADHD, ODD/CD is with a comorbidity rate of 40–70% much more frequent, and the reasons for this are still under investigation (Newcorn and Halperin, 2005). It was found that ADHD may be a predictor for ODD, and that ODD may predict CD (Burke et al., 2005).

ODD/CD is associated with a number of neurobiological abnormalities. At first, children with ODD/CD may show impaired stress reactivity, which is mediated by activity in the hypothalamic-pituitary-adrenal (HPA) axis and expressed in the release of cortisol, which was moderately inverse associated with aggressive symptoms (van Goozen et al., 2007). This may result in low sensitivity to punishment that may in turn hamper learning from the consequences of inappropriate behavior (Matthys et al., 2013). Further, activity of the autonomic nervous system (ANS), via the interplay of its sympathetic and parasympathetic branches responsible for the regulation of arousal and energy generation, may be lower (as indicated by lower heart rate and skin conductance reactivity) in aggressive or antisocial individuals (Lorber, 2004), suggesting underarousal and consequently “ fearlessness” (Raine, 2002) or risk taking and “ sensation seeking” (Zuckerman, 1994).

Moreover, there are also studies linking lower serotoninergic activity (5-HT) and monoamine-oxydases (MAO) to aggression, and selective serotonine reuptake inhibitors are frequently used for reducing aggression in patients (Carrillo et al., 2009).

In a series of neuroimaging experiments, Rubia et al. showed that children with ADHD may be characterized by “ cool” cognitive deficits like inhibition, attention and timing related to abnormal activity in inferior frontal, striatal and parietotemporal brain regions, whereas ODD/CD was associated with “ hot” deficits in the regulation of motivation and affect (related to emotional impulsivity) resulting from dysfunctions in the paralimbic system including orbito-frontal and superior-temporal areas and the ACC as well as the limbic system (Rubia et al., 2008 , 2009a , b ; Rubia, 2011). Particularly the latter may lead to a lack of self-control in emotional situations Matthys et al. (2013) .

Besides these differences between ADHD and ODD/CD, there is an ongoing debate, whether children with comorbid ADHD + ODD/CD may form a separate clinical entity as diagnosed in the ICD-10 as “ F90. 1 Hypercinetic Conduct Disorder” (WHO, 1993), or whether the comorbidity of ADHD and ODD/CD may be considered separately as in the DSM-V (APA, 2013).

In earlier electrophysiological studies, Banaschewski et al. studied children with ADHD, ODD/CD, comorbid ADHD + ODD/CD and controls in a 2*2-factorial design assessing additive and non-additive effects of both disorders. During CPT performance, children with ADHD showed slower and more variable response speed, whilst children with comorbid ADHD + ODD/CD

committed more dyscontrol errors. On the level of brain electrical activity, children with pure ADHD were characterized by lower Cue-CNV suggesting preparation problems. Both children with pure ADHD and ODD/CD but not comorbid ADHD + ODD/CD displayed diminished attentional orientation as indicated by impaired P3a to Cues and uncued targets (Banaschewski et al., 2003a). Children with comorbid ADHD + ODD/CD displayed diminished Nogo-P3 related to motor response control (Banaschewski et al., 2004). In the Stop-Task, response inhibition deficits in performance and associated brain activity of both children with pure ADHD and ODD/CD reached significance, whilst the yougsters with comorbid ADHD + ODD/CD did again show overall less severe problems (Albrecht et al., 2005). These findings are supported in a neuropsychological study by Luman et al showing that children with ADHD + ODD/CD were located in between children with ADHD and controls regarding response inhibition speed, timing performance and the impact of incentives or penalty on timing performance (Luman et al., 2009).

Taken together, children with ADHD and ODD/CD may have a broad deficit in performance and brain activity associated with several executive functions. Comorbid ADHD + ODD/CD may show elevated “ hot” cognitive deficits in motivation, affect regulation and impulsivity (and accordingly response control problems), whilst problems with “ cool” attentional orienting and response preparation may be less severe than expected from an additive model of impairments found in both pure ADHD and ODD/CD.

Perspectives for NF. There is evidence that children with comorbid ADHD + ODD/CD may show particularly problems with self-regulation, whilst cognitive deficits may be less severe than expected from typical findings from ADHD and ODD/CD, suggesting that NF interventions may use these cognitive resources and may dwell on the enhancement or compensation of diminished self-regulation skills accordingly. Since ADHD may precede ODD/CD in child development, early interventions may be particularly promising. Moreover, combined NF SCP and theta/beta training yielded, besides particular reductions of teacher and parent-rated ADHD symptoms, also effects on parent-rated oppositional behavior and conduct problems when compared to a standardized computer attention training (Gevensleben et al., 2009), indicating that NF may also be beneficial in treating ODD/CD.

ADHD and Tic Disorder

Tic disorders (TD) are characterized by involuntary, sudden, short, repetitive and non-rhythmic fragments of usual movements and/or vocal expressions. Tics are ranging from mild (e. g., eye blinking or sniffing) to severe (e. g., strong head or body jerking, shouting) intensity and simple (e. g., shoulder shrugging, grunting) to complex (e. g., turning, vocalizing complex words or sentences) extent that do not fulfil any subjective purpose (Leckman, 2002). TD are considered as " Neurodevelopmental Disorders" in the DSM-V (APA, 2013); more details about clinical assessment and treatment options may be found in the European Guidelines on TD (Cath et al., 2011 ; Muller-Vahl et al., 2011 ; Roessner et al., 2011 ; Verdellen et al., 2011).

Tics do often occur in bouts and are particularly present during stress or in positive or negative emotional situations. Particularly patients older than 10

years may realize sensory-motor phenomena (e. g., an urge to execute a tic) before and/or after tic, and are often able to suppress their tics for a limited period of time (Banaschewski et al., 2003b). Urges and uneasy sensory-motor feelings may be a part of the impairment (Swain et al., 2007).

The situation of patients with Tics is further complicated by frequent comorbidities with ADHD, anxiety, obsessive-compulsive disorder or mood disorder. ADHD + TD may be present in about half of children with TD, particularly in patients with Tourette's syndrome.

Assessment of the psychopathological profile revealed particularly mood, thought, attention and social problems as well as somatic complaints in children with TD, which do partly overlap with difficulties found in ADHD. Importantly, effects were (with the exception of somatic complaints) additive in ADHD and TD (Roessner et al., 2007).

TD is probably associated with disturbances in cortico-striato-thalamo-cortical neuronal networks which may be partly compensated by increased prefrontal activity instrumental in tic suppression (Leckman et al., 2006 ; Swain et al., 2007 ; Wang et al., 2011). Studies on structural imaging via voxel-based morphometry (VBM) or diffusion tensor imaging showed abnormalities in a number of brain regions including the basal ganglia, putamen, thalamus, corpus callosum and in the prefrontal cortex, which may reflect pathological as well as compensatory alterations (Peterson et al., 2003 ; Plessen et al., 2004 ; Jackson et al., 2011 ; Liu et al., 2013 ; Müller-Vahl et al., 2014). However, a recent VBM study with younger medication naïve boys with Tourette's syndrome without comorbid conditions did not

replicate abnormalities in gray or White matter, (Roessner et al., 2009). Thus, it remains open whether the above mentioned structural abnormalities may be a consequence of long-term tic suppression or comorbidities in Tic disorders.

A recent imaging study in adults generally replicated an earlier study of Bohlhalter by further elucidating the progression of brain activity in the cortico-striato-thalamo-cortical circuit preceding a tic and additionally suggesting the role of DMN activity in tic generation (Bohlhalter et al., 2006 ; Neuner et al., 2014). Peterson found increased activity during tic suppression in the prefrontal cortex and basal ganglia, which were inversely related to tic severity in everyday life (Peterson et al., 1998).

Moreover, studies on excitability of the motor system using transcranial magnetic stimulation indicated reduced motor inhibition in individuals with TD (Ziemann et al., 1997), which improves with development (Moll et al., 2006). Reduced inhibition within the motor circuit was also seen in ADHD, and shows again additive effects in individuals with comorbid ADHD + TD (Moll et al., 2001 ; Orth and Rothwell, 2009 ; for a review see Orth, 2009).

Studies on higher order cognitive functions in TD suggest that patients may not show general impairments, but may at most be affected as a consequence of their tics or potential compensatory mechanisms; studies addressing the co-existence of TD + ADHD often found deficits explained by ADHD following an additive model (Schuerholz et al., 1998 ; Roessner et al., 2008 ; Greimel et al., 2011). However, this may not hold for electrophysiological parameters of preparation and self-regulation after

decision making, as children with ADHD + Tic may be more similar to children with pure Tic disorder, following a sub-additive model (Yordanova et al., 1996 , 1997). Diminished preparatory slow-wave CNV in children with Tics was furthermore associated with tic severity, suggesting a possible functional link with tic suppression (Siniatchkin and Kuppe, 2011).

Functional imaging studies particularly in adults with TD yielded mixed results, and the interpretation of functional data in TD may be complicated by the interplay of both activity reflecting pathophysiological mechanisms and potential compensatory activity required during tic control (Gerard and Peterson, 2003 ; Vloet et al., 2006). This is supported by a cross-sectional developmental study in children and adults with the Stroop-task, showing normal performance during interference control, but elevated fronto-striatal activity and deviant development of activity in prefrontal and posterior cingulate areas in patients with Tic disorder compared to healthy controls (Marsh et al., 2007).

Perspectives for NF. In sum, ADHD + TD is probably not a separate clinical entity as it is the case for ADHD + ODD/CD. Individuals with ADHD + TD may share difficulties associated with both disorders often following an additive model, which may however be a special challenge to treat. SCP-NF may be used to ameliorate diminished slow-wave activity during preparation, which may be a common psychopathological impairment in both ADHD and Tic disorders. Typical interventions used in the treatment of TD that rely on intact cognitive control mechanisms or executive functions such as habit reversal may be less effective when ADHD is associated.

Nevertheless, NF may be a promising component of a multi-modal therapy, as it combines training of potentially problematic brain activity with direct feedback and reward.

In previous intervention studies, Theta-SMR-protocols have been applied in Tic-/Tourette disorder, from a traditionally point of view aiming at inhibiting over-activity in senso-motor cortical regions (Tansey, 1986). There is some evidence for positive effects of NF in subjects with Tic-/Tourette disorder from several single-case trials (see Rothenberger and Gevensleben, 2013 for a short overview). Further promising results evolved from a pilot study comparing the impact of sensory motor rhythm (SMR; 12–15 Hz) vs. SCP-NF training on Tic-/Tourette symptoms (Gevensleben et al., 2014b). Under both conditions Tic-severity was reduced by about 25% after 24 units of NF. Interestingly, in those patients who additionally suffered from ADHD (about 50% of the sample) ADHD symptoms are reduced significantly only after SCP training (not after SMR), indicating a potentially specific effect of SCP training on ADHD (at least in patients suffering from comorbid ADHD + TD).

Conclusion

ADHD as a neurodevelopmental disorder is associated with pathophysiological problems during cognitive demands, reward processing and during rest. It is further complicated by a number of heterogeneities regarding clinical characteristics, sex differences, and frequent comorbid disorders. The current manuscript introduced associated pathophysiological characteristics and discussed their potential relevance for NF intervention in ADHD.

It is argued that cognitive deficits during preparation for an upcoming event and response inhibition problems associated with deficient activity in the prefrontal cortex and in the ACC, as well as impaired resting-state brain activity may be ameliorated by respective NF trainings. Tomographic NF interventions using high density EEG recordings, fMRI or NIRS targeting specific brain areas may allow more direct training of brain activity impaired in ADHD. Motivational problems during reward processing may rather be compensated by the acquisition of self-regulation skills.

NF interventions may be used for hyperactive/impulsive and inattentive subtypes, and may not require sex-specific adaptations. It may in general be useful for children with comorbid ADHD and conduct disorders characterized in many ways by sub-additive cognitive deficits of both pure disorders but pronounced self-regulation deficits, as well as for ADHD and associated Tic disorder characterized largely by additive impairments.

Taken together, NF intervention in ADHD may be applied in order to ameliorate specific deficits, and/or to acquire self-regulation skills to use them for the compensation of difficulties in other domains.

Conflict of Interest Statement

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

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