Neurobiological basis of ADHD adults: identification of functional biomarkers of motor response preparation and response inhibition, and delineation of age related changes using high density EEG

PhD Thesis

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a childhood onset neurodevelopmental disorder which, based on data from epidemiological studies across the world, continues into adulthood in a high proportion of cases, with an estimated prevalence of 1.5-5%. The disorder is characterized by three basic symptom dimensions: inattention, hyperactivity and impulsivity, which are termed as core symptom domains in the pertinent literature. Theories of ADHD posit that neurocognitive impairment as well as deficit of executive functions including cognitive control processes may be behind the disorders' core symptoms, especially the impulsivity and hyperactivity. In the studies outlined below, I examined in adult patients with ADHD the neurobiological basis of those cognitive control, behavior monitoring and inhibition processes that may play an important role in the development of clinical symptoms and psychopathological manifestations that characterize the disorder. The neurobiological alterations and the concomitant neuropsychological and psychopathological deficits may lead, through a causal chain, to a cascade of events that limits functioning in everyday life to a great extent, and results in a life-long functional impairment in a substantial proportion of ADHD patients.

I studied the neurobiological basis of cognitive control deficits on the basis of the Dual Mechanisms of Control (DMC) model as proposed by Braver 2012. Specifically, I investigated neurophysiological processes that are associated with the preparation of motor response (proactive control) as well as the behavioral response inhibition (reactive control). Proactive control can be characterized as the preparation for the motor response, whereas reactive control represents the series of processes associated with the execution of the actual response. The delineation of the neurobiological basis of the above processes has fundamental importance from the perspective of the identification biomarkers of ADHD. Despite that alterations in the prefrontal cortex and their connections have long been described in the literature, the characterization of the neurobiological background of the disorder, and of the process that leads to the adult form of ADHD remains still unresolved. According to our knowledge, the neurobiological background of the proactive control has not been examined before. The aim of the 1st study described in this dissertation was to fill this gap in the literature. Prior research into ADHD has mainly focused on the reactive control processes, particularly on the behavioral and neurobiological changes associated with error commission. However, the developmental changes of reactive control processes with age

in adults with ADHD have not been studied. In our study, I focused on such developmental changes based on electrophysiological measures using a behavioral response inhibition paradigm. Among impairments in cognitive function in ADHD, behavioral response inhibition (BRI) has gained prominence in the literature since it may play an important role in symptoms of the disorder. BRI is essential from the point of view of executive functions adaptive social functioning, its impairment leads to behavioral dyscontrol, distractibility, and deficits in sustained attention. The development of BRI starts in early childhood, and its maturation continues until the early 20 years of age. Deficient BRI plays a role in the processing of emotional stimuli in the environment. The P3 event related potential (ERP) component is an electrophysiological measure which allows for the in investigation of the developmental maturation of BRI and the neural processes associated with changes across lifetime. Investigation of developmental changes in ADHD is particularly important because by adulthood the disorders subsides in a substantial proportion of cases, i.e., ADHD is being “grown out”, with a clinically significant amelioration of symptoms. Prior MRI studies into the neurobiological basis of ADHD revealed a delayed developmental maturation in several cortical areas especially in the frontal regions.

However, previous MRI studies examined only a limited age range including primarily childhood and adolescence, and in most cases failed to focus on changes in adults.

OBJECTIVES

1st study

- Delineation of response preceding brain activity, especially of the response preceding negative shifts (RPNS) in the EEG of adult ADHD patients as compared to healthy controls.
- To examine whether alterations in RPNS in patients with ADHD show an association with potentially important covariates, including the core psychopathological symptoms of ADHD; the neuropsychological indices of attention allocation and executive functions; and the intra-individual moment-to-moment fluctuations of reaction times.

2nd study

- Investigation of changes in P3 associated with age in adult ADHD, considering that P3 is a sensitive index of behavioral response inhibition and of the maturation of cognitive processes and aging.
- Examination of P3 alterations as a function of emotional valence of the stimuli, considering that the deficit of control of

emotional inputs, i.e., emotional dysregulation has often been regarded as the fourth core symptom of ADHD.

METHODS

1st study

A total of 62 subjects participated in the 1st study: 33 patients with ADHD and 29 healthy controls. Healthy control subjects were matched to ADHD patients on the basis of gender, age (+/-5years) and education level. Subjects enrolled in the study belonged to the combined subtype of ADHD according to the DSM-IV diagnostic system.

Healthy control subjects were recruited from a community sample through friends and acquaintances of the office and medical staff at the University. The 90-item Symptom CheckList (SCL-90R) was used to select controls with no current psychiatric comorbidity. The Conners' Adult ADHD Rating Scale (66-item version) was used to describe ADHD symptom severity across core psychopathological domains of ADHD: Inattention, Hyperactivity, Impulsivity and Problems with Self-Concept. The Stroop Color-Word Incongruency task (CWI) was applied to characterize executive functions and conflict processing. The CWI is a standard measure of

attention and executive functions, and ADHD patients have been shown to exhibit impaired performance on this task. EEG was acquired through a 128-channel active electrode system at a digitization rate of 1024 Hz, with a band-pass filter of 0.5-70 Hz using the BioSemi recording system with the average reference. Stimuli comprised capital letters, and each letter was presented at the central fixation point for 200ms. Subjects were asked to push a button as soon as possible upon the appearance of the letters; they were, however, asked to withhold response in case a letter was repeated (NoGo trials). The primary statistical analysis for group difference between ADHD and Control subjects was based on the random regression hierarchical linear model (HLM). Amplitude (voltage) values within the time-window of interest (100-msec prior motor response) for response-preceding activity were used as dependent variable in the HLM. Group, time (sampling point) and their interaction were used as independent variables; age and gender served as covariates.

2nd study

Patients who met DSM-IV criteria for adult ADHD (n=45) and had no history of neurological illness were recruited for the study. Healthy controls (n=41) with no history of psychiatric disease were individually matched to patients on age, gender

and education level. All patients met the DSM-IV criteria for the ADHD combined subtype. High-density EEGs were recorded using a 128-channel BioSemi ActiveTwo system, at a digitization rate of 1024 Hz. Data were stored and analyzed off-line using the Electromagnetic Source Signal Imaging (EMSE) Suite as well as the Statistical Analysis System (SAS 9.4) software. EEG was re-referenced off-line to the common average potential and filtered between 0.5 and 70 Hz using zero-phase shiftforward and reverse IIR Butterworth-filter. Additionally, the signal was filtered using the 48-52 Hz Parks-McClellan stop-band Notch filter. The notch filter was used to remove any potential electric-interference from the 50-Hz line. Fronto-central P300 responses were measured while subjects performed a complex visual Go/NoGo task. The International Affective Picture System (IAPS), a set of images with neutral, positive, and negative valences, were used as stimuli, and presented in random sequence. The frontal P3 component time-window included the post-stimulus epoch of 300–450 msec. The ERP analysis was based on random-regression hierarchical linear modeling. P3 amplitude was the dependent variable, while study group (between-subjects factor), and emotional valence (within-subject factor) were the independent variables. Time (sampling point in the component window, relative to stimulus on-set) was also included in the

analysis as a within-subject factor. Gender was a covariate. Age was used as a continuous regressor. Interaction between group, emotional valence and age (used in linear and quadratic form) was investigated. The interaction of group with age tested whether the groups had a different developmental trajectory with age.

RESULTS

1st study

The analyses indicated no significant difference between the two study groups in terms of age ($F=0.14$; $p=0.71$), gender ($Chi^2=0.09$; $p=0.76$) and education level ($F=0.33$; $p=0.57$). ADHD patients evidenced significantly higher symptom severity than the healthy controls as measured by the total score on the SCL-90R scale. In all four domains of the CAARS scale, including Inattention, Hyperactivity, Impulsivity and Problems with Self-concept, the symptom severity of the CAARS scale was significantly higher in the ADHD group as compared to the healthy controls. Furthermore, in the Stroop CWI task condition the ADHD patients showed a significantly ($F=10.1$, $df=1.61$, $p=0.0024$) lower performance than the healthy controls (ADHD error rate mean=4.3% [SD=5.9%]; control error rate mean=1.8% [SD=2.5%]).

The quantile regression analysis indicated a significant group difference in median reaction time (Wald Chi-square test statistic=4.46, df=1, p=0.035) and in the lower 25% quartile of the reaction time distribution (Wald Chi-square test statistic=7.27, df=1, p=0.007). Specifically, the median reaction time in the control group was 459.5ms (interquartile range: 25%=432.8 and 75%=484.9ms), while in the ADHD group the analogous median value was 433.1ms (interquartile range: 25%=388.6 and 75%=477.4ms).

In addition to the faster reaction time, we observed higher intra-individual reaction time variability in the ADHD group (median intra-individual SD of reaction times=150.8ms) than in the healthy controls (median intra-individual SD of reaction times =129.4ms); the difference was statistically significant (Wald Chi-square test statistic=4.44, df=1, p=0.034). The results were similar when we characterized the intra-individual variability of reaction times using the Coefficient of Variation (CV). Once again, we found a significantly higher CV (Wald Chi-square test statistic= 4.77, df=1, p=0.029) in the ADHD (median CV=27%) than in the control group (median CV=22%).

In terms of electrophysiological data, we found a gradually developing negative potential shift that started approximately 200-ms before the onset of the motor response, and reached its maximum just after the execution of the motor response. This response preceding electrophysiological activity (RPNS) showed a similar waveform in both groups, but its amplitude was significantly larger in the ADHD group. The association of the RPNS amplitude with the error rate in the CWI task, with the intra-individual variability of reaction times, and with the severity of hyperactivity was detectable in all frontal areas; the association with impulsivity remained significant in the left frontal areas after correction for multiple testing. Post-hoc examination of the direction of the above associations showed that higher error rate in the CWI task was associated with larger RPNS amplitude among patients with ADHD. Furthermore, greater intra-individual variability of reaction times was related to increased RPNS amplitude. Finally, among patients with ADHD the severity of hyperactivity was associated with higher RPNS.

2nd study

A total of 45 patients with ADHD and 41 healthy controls were enrolled in the study. The two groups were almost identical in terms of average age (ADHD=30.4years

[SD=10.9]; control 31.3 years [SD=11.4]). The proportion of males was slightly higher among healthy controls, but the difference did not reach significance (Healthy control=75.6%; ADHD=71.1%). The two groups did not show a significant difference in the level of education. The proportion of subjects with college education or higher was 40% and 46.3% in the ADHD and the control group, respectively. In terms of commission errors, the statistical analyses revealed a significant effect ($p<0.05$) for group and a linear effect of age; the quadratic main effect of age was not significant. Post-hoc analyses indicated a significantly higher error rate for ADHD as compared to control subjects. Furthermore, they show a significantly increasing error rate with increasing age. The main effect of emotional valence, as well as its interaction with age did not obtain statistical significance in the model ($p> 0.1$). The analysis of reaction times revealed a linear main effect with age as a continuous variable ($F_{1,85}=13.7$, $p=0.0004$), but no interaction or quadratic effect. Post-hoc analyses showed that the reaction time increased with age in both groups. With respect to commission errors, patients with age in the middle age range group (>30years) had a significantly lower mean reaction time for each emotional valence (positive, negative, neutral) as compared to the lower age group ($\leq$30 years). Among healthy controls, the decrease

of commission errors in the middle-age group was significant only for the neutral pictures. The decrease of reaction times as a function of age was numerically higher for all three emotional valences; the increase, however, reached statistical significance only in the case of the controls.

The developmental trajectory of the P3 amplitude was significantly different between the patients and the controls: patients with ADHD evidenced a significant amplitude reduction at younger age ($\leq$30 years) as compared to healthy controls. The size of the amplitude reduction was diminished in the middle age range, but with a further increase of age the reduction started to increase again. Even though the controls showed a slight numerical increase with age, the aforementioned group differences were driven by the markedly more pronounced changes in the ADHD group. Our further analysis also revealed a main effect of group ($F_{1,85}$=6.15, p=0.015), as well as an interaction between group and emotional valence ($F_{1,85}$=4.04, p=0.019). We found that the P3 amplitude decreased in the ADHD group as compared to controls with respect to all three emotional valences (NEG p=0.0043; NEU p=0.038; POZ p=0.023). Nonetheless, the P3 amplitude reduction in the ADHD group compared to controls was the most pronounced for the negative pictures.

CONCLUSIONS

In the two studies presented in this dissertation, based the DMC model we investigated the processes of cognitive control in patients with adult ADHD through the analysis of neurobiological changes accompanying motor response preparation (1st study) and response inhibition (2nd study).

1st study. According to our knowledge, examination of the proactive control processes that precede motor response has not previously been taken place by using a neurobiological approach. This study extends previous investigations which indicate impairments ADHD in adaptive control processes (e.g., in retroactive control, as shown by error-related negativity). We found that the response preceding negative potential shift (RPNS) shows increased amplitude in patients with ADHD as compared to healthy controls. The augmentation of RPNS amplitude in ADHD patients occurred in regionally specific manner, and was restricted primarily to the frontal areas. It is important to highlight that from the perspective dimensional approach of ADHD, which has been forwarded in the literature, the RPNS increase, in addition the presence of the disorder, showed also an association with the severity of the clinical symptoms. Taken together, our results

reveal that EEG activity that precedes motor response shows an augmentation ADHD patients, which in light of the literature may indicate an increased activity in the prefrontal neural circuits. Considering that the RPNS alterations in ADHD patients show an association with neuropsychological and psychopathological variables, these alterations may play a critical role in the core symptoms of ADHD, including the premature ("careless") behavioral responding and motor hyperactivity.

2nd study: The results of this study indicate delayed developmental maturation of fronto-central NoGo P3 in young adulthood in patients with ADHD as compared to healthy controls. The normalization of the developmental delay in adulthood in ADHD patients was restricted to a certain age range, beyond which the difference as compared to healthy controls started to increase again. Since the fronto-central NoGo P3 reflects the functioning of frontal brain areas (which show a delayed development in ADHD), the findings are consistent with the "last in, first out" hypothesis, which refers to the mirror-symmetrical pattern of human brain development and aging. Therefore, our findings raise the possibility that ADHD – particularly in those patients whose symptoms persist in adulthood – is not only associated with a delayed

neurodevelopmental trajectory but also with relatively early deterioration, at least in certain areas of neurophysiological functioning. The reduction of P3 amplitude in ADHD patients as compared to controls is the most pronounced for negative pictures. This may indicate deficits in executive functions, and is thereby consistent with the hypothesis of emotional dyscontrol in ADHD.

Main limitations of the 1st and 2nd study: As some of the patients received medication, further studies are needed to examine medication effects, despite our finding that patients with and without medication showed no difference in terms of RPNS augmentation in the 1st study. The 2nd study was a cross-sectional investigation, which due to the potential confounding by "age-cohort" effects does not allow for an interpretation of our results in a causal context. Nonetheless, since we continuously sampled patients in the age-range that we examined (18-65 years), and applied a regression approach, such a confounding by age-cohort effects appears unlikely.

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