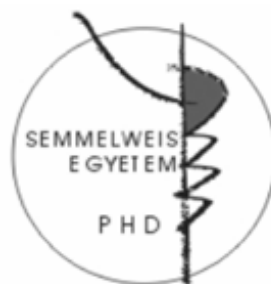


# **Investigation of clinical, neuropsychological and electrophysiological characteristics of adult attention deficit hyperactivity disorder (ADHD)**

PhD thesis

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Budapest  
2013

## **INTRODUCTION**

Structural and functional imaging studies in adults with ADHD have suggested dysfunction of prefrontal, anterior cingular and parietal gray matter, and alterations in white matter connections subserving cognitive functions as attention and executive functions. Additionally, the disturbance of cognitive functions in adults with ADHD was also revealed by neuropsychological and electrophysiological investigations.

Furthermore, there is an association between clinically significant functional impairment and the symptoms of ADHD, particularly inattentiveness. This association is independent of the fulfillment of diagnostic criteria of ADHD. The contribution of executive function deficits to functional impairment in adult ADHD is still an open question.

## **AIMS**

The broad aims of my research were to investigate the neurobiological background of cognitive dysfunctions, particularly attentional and executive dysfunctions, in adult ADHD, and the investigation of the associations between cognitive dysfunctions and clinical symptoms of ADHD and functional impairment related to the symptoms.

### **Aims of the first investigation**

#### *Investigation of P3 event related potential in adults with ADHD*

The use of event-related potentials (ERP) plays an important role in exploring neural underpinnings of cognitive functions due to their high time resolution. P3, the widely examined late ERP component, has been incriminated in various psychiatric disorders and has been supposed to reflect executive and attentional functions, including updating of working memory, event categorization, attentional resource allocation as well as attentional reorientation. These are all important cognitive domains in ADHD. There is a scarcity of P3 studies in adult ADHD and the synthesis of these data has not been carried out.

The aims of my first investigation were to answer the following questions:

1. Is there a difference between adults with ADHD and healthy subjects in terms of target related P3 characteristics?
2. Does target related P3 vary as a function of age and gender in adults with ADHD?

### **Aims of the second investigation**

*Investigation of the associations between the symptoms of ADHD, the executive and attentional functions and functional impairment in a community sample*

The aims of the second investigation were to answer the following questions in a community sample of adults positively screened for ADHD:

1. Does the presence of clinically significant functional impairment correlate with the clinical features of ADHD (as indexed by the type and number of symptoms)?
2. Does the presence of clinically significant functional impairment correlate with attentional and executive dysfunctions measured by neuropsychological tests?

## **METHODS**

### **Methods of the first investigation**

We investigated the characteristics of target related P3 in adults with ADHD with the meta-analysis of relevant publications. The use of this method makes possible the synthesis of previous data and the resolution of contradictions, and - with the increase of sample size - increases the statistical power.

### *Search strategy*

We searched the Ovid Medline and PsycINFO databases applying the time limit from January 1994 to December 2009 as a search window for the relevant publications. Keywords were: ADHD, adult, adulthood, EEG, electroencephalography, ERP, evoked potential, event related potential, electrophysiology, psychophysiology and neurophysiology. Reference lists of identified papers were also reviewed.

To be included, studies must have been written in English, contained both adult ADHD and matched healthy control groups, used DSM-IV criteria for ADHD diagnosis and must have presented target related P3 data assessed in both groups. Two studies reporting stop P3 data were excluded, as this component fell outside the range of interest of the meta-analysis. Based on these inclusion and exclusion criteria, six studies were identified for the purpose of our meta-analysis.

### *Data extraction*

These six studies were heterogeneous regarding their methodology. They reported data that were acquired in different task conditions with regard to the neuropsychological paradigm that they used as well as to their stimulus modality (auditory or visual), interstimulus interval (ISI) (550-8400 ms), target probability (18-75%) or the electrode sites (central or parietal sites) used for the registration of ERP components (P3, P3b). For the purpose of the current meta-analysis, an attempt was made to include those data from the individual publications that were deemed comparable across studies. Considering the small number of studies, we included the data of two different ISI conditions from two studies.

### *Statistical analyses*

Pooled effect size (Cohen's  $d$ ) was calculated across the studies to define the differences between the adult ADHD and the control groups. Cohen's  $d$  was defined as the difference between two means divided by the pooled within-group standard deviation of both groups. The closer the Cohen's  $d$  approaches zero, the smaller the difference between the two groups. We consider absolute values of Cohen's  $d$  between 0.20 and 0.39 as small, between 0.40 and 0.69 as medium, and from 0.70 as large effect sizes.

A random effect meta-regression analysis was applied to estimate the pooled effect size of the difference between the ADHD and control groups across various studies and in order to investigate the association between the effect size in relation to age and gender. The meta-regression analysis was based on van Houwelingen et al.'s general linear mixed model technique using the approximate likelihood approach. In particular, the effect size from each study was regressed on an intercept and on study-level demographic covariates, which included mean age (years) and gender composition (% of males) in each of the individual studies. A common weighted statistical effect-size estimate for the ADHD group versus control group difference was calculated using the DerSimonian–Laird estimator, based on the random effect component of the mixed model that incorporated both fixed and random effects.

### **Methods of the second investigation**

This investigation was part of a larger study examining the epidemiology, clinical features, psychopathology, neuropsychology and genetic background of adult ADHD in Hungary in a community sample. The study had a screening phase and a diagnostic phase.

From June 2006 to June 2007, 3529 patients of 17 GP practices in the area of Budapest, Hungary were screened for ADHD with the screener version of the ASRS (a self-rating scale developed by WHO). All subjects included in the study were between 18 and 60 years of age from both genders without any major neurological disorder in their clinical history. Of the 279 positively screened subjects 82 refused participation and 39 failed to show up for the further investigation.

The 161 subjects who entered the diagnostic phase of the study, participated in a clinical interview conducted by trained interviewers, underwent an assessment of comorbid disorders and neuropsychological functions, and provided a genetic sample (for which they received 2000 HUF as a compensation). The study was carried out in accordance with the latest version of the Declaration of Helsinki. The study was approved by the local ethics committee and all included subjects provided written informed consent.

**In our investigation** we analysed the clinical data and the neuropsychological results of the second phase of the parent study. Due to incomplete data, we included 158 of the 161 subjects into our investigation (42 males and 116 females with a mean age (SD) of 41.54 (11.6) years).

#### *Clinical measures*

The clinical interview had two parts: a structured diagnostic interview developed by the study group using symptom list (18 symptoms) and further diagnostic criteria of ADHD in DSM-IV (age of onset and functional impairment); and a free clinical interview in order to collect relevant background information for supporting the validity of the clinical diagnosis. The presentation of functional impairment (yes/no) was established based on whether the symptoms were present and caused problems during the past half a year.

#### *Psychopathological and neuropsychological measures*

The neuropsychological domains and indices we chose were based on their relevance as potential cognitive endophenotypes for ADHD. These indices were the following: reaction time variability, response inhibition, processing speed, working memory and set shifting. Additionally, we measured full-scale IQ, and CAARS-S was also investigated.

**Conners Adult ADHD Rating Scale–Self-report** is a 66-item self-report scale that measures the presence and severity of symptoms of adult ADHD across clinically significant domains. We used the score for DSM-IV Total ADHD Symptoms subscale and scores for four factor-derived subscales: Inattention/Memory Problems, Hyperactivity/Restlessness, Impulsivity/Emotional Lability and Problems with Self-concept.

**Wechsler Adult Intelligence Scale–Revised** was used to estimate the full-scale IQ of participants. Furthermore, we report the scores for four subtests that measure domains proven to be relevant in ADHD in relation to executive functioning: *Digit Span forward* (short-term memory, attentional capacity); *Digit span backward, Arithmetic* (working memory); *Digit Symbol* (set shifting, processing speed).

**Conners Continuous Performance Test** is a standardized computer-administered test that measures attention functions and provides several variables, of which we report the following: number of omissions (missed targets) and reaction time variability (i.e. overall standard error for mean reaction time) as measures of sustained attention; number of commissions (false hits) and mean reaction time for correct responses as measures of impulsivity and response inhibition; and score for the change of mean reaction times at the different ISIs to assess how the level of activation/arousal changes as a function of task difficulty.

**Trail Making Test A and B** times were considered as a measure of sustained vigilance and processing speed, and as an index of set shifting abilities and working memory, respectively.

**Wisconsin Card Sorting Test** is a widely used task assessing working memory and set shifting abilities. We reported the scores for categories completed, conceptual responses, total errors and perseverative errors.

Following the second phase of the study, participants (158) were divided into two groups, depending on whether they had functional impairment (73) or not (85). We investigated the differences between the two groups in terms of demographic data (age, gender and years of education); full-scale IQ; symptom presentation according to DSM-IV and CAARS-S; and neuropsychological measures.

We note that our sample had two specific features. First, unlike clinical investigations that comprise predominantly male subjects, a little over two-thirds (73%) of our sample was female. Second, due to the screening approach, our sample differed both from healthy subjects and subjects diagnosed with ADHD in terms of symptom severity.

#### *Statistical analyses*

Differences between the study groups on continuous variables were investigated using analysis of covariance. Each variable of interest was used separately as a dependent variable in the analyses (number of symptoms, CAARS-S total and subscale scores, neuropsychological measures). Study group served as the independent variable. Since the two Fi groups showed a difference in age and gender proportion, these variables were included as covariates in the inferential statistical analyses.

Predictive association between Fi and overall symptom count as well as the number of symptoms on the individual CAARS-S subscales was investigated using logistic regression analyses. The dichotomous variable Fi (yes/no) was used as a dependent variable in these analyses; symptom on CAARS-S total and independent subscales served as independent variables in the logistic regression. The odds ratio (OR) statistic ( $\pm 95\%$  confidence limits) was used to characterize the strength of the association. The two sided alpha level of 0.05 was adopted for statistical significance. SAS 9.2 version was used for all statistical analyses.

## RESULTS

### Result of the first investigation

Across the six studies included in the meta-analysis there were a total of 154 ADHD and 140 control subjects matched according to age and gender. The mean age (SD) and age range were 27.6 (5.3) and 17–57 years for the ADHD and 26.2 (6.2) and 17–57 years for the control subjects, respectively. The mean percentages of males in the ADHD and control groups were 78.9% and 87%, respectively.

Results of the meta-regression analysis of the P3 amplitude across studies indicated that the medium pooled effect size in terms of Cohen's  $d$  was  $-0.55$  ( $p=0.0006$ , 95% confidence interval (CI) =  $-0.76$  to  $-0.33$ ). The negative value of the estimate of the effect size (with a 95% CI that excludes zero) indicates that overall compared with the control subjects, the adult ADHD patients show a statistically significant decrease in P3 amplitude during target detection. Effect sizes for individual studies, ranging from  $d = -1.93$  to  $d = 0.58$ . We note that a positive effect size was found in only one of the studies. We found a significant association between the effect size for P3 amplitude and target probability in an individual study ( $\beta = -0.019$ , 95% CI =  $-0.03$  -  $-0.008$ ,  $t = -4.29$ ,  $p = 0.0078$ ): the more frequent the target, the more negative (i.e. the higher in absolute value) the effect size for P3 amplitude.

In addition, we investigated whether the effect size for the group difference in terms of P3 amplitude varied across studies as a function of age and gender. Results of the meta-regression analysis revealed a significant association ( $\beta = -0.094$ , 95% CI =  $-0.151$  to  $-$



0.036,  $t = -4.18$ ,  $p = 0.0087$ ) between the effect size for P3 amplitude and the mean age of ADHD patients in an individual study: the higher the mean age of adult ADHD patients, the more negative the effect size for P3 amplitude.

The association between the effect size for P3 amplitude and gender composition (percentage of males) of the ADHD group in a particular study was also statistically significant ( $\beta = 0.022$ , 95% CI = 0.008 – 0.036,  $t = 4.02$ ,  $p = 0.01$ ): the higher the percentage of males in the ADHD group in a particular study, the less negative (i.e. the smaller in absolute value) the effect size for P3 amplitude.

### **Results of the second investigation**

Analysis of demographic characteristics revealed significant differences between groups of participants who had and had not functional impairment in terms of age and gender. Participants with impairment were significantly younger (38.68 (11.53) years vs. 43.99 (11.79) years,  $p = 0.0335$ ) and there were significantly more males (34.25% vs. 20%,  $p = 0.0433$ ) among them as compared to those without any impairment. We did not detect a group difference in years of education ( $p > 0.1$ ) and full-scale IQ ( $p > 0.1$ ).

Logistic regression analysis indicated significant associations of the increase in probability of functional impairment with an increasing number of overall as well as inattentive, hyperactive and impulsive symptoms in the whole study population. In particular, odds ratio of impairment was 1.38 for overall symptoms (95% CI = 1.23–1.53,  $p = 0.0001$ ); 1.51 for inattentive symptoms (95% CI = 1.29–1.76,  $p = 0.0001$ ); 1.57 for hyperactive symptoms (95% CI = 1.28–1.92,  $p = 0.0001$ ); and 2.01 for impulsive symptoms (95% CI = 1.47–2.74,  $p = 0.0001$ ).

In the two study groups, we found highly significant differences in terms of both DSM-IV symptoms and self-rating of symptoms by the CAARS-S. The proportion of participants who fulfilled the DSM-IV symptom criterion of ADHD (53.42% vs. 23.53%) as well as the number of overall ( $p < 0.0001$ ), inattentive, hyperactive and impulsive symptoms ( $p < 0.0001$  in every symptom domain), was significantly higher among subjects with functional impairment. Furthermore, participants with functional impairment achieved significantly higher scores on each index and subscale of the CAARS-S (in a range of  $p = 0.0001$ -0.0384). We underscore this significant difference

between the two study groups regarding the Problems with Self-concept subscale score. This subscale, as opposed to other CAARS-S subscales, indexes symptoms and complaints that are not part of the ADHD diagnostic criteria. These results, taken together, indicate substantially more complaints and self-rated symptoms in the group of subjects with functional impairment.

With regard to neuropsychological measures, we did not detect a significant group difference on any of the variables ( $p > 0.1$  for every variable).

We also note that adjustment for the fulfillment of the symptom criterion of ADHD (symptom criterion met, yes = 1, no = 0) did not change substantially our results.

## **CONCLUSIONS**

### **Conclusions of the first investigation**

The principal finding of the meta-analysis was that adult patients with ADHD had significantly reduced target related P3 amplitude as compared to healthy controls. The pooled effect size defining this difference was in the medium range (Cohen's  $d = -0.55$ ) that was comparable with effect sizes published in the adult ADHD literature in terms of attentional and executive dysfunctions and alterations in frontal lobe morphology.

Although P3 has also been related to other psychiatric disorders, our investigation revealed that it may be a marker of the dysfunction of target-related attentional processes in adult ADHD. Particularly, it may be related to the dysfunctions of the ventral attention network and attentional resource allocation.

### **Conclusions of the second investigation**

The main results of the second investigation indicated significant associations between the number of ADHD symptoms and the presentation of functional impairment in adults with and without the diagnosis of ADHD.

In addition to previous findings for inattentiveness, we found the highest effect size in terms of odds ratio for impulsive symptoms.

Our finding of self-reported complaints of self-concept, together with the lack of contribution from executive deficits and attentional dysfunction as measured by neuropsychological tests, underlines the importance of assessing behaviors not defined in DSM-IV as diagnostic criteria of ADHD to predict functional outcome in adults with ADHD symptoms.

## **LIST OF PUBLICATIONS**

### **Publications linked to the topic of the dissertation**

**Szuromi B**, Czobor P, Komlosi S, Bitter I. (2011) P300 deficits in adults with attention deficit hyperactivity disorder: a meta-analysis. *Psychol Med*, 41: 1529-1538.

**Szuromi B**, Bitter I, Czobor P. (2013) Functional impairment in adults positively screened for attention deficit hyperactivity disorder: the role of symptom presentation and executive functioning. *Compr Psychiatry*, doi: 10.1016/j.comppsy.2013.04.002.

### **Publication independent from the topic of the dissertation**

Rajna P, Hidasi Z, Pal I, Csibri E, Veres J, **Szuromi B**. (2009) Measurement of mental fatigability by task related spectral eeg. A pilot study. *Ideggyogy Sz*, 62: 36-40.