Electrophysiological and behavioral correlates of error monitoring in adult attention deficit/hyperactivity disorder (ADHD)

PhD Thesis

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INTRODUCTION

Heterogeneity of ADHD and variability of symptom presentation over the course of the illness pose a significant challenge to diagnosing ADHD in adulthood. Since there are several subjective factors potentially confounding the diagnosis, interest towards predictive biomarkers has increased substantially.

The overlap between the localization of structural and functional impairments characterizing ADHD and the brain structures that play a role in performance monitoring has turned the focus toward the investigation of error monitoring. Even though researchers have turned to analysing the behavioural indices of error monitoring with increasing interest (such as error rate or reaction time indices), published data on error-related ERP components are scarce in the adult ADHD literature.

Our aim was to investigate the nature of error processing impairment in adult ADHD at a neurophysiological and behavioral level that would possibly render implications for broader levels of information-processing impairments in the disorder.

OBJECTIVES

General objectives

The goal of our first and second study was to examine the post-error slowing in ADHD based on the previous literature and on empirical data collected in our own investigation. In our third study, we adopted an electrophysiological approach to examine whether the affective content of the stimuli modulates the components of the event related potentials (ERPs) in adult ADHD patients during error monitoring.

Aims of the first study

Based on prior literature, post-error slowing is considered to be a cognitive adaptation mechanism, which, allowing more time to error processing, elicits more careful response style to make the necessary adjustments after an error. The aim of our first study was to conduct a meta-analysis of the PES data available in the literature for child and adult ADHD patients. Our questions were:

1. Is there a difference between adult ADHD patients and healthy control subjects in post-error slowing?

2. What are the effect sizes of this difference between the ADHD subjects and the healthy controls.

3. What are the subject and the task related variables that influence the length of the post-error slowing in adult ADHD?

Aim of the second study

In our second study we investigated the post-error slowing in our adult ADHD patient group focusing on the following question:

1. Is there a difference in post-error slowing between adult ADHD patients and healthy control subjects?

Aims of the third study

Although it is well-known that the emotional content has an effect on the cognitive processes, there are only a few studies about the influence of this emotional content on the electrophysiological components of error processing in ADHD patients. Our goal was to investigate how the affective valence of the stimuli modulates response inhibition and error related ERPs.

We intended to address the following questions:

1. Regarding neutral stimuli, is there a difference between healthy subjects and adult ADHD patients in the component of error related negativity and positivity during error processing?

2. How the affective content of the stimuli modulates the electrophysiological components of the error processing in adult ADHD patients?

3. Is there an association between the severity of the ADHD symptoms and the error-related ERPs?

METHODS

Methods of the first study

In our first study we investigated the characteristics of the post-error slowing (PES) in adult ADHD patients and healthy subjects by conducting a meta-analysis of the data available in the literature for ADHD.

Data Sources

Relevant publications were identified through the Medline and PubMed search engines. We searched for studies published up to 2012 December in English, using the following search terms: ('adhd') AND ('post-error slowing' or 'post error slowing') OR ('reaction time', and 'error' or 'error monitoring'). Reference lists of identified papers were also reviewed.
Inclusion criteria for our meta-analysis are listed below:

- child and adult ADHD group and matched healthy control group
- diagnosis of ADHD based on DSM criteria

- patients taking stimulant treatment were off medication for at least 12 hours before testing
- task condition of continuous performance test (CPT)
- availability of information on the method used to calculate post-error slowing
- publications in English language

Characteristics of the relevant studies

Based on these inclusion criteria 15 relevant studies were identified, which reported a total of 26 pairs of comparisons. The included studies differed in their methodology. Tests were classified into three categories 1) go/no-go paradigm, 2) choice reaction time task, and 3) choice reaction time task with auditory or visual oddball sign. Based on the level of difficulty, tasks were classified into two categories. Combined choice reaction time tasks with a visual or auditory oddball sign were classified among the more difficult tasks. The duration of the inter-stimulus interval (ISI) varied greatly across studies. Instructions pertaining to speed and accuracy were emphasized to the same extent in most studies.

Meta-analytic procedure

Pooled effect size (Cohen’s d) for PES was calculated across the studies to investigate whether there is a significant overall difference between the ADHD subjects and the healthy controls. The Cohen’s d for group difference was computed as the difference between the two group's means divided by the pooled standard deviation of the two groups. By convention we consider absolute values of Cohen's d of 0.20-0.39 as small, 0.40-0.69 as medium, and 0.71 as large effect sizes. The meta-analysis based on the random-effect model described by Van Houwelingen et al., a meta-analytic technique of multivariate linear regression across studies to estimate pooled effect size for the difference between the ADHD and healthy control groups. Age and gender served as covariates.

Methods of the second study

Our second study was focused on the analysis of PES in our own adult ADHD patient sample.

Participants

A total of 51 subjects participated in the study: 22 patients with ADHD (17 men and 5 women, mean age: 30.6 years, SD: 9.7, mean number of school years: 14.5 years) and 29 healthy control subjects (19 men and 10 women, mean age: 30.1 years , SD: 9.0, mean number of school years: 15.7 years). All patients included in the study fulfilled the criteria for the combined subtype of ADHD using the DSM-IV criteria. Patients were recruited at the Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary, which provides outpatient service for patients with adult ADHD. Control subjects were individually matched to patients on age (within 5 years), gender and level of education. Healthy controls were recruited from a community sample through friends and acquaintances of the office and medical staff at the University. Participants in both the ADHD and the healthy control groups completed the 66-item version of the Conner's Adult ADHD Rating Scale (CAARS). The 90-item Symptom Checklist (SCL-90R) was used to select controls with no current psychiatric comorbidity.

Stimuli and procedure

We applied an emotional go/no-go response inhibition task, which was implemented by the Presentation 13.0 software (Neurobehavioral Systems, Inc.). We used pictures from the International Affective Picture System (IAPS) as stimuli; they comprised images with positive, negative and neutral affective contents. Each participant was instructed to respond with a "go" button when a picture appeared on the screen, and to withhold responding when the picture was repeated in the consecutive trial. Furthermore, participants were instructed to respond as quickly and accurately as possible. Each block consisted of 139 stimuli comprising 85% of go stimuli and 15% of no-go stimuli. All participants completed 2 experimental blocks. All stimuli were presented for 800 ms and were followed by an inter-stimulus interval (ISI) of 600 ms.

Behavioral measures

PES was calculated as the difference between the reaction times on correct after error trials (RTec) and reaction times on correct after correct trials (RTcc). Mean reaction time and the proportion of omission and commission errors were also identified. In this study behavioral measures were not broken down by emotional valence.

Methods of the third study

The participants of this study were recruited from two electrophysiological studies using identical paradigms. In my thesis, I discuss the electrophysiological correlates related to error monitoring.

Participants

We enrolled twenty-six patients meeting the DSM-IV criteria for adult ADHD (20 men and 6 women, mean age: 26.7 yr, SD = 5.7, inattentive type:12, hyperactive/impulsive type: 7, combined type:7) and fourteen healthy controls (11 men and 3 women, mean age: 31.5 yr, SD = 11.4), matched by age (+/- 5 years), gender and level of education in the study. Participants provided written informed consent according to procedures approved by the Institutional Review Board of the Semmelweis University, Budapest, Hungary. Patients were recruited from the adult ADHD outpatient clinic of the Department of Psychiatry and Psychotherapy of the Semmelweis University, Budapest. Participants in both the ADHD and the healthy control groups completed the 66-item version of the Conner's Adult ADHD Rating Scale (CAARS). The 90-item Symptom Checklist (SCL-90R) was used to select controls with no current psychiatric comorbidity. Patients taking stimulant treatment (n=10) were off medication at least 24 hours before testing. Lack of history of psychiatric disease was required for the inclusion in the control group. The main exclusion criteria for participants in the control group were: any present or past neurologic disorder and history of head injury with loss of consciousness.

Stimuli and procedure

Our paradigm was the same emotional go/no go task that was used in the second study.

EEG recording and pre-processing

The BioSemi recording system (sample rate=1024 Hz, band-pass filter= 0.5– 70 Hz) with average reference was used to acquire EEG. A standard BioSemi 128-electrode head cap system with electrodes labeled in 4 blocks of 32 electrodes was applied. Data were analysed off-line using the Electro-magnetic Source Signal Imaging (EMSE Suite v.5.0, Source Signal Imaging, Inc., San Diego, CA) Suite and the Statistical Analysis System (SAS9.4) software. Response-locked data were segmented into epochs of 200 ms from before to 400 ms after response.

ERP analysis and behavioral measures

The ERN was defined as the average amplitude in microvolts occurring in the window from 20 ms to 70 ms post-response. The Pe was defined as the average amplitude in microvolts peak within 100-300 ms of the response. The mean reaction time and the proportion of commission errors were examined as behavioural measures.

RESULTS

Results of the first study

Sample characteristics

A total of 1053 ADHD and 614 control subjects were enrolled in the studies included in the meta-analysis. The 15 relevant studies we identified reported results for a total of 26 pairs of comparison groups (ADHD and control). The mean age across groups (SD, range) was 12.2 (SD= 7.9, range: 6-41 years) for the ADHD and 12.1 (SD= 7.8, range: 6-40 years) for the control subjects, respectively. The proportion of males was 80% in the ADHD and 69% in the control group.

Meta-analytic estimates of group differences

Results of our meta-analysis across all studies indicated that ADHD patients show a statistically significantly diminished PES after committing an error as compared with healthy controls (ADHD: 15 ms, SD:143.6; control 53 ms, SD: 149; F value=7.56, p=0.01). Although the error rate was higher in the ADHD group (ADHD: 32.7%, control: 25.8%), the difference did not reach statistical significance.

We calculated the effect sizes for each study included in our meta-analysis, and used the meta-regression approach to estimate the pooled effect size. The overall (pooled) effect size of 0.42 (95% confidence interval, CI=0.12-0.73) was in the medium range. In additional analysis based on the observed data, we calculated the effect sizes for those studies that applied ISI longer than 2500 ms. Results of these analyses yielded effect sizes that fell in the upper range of the medium effect size (Cohen's d=0.65, 95% CI=0.26-1.03).

Demographic variables, study design and PES

Our analyses indicated no relationship between age, or gender, and PES either in the ADHD or the healthy control groups ($p>0.05$ for both age and gender).

We conducted a sensitivity analysis by excluding those studies that adopted an approach other than the prevailing method (i.e., RTec-RTcc) to calculate PES; our results indicated essentially no change in the statistical effect size for the PES difference between the ADHD and controls groups.

Group differences with respect to the task variables studied other than the one for ISI described above were not identified. The PES was significantly longer in both the ADHD patients and the healthy control subjects if the duration of ISI was fixed in the task. The PES was significantly longer in both groups following inhibition error compared to choice error ($F=5.16$, $df=1,49$, $p=0.028$). In both study groups a positive association was found between the duration of the PES and the difficulty of the task ($F=9.41$, $df=1,49$, $p=0.0036$).

Results of the second study

Behavioral markers, PES

In our study although the control group was characterized by longer post-error slowing (ADHD: 48.3 ms, SD: 14.8, control: 67.9, SD: 14.9) the difference between the two groups did not reach statistical significance (Wald-Chi-square statistics= 2.10, p=0.1555). The ADHD group showed a significantly lower performance compared to the control group (commission errors for ADHD group: 39.1%, SD:22.5 and for controls: 14.9%, SD:7.0). In terms of the proportion of omission errors (ADHD: 1%, SD: 2.3, control: 0.3%, SD: 0.4) and the duration of the mean reaction time (ADHD: 411.2 ms, SD: 95.6, control: 435.9 ms, SD: 63.5) there was no significant difference between the two groups.

Results of the third study

Demographics and basic descriptive characteristics

The proportion of male participants was higher in both the ADHD and the control groups (proportion of males in the ADHD group was 76.9% and 78.6% in the control group). Mean age in the control group was 31.5 years (SD:11.4), and 26.7 years (SD:5.7) in the ADHD group.

Task performance

The ADHD group made more commission errors compared with the healthy control group in all three classes of stimuli, with the most pronounced difference occurring in the cases of neutral and negative stimuli (ADHD: 41.1% , control: 21.7% for neutral stimuli; ADHD: 40.1%, control: 23.6%, for negative stimuli). In particular, the difference was significant for the neutral and the negative stimuli (Wald Chi-square test statistics= 5.97, df=3, p= 0.0021 for neutral and Wald Chi-square test statistics= 4.23, df=3, p= 0.0117 for negative stimuli). In the case of positive stimuli the ADHD group committed more errors without a significant group difference (ADHD: 40.7%, control: 30.4%, Wald Chi-square test statistics= 1.57, df=3, p= 0.2135). There were no group differences with regard to the mean reaction time.

Error-related ERP activity

Error-related activity had similar waveforms in both groups. Significant group differences with negative stimuli were detectable for the ERN at the FCz, Cz and Pz electrodes (for FCz F=14.15, p=0.0013; for Cz F=288.74, $p<0.0001$, for Pz F=75.65, $p<0.0001$) with lower amplitudes in the patient group. For neutral stimuli we found a significant ERN amplitude difference only at the Cz electrode (F= 12.17, p=0.0028). No significant differences were found in ERN for the positive stimuli. The analysis of the Pe revealed significantly reduced amplitudes in the ADHD group for neutral stimuli at the electrodes FCz, Cz and Pz (for FCz F=54.81, $p<0.0001$, for Cz=109.29, $p<0.0001$, for Pz F=86.26, $p<0.0001$). Group difference for Pe was not observable for the positive and the negative stimuli.

Covariates of altered error-related activity in the ADHD group

For the ERP group differences which reached the level of statistical significance we performed a follow-up analysis based on CAARS symptom dimensions. After adjustments for multiple comparisons, we found associations between ERN amplitude and Impulsivity factor at the FCz electrode and between CAARS Hyperactivity factor at the Cz electrode. Investigation of the direction of the relationship indicated larger ERN amplitude among those ADHD subjects who had higher severity on Impulsivity as compared to patients who had lower severity on it. Lower Hyperactivity was associated with larger ERN amplitude as compared with higher Hyperactivity. We found no association with CAARS dimensions in terms of Pe amplitude. The relationships between error-related activity and CAARS symptom dimensions are shown in *Table 3*.

CONCLUSIONS (1-3. STUDY)

Errors of response inhibition characterising ADHD and the electrophysiological as well as neuropsychological examination of the subsequent error processing constitute the focus of my thesis.

In our first and second studies we investigated the post-error slowing phenomenon through analysing data available in the literature for both child and adult ADHD patients as well as using our own empirical data obtained from adult ADHD patients.

Our meta-analysis concluded that the post-error slowing phenomenon could potentially serve as a behavioural index for ADHD? with its effect size falling in the moderate range. Another observation pertaining to practice is that, in contrast to healthy controls, in ADHD patients the extent of slowing is irrespective of the length of the ISI applied; as a result, the sensitivity of the index can be further improved by the use of longer inter-stimulus intervals. There were no differences between the ADHD and control subjects with respect to gender, age, complexity of the task and consistency of the ISI. In our second study, while the post-error slowing was smaller in the adult ADHD patients than in the control subjects, the difference did not obtain statistical significance.

The objective of our third study was the investigation of whether the electrophysiological correlates of error processing, such as the ERN and Pe, are associated with the diagnosis of ADHD. Both neutral and emotionally-valenced stimuli were applied in our paradigm. In the case of neutral stimuli, a significant decrease in the Pe amplitude was observed in the ADHD group, while stimuli with negative emotional content were associated with reduced ERN amplitudes in patients with ADHD.

Our findings reveal that post-error processing in adult patients with ADHD differs from that of control subjects in terms of both early and late error processing as well as with respect to adaptive functions. With its methodological characteristics optimised, behavioral and electrophysiological indices obtained from the continuous performance test might serve as a useful addition to clinical diagnostics in the long-run.

LIST OF PUBLICATIONS

Publications related to the dissertation

Balogh L, Czobor P. (2014) Post-Error Slowing in Patients With ADHD: A Meta-Analysis. J Atten Disord, 20(12):1004-1016.

Czobor P, Kakuszi B, Németh K, Balogh L, Papp S, Tombor L, Bitter I. (2016) Electrophysiological indices of aberrant error-processing in adults with ADHD: a new region of interest. Brain Imaging Behav. Doi:10.1007/s11682-016-9610-x.

Balogh L,Czobor P. (2010) Hibázához kötött eseményfüggő EEG potenciálok a pszichiátriai betegségekben: irodalmi áttekintés. Psychiatria Hungarica, 25(2): 121-132.

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Balogh L, Kakuszi B, Papp S, Tombor L, Bitter I, Czobor P. (2017) Neural correlates of error monitoring in adult attention deficit/hyperactivity disorder (ADHD) after failed inhibition in an emotional go/no-go task. Journal of Neuropsychiatry and Clinical Neurosciences. Doi: 10.1176/appi.neuropsych.16100183.

Publications unrelated to the dissertation

Papp S, Tombor L, Komlósi S, Balogh L, Simon V, Czobor P (2010): Gamma oszcilláció szinkronizáció szkizofréniában: irodalmi összefoglaló. Psychiatria Hungarica 25(3): 190-201.

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