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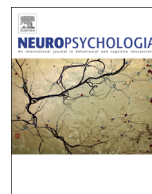
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EEG correlates of visual short-term memory as neuro-cognitive endophenotypes of ADHD

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) frequently persists into adulthood. A reduction in visual short-term memory (vSTM) storage capacity was recently suggested as a potential neuro-cognitive endophenotype, i.e., a testable marker of an individual's liability for developing ADHD. This study aimed at identifying markers of the brain abnormalities underlying vSTM reductions in adult ADHD. We combined behavioral parameter-based assessment with electrophysiology in groups of adult ADHD patients and healthy age-matched controls. Amplitudes of ERP markers of vSTM storage capacity, the contralateral delay activity (CDA) and the P3b, were analyzed according to (i) differences between individuals with higher vs. lower storage capacity K and (ii) differences between ADHD patients and control participants. We replicated the finding of reduced storage capacity in adult ADHD. Across groups, individuals with higher relative to lower storage capacity showed a larger CDA and P3b. We further found differences between the patient and control groups in the ERPs: The CDA amplitude was attenuated in an early time window for ADHD patients compared to control participants, and was negatively correlated with ADHD patients' symptom severity ratings. Furthermore, the P3b was larger in ADHD patients relative to control participants. These electrophysiological findings indicate altered brain mechanisms underlying visual storage capacity in ADHD, which are characterized by deficient encoding and maintenance, and increased recruitment of control processes. Accordingly, (quantifiable) ERP markers of vSTM in adult ADHD bear candidacy as neuro-cognitive endophenotypes of the disease.

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1. Introduction

Attention deficit hyperactivity disorder (ADHD) persists into adulthood in more than sixty percent of cases (Biederman, 2005; Kessler et al., 2006). Neuroscientific models propose that genetic abnormalities, e.g., in dopaminergic receptor genes and the Catechol-O-methyltransferase (COMT) gene (Biehl et al., 2015; Boonstra et al., 2008; Tomlinson et al., 2015), lead to aberrant neuromodulation (Störmer et al., 2012) and other neurobiological alterations in fronto-striatal, fronto-parietal, and sensory circuits in children and adults with ADHD. The neural abnormalities are

assumed to affect basal cognitive abilities, manifesting in patients' experienced problems in complex tasks, in deficits in neuropsychological tests, and in symptoms of inattention, hyperactivity, and impulsivity as secondary consequences (Alderson et al., 2013; Castellanos et al., 2006; Cubillo et al., 2012; Faraone et al., 2000; Spencer et al., 2007). A central research aim is to identify latent (unobserved), quantifiable neuro-cognitive measures that index the liability for ADHD (Castellanos and Tannock, 2002), i.e., endophenotypes for the disease (Seidman, 2006; Woods et al., 2002). These might correspond more closely with phenotypic disease-specific deficits and genetics compared to overt symptom ratings, and thus could be useful, e.g., for psychiatric genetics (Robbins et al., 2012). The degree of such a trait's manifestation, and its change across the lifespan, is assumed to be influenced by a patient's compensatory abilities (Halperin and Schulz, 2006).

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Attention and working memory, in particular, are central functions thought to be compromised in ADHD (Chamberlain et al., 2011; Engelhardt et al., 2008; Manly et al., 2001; Westerberg et al., 2004). They can be precisely quantified based on the computational “Theory of Visual Attention” (TVA, Bundesen, 1990). Several distinct, mathematically independent parameters can be estimated from modeling an individual's performance in simple psychophysical tasks; e.g., the parameter visual short-term memory (vSTM) storage capacity K refers to the maximum number of items that can be maintained in vSTM (Cowan, 2001; Luck and Vogel, 1997), and the parameter processing speed C reflects the rate of perceptual information encoding (Duncan et al., 1999; Finke et al., 2005). The method's sensitivity to neurological and neuropsychiatric conditions was documented in several studies (see Habekost, 2015). In particular, for adult ADHD patients, a selective reduction in the TVA parameter vSTM storage capacity K was revealed (Finke et al., 2011), which represents a latent, continuously measurable cognitive change associated with the disease. This is particularly promising since several studies failed to detect persisting working memory deficits adult ADHD. Meta-analytic reviews suggested that inconsistencies result from methodological variability among studies, and that future studies should focus on particular tests and testing conditions in order to achieve a higher level of specificity (Alderson et al., 2013; Hervey et al., 2004; Holst and Thorell, 2013).

According to Castellanos and Tannock (2002), endophenotypes for ADHD should be neuro-scientifically grounded. Thus, to further investigate the usability of reductions in vSTM storage capacity K as a candidate endophenotype of adult ADHD, we examined whether these are related to specific brain activity abnormalities – by comparing behavioral measures in combination with event-related potentials (ERPs) in adult ADHD patients and matched healthy controls (e.g., Cross-Villasana et al., 2015). While ERPs have been recently suggested to reflect a promising tool for detecting intermediate endophenotypes of ADHD (Tye et al., 2011), arguably, more research is needed to demonstrate the clinical relevance of the observable disease-related ERP modulations (Lenartowicz and Loo, 2014). While a number of studies investigated ERPs in children with ADHD (Barry et al., 2003; Johnstone et al., 2013), studies on adults with ADHD are still sparse (Szuromi et al., 2013). The majority of previous ERP studies on ADHD patients focused on abnormalities in the P3, a component complex with a broad central topography that is observed in a wide range of cognitive tasks (Donchin and Coles, 1988; Polich, 2007). Specifically in vSTM paradigms, the amplitude of the more posteriorly distributed sub-component P3b has been linked to encoding-related allocation of attentional resources (Kok, 2001; Busch and Herrmann, 2003).

In this study, we used a recently developed approach designed to link different TVA parameters to distinct ERPs (Wiegand et al., 2014a, 2014b). Importantly, vSTM storage capacity K was previously shown to be associated with two ERP components. First, individuals with higher, as compared to lower, storage capacity exhibited a larger Contralateral Delay Activity (CDA). The CDA is quantified as the difference in activity contra- versus ipsilateral to a lateralized, to-be-memorized stimulus array, and is assumed to index the number of objects maintained in vSTM (Klaver et al., 1999; Vogel and Machizawa, 2004). Second, within a participant group characterized by vSTM storage capacity reductions (elderly individuals), those exhibiting relatively preserved levels of storage capacity displayed an increased right-distributed central positivity (RCP) in the P3 time range. This positivity was proposed to reflect compensatory recruitment of attentional control to facilitate efficient encoding and storage of visual information (Wiegand et al., 2014b).

To identify neurophysiological correlates of the reduced vSTM storage capacity in adult ADHD, we measured TVA parameters in a

lateralized letter whole-report task and recorded EEG in groups of adult ADHD patients and controls. Examination for group differences focused on EEG components selectively associated with vSTM storage capacity: the CDA and the P3b. Moreover, we examined whether differences in EEG activity displayed by ADHD patients as compared to controls in these two components would further predict higher self-reported symptom severity.

2. Material and methods

2.1. Participants

Sixteen adult ADHD patients and sixteen control participants were included in the study. Groups were demographically matched (Table 1). Two further control participants and three further patients were tested but excluded from the study due to poor EEG data quality (in particular, excessive eye-movements and/or artifacts in more than 40% of the trials).

The patients were recruited and diagnosed at the outpatient clinic of the Department of Psychiatry of the LMU Munich. Two psychiatric interviews (according to DSM-IV, APA, 2000) were conducted by experienced clinicians, one psychiatrist and one experienced neuropsychologist, working in the ADHD outpatient clinic or in clinical practice. Of the 16 patients included in the study, eight were classified as of the inattentive sub-type, and eight as of the combined sub-type. Patients were only included when both examiners agreed and rated them as ADHD patients. A psychologist trained in ADHD assessment collected collateral information from different sources. Childhood onset according to the obligatory DSM-IV symptoms for childhood ADHD had to be confirmed by prior diagnoses during childhood and adolescence or elementary school reports (which, in Germany, contain comprehensive descriptions of learning performance, social behavior, and daily structure, differentiated according to cognition, emotion, and motor behavior). Patients were only included if descriptions of the respective symptoms were reported at an age < 7 years, and persisted according to the above-mentioned developmental reports. Furthermore, prior psychiatric diagnoses, or third-party “informants” (siblings, parents, and/or spouses), had to confirm that these symptoms were also displayed at home and that there had been no alternative, suspected exclusion diagnosis (testified by SCID-I/II interview, First and Gibbon, 2004).

The control participants were recruited through advertisement in local stores (flyers) and the participant database of the General and Experimental Psychology Unit, LMU Munich. The German version of the Beck Depression Inventory (BDI-II, Beck et al., 1996) was administered to rule out depressive symptoms in control participants. Given that depression is highly correlated with ADHD (Kessler et al., 2006), five patients with mild and two with moderate (but not with severe) depression levels were included in the study. Accordingly, the control participants' BDI scores were significantly lower than those of the patients (ADHD: Mean (SD) = 9.4 (6.1); Controls: Mean (SD) = 2.3 (2.8); $t = 4.20$; $p < .001$; $\eta^2 = .38$). Three ADHD patients were further diagnosed as suffering from dyslexia.¹ Two patients were treated with selective serotonin re-uptake inhibitors and were not required to interrupt medication. Five patients were taking methylphenidate, but were off medication for at least 24 h prior to participating in the experiment.

All participants gave informed consent according to the Declaration of Helsinki II and received payment of 8€/h for participating. The study was approved by the ethics committee of the medical faculty of LMU Munich participants' IQ was screened using a German word recognition test (Mehrfachwahl-Wortschatz Intelligenz Test; Lehrl, 2005), which is functionally equivalent to the widely used NART test (Nelson and O'Connell, 1978); values corrected according to Satzger et al. (2002).

2.2. ADHD symptoms

Current ADHD symptoms were assessed using the long version of Conners' Adult ADHD Rating Scales (CAARS, Conners et al., 2002) and retrospective childhood symptoms using the Wender Utah Rating-Scale (WURS, Ward et al., 1993). As expected, ADHD-related symptom ratings were significantly higher for the ADHD compared to the healthy control group, on both measures. Average ratings were above the cut-offs (CAARS: T -values of all subscales = 60; WURS: Score = 46) for the adult ADHD group and below the cut-offs for the control group, corroborating that clinically relevant symptoms were present only in the patient group (Table 2).

¹ We repeated all analyses without the three patients who had a diagnosis of dyslexia, so as to rule out that a potentially found relationship between (the diagnosis of) adult ADHD and the ERP correlates of TVA parameter storage capacity would be attributable to this comorbidity.

Table 1
Group demographics.

	ADHD (n = 16)	Controls (n = 16)	
Age (years)	30.0 (9.8) 17–48	30.4 (9.8) 19–48	$t=0.1; p=.90;$ $\eta^2<.001$
IQ (MWT-B)	98.1 (12.9) 80–125	102.7 (10.4) 87–125	$t=1.2; p=.28;$ $\eta^2=.04$
Sex (F/M)	9/7	10/6	$\chi^2=0.1; p=.72$
School (years)	12.6 (0.9) 9–16	12.3 (1.9) 10–14	$t=0.3; p=.58;$ $\eta^2<.001$
Occupational status (S/J/U)	9/7/0	6/9/1	$\chi^2=1.85; p=.40$

Mean (and associated SD) and range of age, IQ, sex (F: female, M: male), attended school years, and current occupational status (S: high-school scholar or university student, J: in job or job training, U: unemployed) for the ADHD and control groups, along with statistics for group differences (based on independent t -tests and, respectively, χ^2 -tests).

Table 2
Symptom ratings.

	ADHD (n = 16)	Controls (n = 16)	
Current symptoms CAARS-H	72.7 (8.2) 58–90	47.1 (6.2) 35–56	$t=9.7; p<.001;$ $\eta^2=.76$
Retrospective symptoms WURS	50.8 (15.7) 25–74	12.0 (7.4) 2–28	$t=8.9; p<.001;$ $\eta^2=.72$

Mean (and associated SD) and range of ADHD rating scales for the ADHD and control groups, along with statistics for group differences (independent t -tests). CAARS: Conners' Adult ADHD Rating Scales, with T -values of subscale H (ADHD index); WURS: Wender Utah Rating Scale.

2.3. Stimuli, task, and study design

Participants completed two testing sessions, first the standard TVA whole-report, and between 5 and 10 days later the EEG report task (Fig. 1). Daytime, location, equipment, viewing distance, stimuli (type, size, position, luminance), and screen background were the same for both sessions. The PC-controlled tests were conducted in a dimly lit room, with stimuli presented on a 17-inch monitor (1024 × 768-pixel screen resolution; 85-Hz refresh rate) at a viewing distance of ≈ 65 cm. Participants were instructed to maintain central eye fixation throughout the experimental blocks. Their task was to report the identities of letters from a

briefly presented array, which they had recognized 'fairly certainly'. There was no stress on response speed. The experimenter, who was trained in the assessment procedure, entered the response(s) on the keyboard and started the next trial. Four letters were chosen from a set of letters (ACEHJOPRSTWX). They were presented at a size of 1.1° of visual angle at lateral positions on an imaginary circle (radius: 2.5°) around a central white fixation cross on a black background. Letters were iso-luminant, and the same letter appeared only once in each trial display.

2.3.1. Standard whole-report procedure

Individual exposure durations for optimal modeling of parameters were identified in a pre-test consisting of 24 masked-array trials. The presentation time at which report accuracy was about 20–25% was chosen as intermediate exposure duration for the experiment, together with a shorter (half as long) and a longer (twice as long) exposure duration. In the standard TVA whole-report experiment, the fixation cross was presented for 300 ms. Following a blank screen of 100 ms, the letter array was presented. Letters were presented either on the left or the right side of central fixation, randomly chosen to be either red or green. In half of the trials, the array was followed by a mask presented for 500 ms at each stimulus location, which consisted of a square filled with an "×" and a "+" (1.2° visual angle). Owing to visual persistence, exposure durations are effectively prolonged in unmasked- compared to masked-array conditions (Sperling, 1960). Together with the 3 varying exposure durations, this resulted in 6 different *effective* exposure durations. Exposure duration (short, medium, long), masking (masked, non-masked), and hemifield (left, right) varied randomly, resulting in 12 conditions presented in 6 blocks of 40 trials each. The first block served as practice block, and data were modeled based on the 200 remaining trials.

2.3.2. Report procedure in the EEG experiment

In the EEG experiment, an adapted paradigm suitable for analyzing ERPs was used. Based on Vogel and Machizawa (2004) classical lateralized vSTM paradigm used in EEG experiments, letters were presented bilaterally (4 in each hemifield) to ensure balanced physical stimulation across hemifields, with the to-be-attended hemifield being indicated by a 100%-valid central pre-cue (spatial arrow; 0.9° of visual angle). Target and filler letters were presented in randomly changing colors, that is, either green target letters in one hemifield and red filler letters in the other, or vice versa. Each trial started with a central fixation cross presented for 100 ms, followed by the cue shown for 200 ms. Then the letter array was presented for 200 ms. After a delay of 900 ms with a blank screen, a question mark appeared to prompt the verbal report (Fig. 1). Following a practice block of 16 trials, the EEG recording was started and a total of 240 trials, divided in 2 blocks with a self-paced break in between, were run.

2.4. Parameter estimation

Individual parameter estimates were derived from performance in the standard whole-report procedure (Duncan et al., 1999; Dyrholm et al., 2011; Kyllingsbæk, 2006). The variation of exposure duration generated a broad range of performance, specifying the whole probability distribution of the number of correctly reported elements as a function of the effective exposure duration. The modeling involved maximum likelihood estimation of 4 parameters defining the function: (1) parameter t_0 , the minimal effective exposure duration; (2) parameter μ , the persistence of the iconic memory trace; (3) parameter C , the visual processing speed (elements

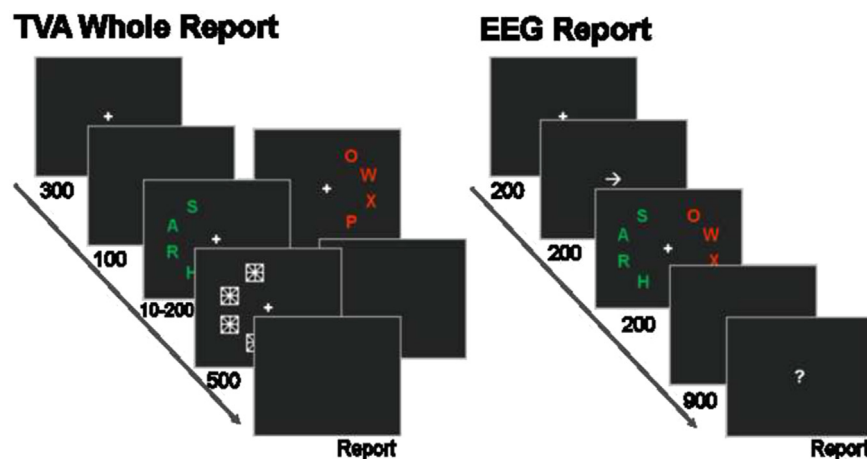


Fig. 1. Procedure. In the procedure used for TVA parameter assessment (A), four equidistant letters arranged in a half circle were presented in either green or red (randomly changing across trials), and on either the left or the right side of the display, with three different, individually adapted exposure durations. In half of the trials, the letter arrays were subsequently masked. In the procedure used for the EEG acquisition (B), letters were presented for a fixed duration of 200 ms on both the left and the right of the fixation cross, with the letters in one hemifield (randomly changing across trials) being green and those in the other being red. The to-be-attended side was indicated at the start of a trial by an arrow pre-cue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

processed per second); and (4) parameter K , the vSTM storage capacity (maximum number of elements in vSTM). C reflects the slope of the exponential function at its origin t_0 . Thus, the C estimate is mainly based on conditions with shorter exposure durations (closely above threshold t_0). K reflects the asymptote of the exponential function. The K estimate is mainly based on conditions with the longest exposure durations, in which encoding time is sufficient to load the vSTM store to its limit.

2.5. EEG data acquisition

The EEG was recorded from 64 active Ag/AgCl electrodes (acti-Cap System, Brain Products, Munich), placed according to the International 10/10 system (American Psychological Association, 2000). EEG and electrooculogram were amplified by BrainAmp DC amplifiers (BrainProducts, Munich). The data were sampled at 1 kHz and filtered offline with a 0.05-Hz high-pass filter (Butterworth zero phase, 24 dB/Oct). An Infomax Independent Component Analysis (Bell and Sejnowski, 1995), as implemented in the Brain Vision Analyzer software (BrainProducts, Munich), was run to identify components of the EEG that represent ocular artifacts (blinks and/or horizontal eye movements; Jung et al., 2000) and to remove those before backprojection of the residual components. All electrodes were referenced to FCz and re-referenced off-line to averaged mastoids, similar to the prior studies (Wiegand et al., 2014a, 2014b) and other previous studies investigating ERP correlates of vSTM (e.g., McCollough et al., 2007; Töllner et al., 2014, 2015). Horizontal eye movements were recorded by electrodes F9 and F10, and vertical eye movements from Fp1 and an electrode placed beneath the left eye. Before the EEG was segmented into epochs for ERP analyses, the signal was filtered with a 40-Hz low-pass filter (Butterworth zero phase, 24 dB/Oct). Trials with artifacts, defined as any signal exceeding $\pm 60 \mu\text{V}$, bursts of electromyographic activity (voltage step allowed per sampling point $< 50 \mu\text{V}$), and activity $< 0.5 \mu\text{V}$ within intervals of 500 ms, were rejected on an individual-channel basis before averaging. To exclude any trials with potentially remaining horizontal eye shifts, a threshold of $\pm 50 \mu\text{V}$ was applied at electrodes F9/F10. The average number of removed trials was 33.5 for patients and 21.6 for controls; the difference was not significant [$t(30)=1.0$; $p=.33$]. Note, though, that residual eye-movement activity in the F9/F10 difference waves was present [$t(31)=4.41$; $p<.001$], which may have affected the lateralized CDA. Critically, however, mean HEOG activity in the CDA time window did not differ between the adult ADHD patient and control group and can, thus, not account for potential group differences in the CDA. EEG epochs of 1400 ms (from 400 ms before letter array onset to 1000 ms after) were averaged separately for attend-left and attend-right conditions. Baseline correction was based on the -400 to -200 -ms pre-display (i.e., -200 to 0-ms pre-cue) period.² CDA analyses were conducted on mean amplitudes at lateral parieto-occipital electrode sites (P7, P8, PO7, PO8, O1, O2) within the time window 340–640 ms following array onset. Lateralized activity was quantified by subtracting ERPs at electrodes ipsilateral from ERPs at electrodes contralateral to the attended hemifield. The choice of electrodes and time intervals for the P3b were based on visual inspection of the grand-average waveforms, that is, the maximum deflection of group differences in ERPs, which was most prominent at central and centro-parietal electrode sites (CP3, CPz, CP4, P3, Pz, P4) in the time window 300–600 ms following stimulus onset.

2.6. Statistical analyses

Statistical analyses were performed using SPSS Statistics version 22 (IBM, Armonk, NY, USA). Differences in TVA parameter estimates between patients and control participants were examined by independent t -tests (2-tailed). As a measure of Goodness-of-fit, we report the squared correlation between mean observed scores and predicted scores in whole-report conditions (six different exposure durations). We further correlated individuals' parameter value of K and the mean number of letters they reported accurately in the EEG task, in order to ensure that the participants' model fits derived from their standard TVA task performance correspond to their observed raw-data performance measures during the EEG measurement. Finally, we tested for group differences in the raw-data measures (i.e., the average number of letters reported correctly) in the EEG task by an independent t -test (2-tailed).

The CDA and P3b were analyzed according to group differences between ADHD patients and healthy controls, and between varying vSTM storage levels. In each (patient and control) group, individuals were assigned to groups of high K and low K , based on median splits of the individual K -values. We further accounted for group differences in component timing. The CDA was examined in an early time window in which contralateral activity rises (320–370 ms) and the following delay period (370–700 ms) by two ($3 \times 2 \times 2$) mixed-design ANOVAs with the within-subject factor Electrode Site (P/PO/O) and the between-subject factors Group (patients/controls) and K level (high K /low K). The P3b (300–600 ms) was examined by a ($3 \times 2 \times 2 \times 2$) mixed-design ANOVA with the within-subject factors Electrode Position (left/midline/right) and Electrode Site (P/CP), and the between-subject

factors Group (patients/controls) and K level (high K /low K). Significant main effects and interactions were followed up by ANOVAs or t -tests. To examine the clinical relevance of EEG measures in the patient group, we computed Pearson correlations between ERP measures found to differ significantly between ADHD patients versus control participants and subjective severity ratings of both current (CAARS sub-scale-H, ADHD Index) and retrospective childhood ADHD-related symptoms (WURS). Statistical significance of the correlations was tested one-tailed because we hypothesized that a stronger deviation of activity in the ADHD from the control group would be associated with higher symptom ratings.

3. Results

3.1. Parameter estimation

For each participant, the accuracy of letter report in the standard whole report procedure as a function of effective exposure duration was modeled by a TVA-based function. There was a close correspondence between the empirically obtained mean scores and the model-estimated scores (mean Goodness-of-fit: controls: $R^2=.98$; patients: $R^2=.97$). The group comparisons revealed vSTM storage capacity K to be significantly lower for the patient as compared to the control group, but no significant group differences in visual processing speed C and the visual perceptual threshold t_0 (Table 3).

3.2. Average letter report accuracy

The significant difference in parameter vSTM storage capacity K between adult ADHD patients and healthy controls was also robustly reflected in the raw-data scores: The individual K parameter estimates that were derived from the standard TVA measure showed a significant and high correlation with the individual average number of accurately reported letters during the EEG measurement ($r=.79$, $p<.001$). Furthermore, in the EEG task, ADHD patients reported significantly fewer letters correctly than control participants on average and these average values quite closely resembled that of the K estimates derived by TVA-based model fitting [Mean (SD): 3.0 (0.6) vs. 3.4 (0.5); $t(30)=2.3$, $p=.03$].

In Fig. 2, average accuracy scores in the standard TVA-based whole report procedure and in the EEG task are depicted. It can be seen that, in the standard whole report task with varying exposure durations, the number of correctly report letters increases with increasing exposure durations in ADHD patients and controls. A comparable accuracy of both groups at lower duration indicates similar visual processing speed C . A significant difference is found at higher exposure durations and reflects the lower vSTM storage capacity K in patients compared to controls. Similarly, the significant group difference is found in the EEG task with relatively long, constant exposure durations.

Table 3
Parameter estimates.

Parameter	ADHD (n = 16)	Controls (n = 16)
C	35.1 (31.6) 11.8 – 137.7	49.3 (22.2) 27.0 – 106.5
K	3.1 (0.5) 1.8 – 3.8	3.5 (0.4) 3.0 – 3.9
t_0	13.6 (17.9) – 22.2 – 45.9	7.3 (9.9) – 14.0 – 22.0

Mean (and associated SD) and range of TVA parameters Processing Speed C , Storage Capacity K , and visual perceptual threshold t_0 for the ADHD and control groups, along with statistics for of group differences (t -tests; * $p < .05$).

^a The group difference in K was also significant after excluding 3 patients diagnosed with dyslexia [$F(1,27)=4.53$; $p=.043$].

² Note that the present study was not designed to test cue-related effects; however, carry-over effects of cue-related to stimulus-related effects cannot be ruled out.

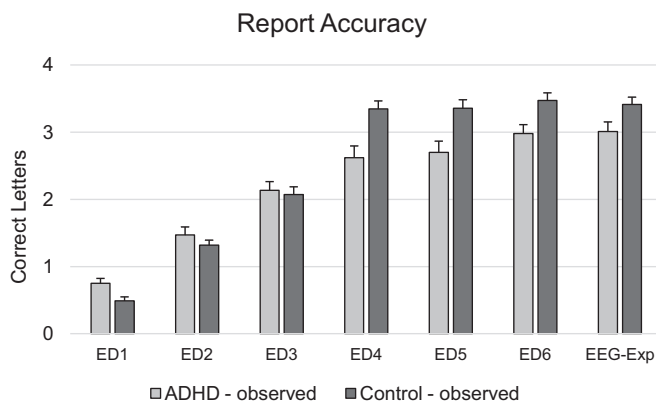


Fig. 2. Observed report accuracy. Number of correctly reported letters in the different exposure duration conditions (ED1–ED6) of the standard whole report procedure and in the EEG task in ADHD patients and controls.

3.3. Event-related potentials

The CDA and P3b waves were analyzed according to differences between ADHD patients and healthy controls and, respectively, between individuals with higher and lower levels of storage capacity K . Across groups, we found both a larger late CDA and a larger P3b for individuals with higher, as compared to lower, storage capacity. Furthermore, we found differences between the patient and control groups in the two components: In an early time window of the CDA, amplitudes were lower in the ADHD patients; with respect to the P3b, the amplitudes were increased for ADHD patients relative to controls.

3.3.1. Contralateral delay activity

Early CDA (320–370 ms): The ANOVA on CDA mean amplitudes in the early time window revealed significant main effects of Group [$F(1,28)=5.17$; $p=.03$; $\eta^2=.16$] and K level [$F(1,28)=8.08$; $p=.008$; $\eta^2=.81$].³ Amplitudes were more negative in the control compared to the patient group, and more negative in participants with higher compared to lower vSTM storage capacity (see Fig. 3A and B). A further main effect of Electrode Site [$F(1,28)=8.67$; $p<.001$; $\eta^2=.24$] resulted from the early CDA being more pronounced at parieto-occipital electrodes than at parietal and occipital electrodes [both $t(28)>3.5$; $p<.01$; $\eta^2>.29$]. The early CDA was significantly correlated with ADHD patients' subjective ratings of retrospective ADHD childhood symptoms ($r=.45$; $p=.039$) and current symptoms ($r=.44$; $p=.043$).

Late CDA (370–700 ms): The ANOVA on the sustained CDA also revealed a significant main effect of K level [$F(1,28)=9.75$; $p=.004$; $\eta^2=.26$],^{4,5} due to increased amplitudes in participants with higher compared to lower storage capacity. However, no significant main effect of Group was found [$F(1,28)=1.57$; $p=.22$; $\eta^2=.05$] (see Fig. 3A). Again, a significant main effect of Electrode Site [$F(1,28)=12.33$; $p<.001$; $\eta^2=.31$] reflected a more pronounced CDA at parieto-occipital electrodes, compared to parietal and occipital electrodes [both $t(28)>3.3$; $p<.01$]. Furthermore,

³ Even after excluding 3 patients diagnosed with dyslexia, the critical effects of K level on the early CDA (320–370) [$F(1,27)=6.55$; $p=.017$; $\eta^2=.21$] and Group [$F(1,27)=4.36$; $p=.047$; $\eta^2=.15$] were significant. The correlation between the early CDA and symptom ratings was of similar size [CAARS: $r=.44$, WURS: $r=.45$], and, owing to the smaller N of 13, was only marginally significant [$p=.06$, $p=.07$].

⁴ The effect of K level on the CDA (370–700) [$F(1,27)=9.48$; $p=.005$; $\eta^2=.28$] was significant even after excluding the three patients with dyslexia.

⁵ The same group differences on CDA amplitudes as for the factor K level were found when participants were split into groups of high/low performance based on their average report accuracy in the EEG task and performance level was used as between-subject factor [$F(1,28)=13.39$; $p<.001$; $\eta^2=.32$].

there was an interaction of Group, K level, and Electrode [$F(2,56)=3.36$; $p=.042$; $\eta^2=.11$]. Post-hoc ANOVAs for each group showed that the main effect of K level was significant for the control group [$F(1,14)=10.75$; $p=.005$; $\eta^2=.43$], but not for the patient group [$F(1,14)=1.23$; $p=.27$; $\eta^2=.08$] (see Fig. 3B). The main effect of Electrode was obtained in both, control participants [$F(1,14)=6.59$; $p=.005$; $\eta^2=.32$] and ADHD patients [$F(1,14)=5.82$; $p=.008$; $\eta^2=.29$].

3.3.2. P3b

The ANOVA on P3b amplitudes revealed a main effect of K level [$F(1,28)=5.71$; $p=.024$; $\eta^2=.17$],⁶ due to increased amplitudes in participants with higher compared to lower storage capacity. In addition, there was a main effect of Group [$F(1,28)=14.59$; $p=.001$; $\eta^2=.34$], resulting from a stronger P3b in the patient compared to the control group⁷ (see Fig. 4A and B). There were further significant main effects of Electrode Site [$F(1,28)=16.48$; $p<.001$; $\eta^2=.37$] and an interaction of Electrode Site with Electrode Position [$F(2,56)=17.98$, $p<.001$; $\eta^2=.39$], which indicated that the positivity was stronger at central than at lateral electrodes, and that this pattern was more pronounced at parietal electrodes [all $t(28)>3.7$; $p<.001$]. In addition, we found an interaction among K level, Group, and Electrode Position [$F(2,56)=3.26$; $p=.046$; $\eta^2=.10$]. Post-hoc analyses revealed an interaction between Electrode Position and K level for patients [$F(1,14)=4.72$; $p=.047$; $\eta^2=.25$], but not for controls [$F(1,14)=.55$; $p=.58$]. This interaction reflects the fact that, within the patient group, those with higher vSTM storage capacity showed a stronger P3b at parietal than at centro-parietal electrodes [$t(7)=2.57$; $p=.037$]; by contrast, the component was equally pronounced at centro-parietal and parietal electrodes in patients with lower vSTM storage capacity [$t(7)=0.72$; $p=.49$] as well as in controls with both higher and lower vSTM storage capacity levels [both $t(7)<.04$; $p>.75$]. The P3b was not significantly correlated with patients' ratings of current or childhood symptoms [both $r<.20$; $p>.20$].

4. Discussion

The present study aimed at identifying neurophysiological correlates of a potential neuro-cognitive endophenotype of adult ADHD, namely: reduced visual short-term storage capacity K , measured as a quantifiable parameter based on the computational TVA framework (Bundesen, 1990). A prior study had demonstrated that parameter K is affected in adult ADHD (Finke et al., 2011) – in line with working memory deficit models of ADHD (Alderson et al., 2013; Castellanos and Tannock, 2002; Westerberg et al., 2004; Engelhardt et al., 2008). We replicated the finding of reduced vSTM storage capacity in adult ADHD patients in the present study, thus lending support to the proposal of Finke et al. (2011) that parameter K has potential as an endophenotype of the disorder. In addition, we found two neural measures specifically associated with this vSTM storage capacity reduction in adult ADHD patients, one of which was significantly correlated with ADHD symptom severity ratings. We thus identified neurophysiological markers of the vSTM deficit, providing relevant neuroscientific support for vSTM storage capacity as a candidate neuro-cognitive endophenotype of adult ADHD.

⁶ The same group differences on P3b amplitudes as for the factor K level were found when participants were split into groups of high/low performance based on their average report accuracy in the EEG task and performance level was used as between-subject factor [$F(1,28)=4.05$; $p=.03$; $\eta^2=.13$].

⁷ Even after excluding the three patients diagnosed with dyslexia, the critical effects of K level [$F(1,27)=4.73$; $p=.039$; $\eta^2=.16$] and Group [$F(1,27)=14.13$; $p=.001$; $\eta^2=.36$] were significant.

CONTRALATERAL DELAY ACTIVITY

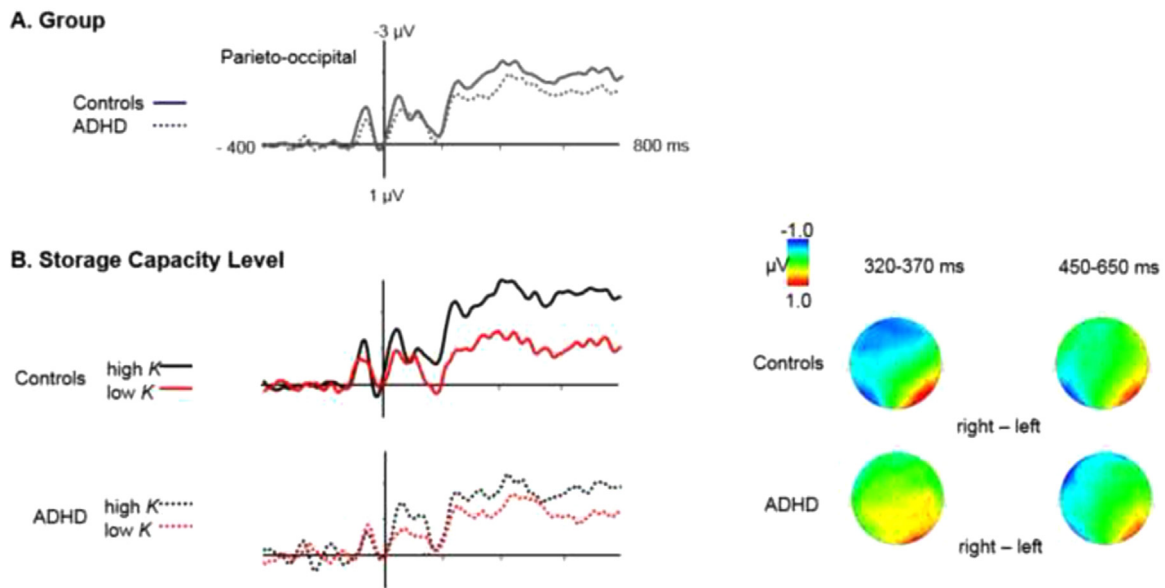


Fig. 3. Contralateral delay activity, CDA amplitudes (left panel), and difference maps (right panel) in an early and late time window of the component. A: Group comparisons of adult ADHD patients and control participants. B: Comparisons of participants with higher and lower storage capacity levels in the control group (upper panel) and in the patient group (lower panel). The CDA was computed by subtracting ipsi- from contralateral activity to target letters in the display, averaged over electrodes P7/P8, PO7/PO8, O1/O2. Difference maps show activity in trials with target letters presented on the left display side subtracted from activity in trials with target letters presented on the right display side.

P3

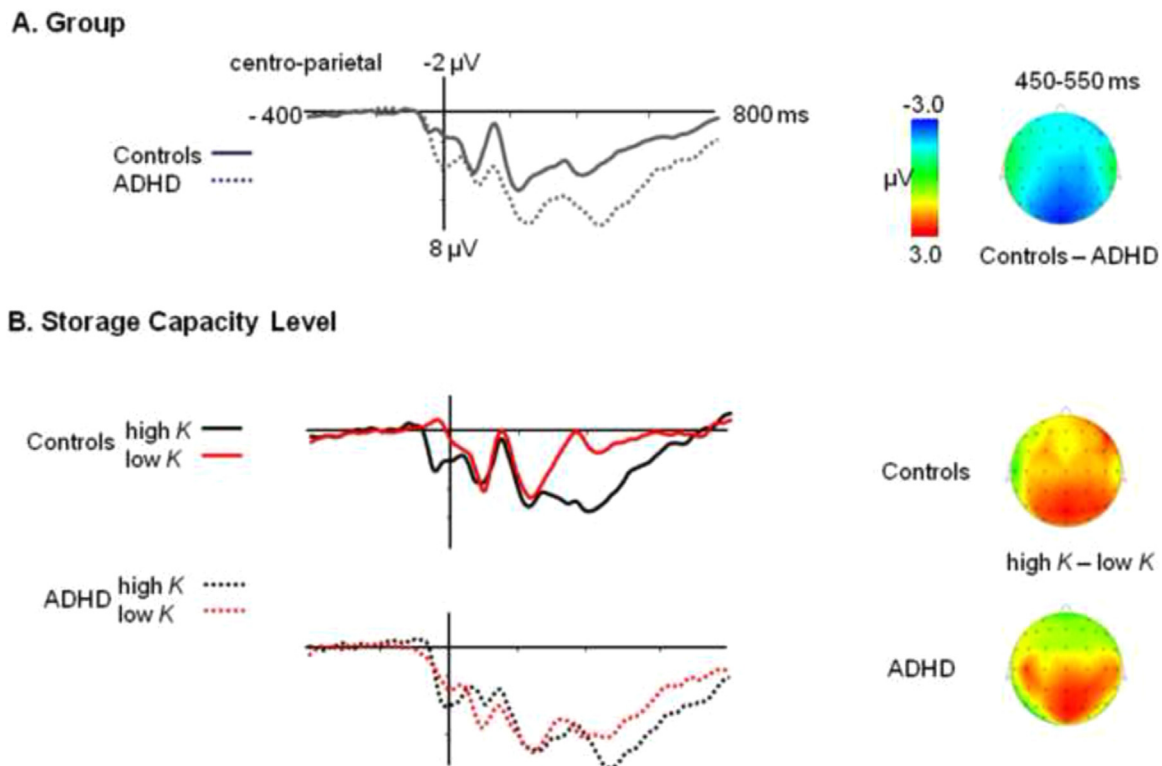


Fig. 4. P3. CP amplitudes (left panel), pooled over electrodes CP3, CPz, CP4, P3, Pz, P4, and difference maps (right panel) of the component for the patient and control groups. A: Group comparisons of adult ADHD patients and control participants. B: Comparisons of participants with higher and lower vSTM storage capacity levels in the control group (upper panel) and in the patient group (lower panel). Difference waves show control-minus-patient activity (upper panel) and high-minus-low K activity for each of the groups (lower panel).

4.1. Reduced visual short-term storage in ADHD

Our analyses of ERP modulations shed light on the neural underpinnings of the visual storage capacity reduction in adult ADHD. First, the CDA, a reliable index of visual working memory maintenance (Vogel and Machizawa, 2004), was significantly reduced for patients as compared to controls in an early time window. The CDA is assumed to result from sustained activation between frontal, parietal, and visual cortical areas (Becke et al., 2015; Reinhart et al., 2012), which is in agreement with the neural circuits underlying storage capacity as described in the NTVA (Bundesen et al., 2005, 2011). Critically, the component's rise was delayed in the adult ADHD patients – indicative of the implementation of the sustained activation for vSTM storage and maintenance being slowed in adult ADHD. Furthermore, the early CDA amplitude was inversely correlated with patients' ratings of current and childhood ADHD symptom severity, demonstrating a specific relation of the electrocortical measure to the psychiatric disorder.

As expected, the late CDA was related to individuals' vSTM storage capacity limit, being larger in individuals with higher relative to lower capacity (e.g., Wiegand et al., 2014a, 2014b; Luria and Vogel, 2011; McCollough et al., 2007). Despite significantly lower storage capacity in the adult ADHD compared to the matched control group, the difference between groups disappeared at this later time window. Furthermore, the link between individuals' vSTM storage capacity and late CDA amplitudes was less reliable in the patient group (Fig. 2). A reduced or lacking association between the CDA and individual vSTM storage capacity has previously been reported in ADHD individuals (Spronk et al., 2013), persons with high anxiety traits (Leonard et al., 2012), and schizophrenic patients (Qi et al., 2014). Thus, our result adds to mounting evidence that the late CDA does not represent a valid neural marker of the vSTM storage capacity limit under psychiatric conditions.

The pattern characterized by similar levels of lateralized activity, but storage of fewer items in vSTM (relative to healthy participants), is indicative of reduced efficiency in the mechanism of information storage in adult ADHD patients. A possible source of this deficit might be the dopaminergic neuromodulation in ADHD, which has been suggested to engender unusually high levels of endogenous (random) noise, contributing to various cognitive difficulties (Sikström and Söderlund, 2007). In terms of NTVA, attentional weight, or neural resources, might be expended on internally generated noise signals in visual cortex, in the absence of sensory stimulation (Bundesen and Habekost, 2008). Accordingly, a typical signal detection problem (Green and Swets, 1966) would arise when actual experimental stimuli have to be discriminated from baseline noise activity to become represented in sensory brain areas. This could lead to increased neural activity coupled with reductions in the vSTM storage capacity parameter K , as observed in adult ADHD patients.

Notably, the only previous study that explored vSTM together with CDA measures in adult ADHD (Spronk et al., 2013) did not report a significant vSTM storage capacity reduction and/or CDA amplitude difference in the patients compared to controls. Importantly, while the paradigm employed in this study provided a suitable way to measure vSTM filtering efficiency, it was, arguably, lacking in sensitivity for detecting differences in maximum vSTM storage capacity: Participants performed a colored-squares change detection task with varying numbers of target and distracter stimuli, where the maximum set size was (just) three items. This limitation made it impossible to measure individuals' capacity > 3 and to detect group differences beyond this value. This could explain why the CDA did not correlate with individuals' (likely underestimated) vSTM storage capacity K in this design. Also of note,

the early time window, in which we found differences in the CDA between the adult ADHD patient and control groups, was actually not analyzed Spronk et al.

4.2. Compensatory attentional control

In both the ADHD and the control group, individuals with higher storage capacity K showed an increased P3b compared to individuals with lower storage capacity. In addition, the P3b was increased in the ADHD relative to the control group (Fig. 3), and more posteriorly distributed exclusively in participants with higher storage capacity in this group.

There is agreement that the canonical P3b, observed in most visual (and also other) cognitive tasks, can be subdivided into several components, which are related to multiple distinct processes within an information-processing cascade following sensory perception of a stimulus (cf. Polich, 2012). The P3b has been associated with attentional control, working memory, and response selection processes (Donchin and Coles, 1988; Polich, 2007); however, despite extensive research, there is no consensus as to which precise cognitive function the P3b represents. Accordingly, the neuro-cognitive mechanisms underlying P3b alterations in clinical groups as ADHD patients are not yet clear either.

With the present approach, we demonstrate a specific link between individual differences in the P3b and the latent vSTM storage capacity parameter derived from the formal TVA model. Specifically, the increased positivity, as compared to healthy controls, suggests that ADHD patients recruit a greater amount of – or even other, additional – resources for vSTM storage. The P3b in ADHD patients may thus be indicative of such individuals strongly relying on fronto-parietal control circuits for performing the task. As a result of the adverse signal-to-noise ratio during vSTM storage (see Section 4.1 above), ADHD patients may require increased sensory evidence for correctly categorizing and maintaining information in vSTM. Thus, the positivity increase in adult ADHD patients may reflect top-down controlled accumulation of a relatively higher amount of sensory evidence, so as to increase the strength of task-critical sensory input relative to irrelevant (i.e., interfering) internal noise. In line with this interpretation, a similar positivity was recently shown to increase with the amount of incoming evidence required for correct perceptual decisions (O'Connell et al., 2012).

Notably, at variance with our finding, most previous studies investigating the P3 in adults and children ADHD have found a reduced positivity in patients compared to healthy controls (Barry et al., 2003; Johnstone et al., 2013; Kim et al., 2014; Szuromi et al., 2011). The divergence is likely attributable to differences in the requirements imposed by the tasks employed. Compared to the complexity of the – mostly 'executive-function' – tasks used in other studies on this issue, the whole-report task used in our study is very simple with respect to instructions, task procedure and demands, and response requirements. With higher demands on attentional control, ADHD patients might not be able to rely on similar compensatory mechanisms as applicable in the current paradigm. By comparison to the other tasks, the vSTM storage capacity measure derived from performing the whole-report paradigm provides a very basic, fundamental measure, completely uninfluenced by stress on motor-response speed. Thus, while the P3 reduction observed in previous studies has been suggested to reflect, at least in part, impaired motor control in ADHD (Szuromi et al., 2011), no such (potential 'confounding' by) motor-related processes could have contributed to the positivity found with our task. Accordingly, we propose that our model-based approach enabled us to extract a sub-component of the P3 complex which is both more specific with regard to the underlying cognitive

operation and more sensitive to pathological alterations. Similarly, we previously documented an age-specific modulation in the P3 time range, the right-central positivity (RCP): a higher RCP was associated with preserved vSTM capacity in older individuals. Accordingly, we interpreted this P3 modulation to reflect compensatory recruitment of fronto-parietal control mechanisms to support visual storage in the face of age-related sensory decline.

4.3. Visual nature of ERP correlates of storage capacity K

In the present whole-report task (different from, e.g., a change detection task with colored shapes), participants could have resorted to verbal rehearsing of the letters during the delay period. We propose, however, that the ERP components examined are primarily sensitive to *visual* maintenance and, thus, capable of revealing group differences in *visual* STM storage. First, the CDA obtained in the present study, as well as former studies that used the same paradigm, is perfectly comparable to that in studies that employed vSTM change detection tasks with shape stimuli (Vogel and Machizawa, 2004). Second, other ERP studies on working memory have shown that the employment of verbal strategies in visual tasks is associated with delay activity over frontal areas in a window much later than those of the CDA and P3b (1.5 s post stimulus; Bosch et al., 2001; Ruchkin et al., 1997).

4.4. Neuro-cognitive markers of ADHD

Our replication of a basic reduction of vSTM storage capacity is in accordance with the idea that ADHD symptoms result from core cognitive deficits (e.g., Alderson et al., 2013; Barkley, 1997). We further provide evidence in favor of a neuro-biological basis of this basal deficit. The delayed rise of the CDA and a less reliable association between CDA amplitudes and individual storage capacity are indicative of inefficient neural mechanisms of vSTM storage associated with adult ADHD. In a neurodevelopmental model of ADHD, it is furthermore suggested that individuals' overt symptom severity is determined by their ability to compensate for core deficits through the adaptive recruitment of higher cortical control functions (Halperin and Schulz, 2006; Campbell et al., 2014). Our finding of an enhanced P3b in adult ADHD patients points to a neural correlate of such a compensation mechanism – though, based on the results of the current, cross-sectional study including adults with persisting symptoms only, we cannot unequivocally conclude whether compensatory mechanisms were developed over the lifespan. On a more general level, our results support the idea that cognitive performance and symptom severity in adult ADHD are determined by the interplay between deficient and compensatory mechanisms. Most importantly, we identified neural measures of the visual storage capacity reduction in adult ADHD, which represents a crucial step towards establishing a testable candidate for a neuro-cognitive endophenotype of adult ADHD.

4.5. Limitations and outlook

A critical limitation of the present study is that the sample size did not allow subgroup analyses with respect to, for instance, diagnosis subtypes. Future studies with larger samples might reveal specific relationships of the identified ERP correlates with specific symptoms, or they might show differences in these relationships between ADHD subtypes. Furthermore, while our results show that the identified neuro-cognitive markers bear candidacy as neuro-cognitive endophenotypes, it remains to be established, in larger studies, whether they fulfill several other, pertinent criteria, in particular: whether they are inheritable, have a higher probability of occurrence in first-grade relatives, and dissociate

between family members with and without ADHD. Finally, also the association between the TVA parameter storage capacity K, its ERP correlates, and alterations in candidate genes suggested to be involved in attention and working memory performance in ADHD, such as dopaminergic receptor genes and the Catechol-O-methyltransferase (COMT) gene (Biehl et al., 2015; Boonstra et al., 2008; Tomlinson et al., 2015), could now be tested in larger studies.

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