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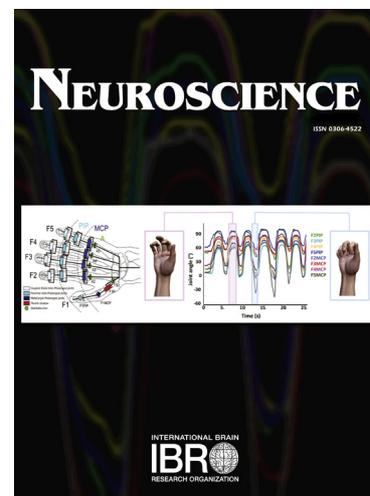
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EEG dynamics and neural generators in implicit navigational image processing in adults with ADHD

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Abstract

In contrast to childhood ADHD that is characterized by inattention, impulsivity and hyperactivity, most adults with ADHD predominantly exhibit inattention. We used a new oddball paradigm using implicit navigational images and analysed EEG dynamics with swLORETA inverse modelling of the evoked potential generators to study cortical processing in adults with ADHD and age-matched controls. In passive observation, we demonstrated that P350 amplitude, alpha-beta oscillation event-related synchronization (ERS) anticipation, and beta event-related desynchronization (ERD) were significantly smaller in ADHD. In the active condition, P100 duration was reduced and N140 amplitude increased for both deviant and frequent conditions in the ADHD. Alpha ERS and delta-theta ERS were reduced in the ADHD in the deviant condition. The left somatosensory area (BA2) and the right parietal lobe (BA31, BA40) contributed more to the P100 generators in the control than in the ADHD group, while the left frontal lobe (BA10) contributed more to the P100 generators in the ADHD. The left inferior parietal lobe (BA40) contributed more to the N140 generators in the control than the ADHD group while the right posterior cingulate (BA30) contributed more to the N140 generators in the ADHD. These findings reinforce the notion that earlier cortical stages of visual processing are compromised in adult ADHD by inducing the emergence of different event-related potentials generators and EEG dynamics in ADHD. Considering that classical approaches for ADHD diagnosis are based on qualitative clinical investigation possibly biased by subjectivity, EEG analysis is another objective tool that might contribute to diagnosis, future neurofeedback or brain stimulation therapies.

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by symptoms of inattention with or without impulsivity and hyperactivity. It is one of the most commonly diagnosed psychiatric disorders in school-aged children (American Psychiatric Association 2013). Historically, ADHD was considered only in children. However, the persistence of symptoms in up to 65% of adults is now widely recognized (Biederman et al., 2011; Cheung et al., 2016; Faraone et al., 2006; Halperin et al., 2008; Seidman, 2006). ADHD actually affects about 5% of adults in the general population (Kessler et al., 2006; Miller et al., 2012; Sibley et al., 2016; Simon et al., 2009). While childhood ADHD is characterized by inattention, impulsive and hyperactive behavior, most adults with ADHD show few externalizing symptoms and predominantly show attentional deficits that manifest themselves as major difficulties in organization, time management, planning and task completion in daily life (Das et al., 2012; Rösler et al., 2010). Deficits in executive functions have been hypothesized to be the main dysfunction underlying ADHD (Martín-González et al., 2008; Nigg et al., 2005; Rodriguez-Jiménez et al., 2006; Roth and Saykin, 2004; Willcutt et al., 2005). Structural and functional neuroimaging studies have documented impairments in neural networks associated with executive functioning in both children and adults with ADHD (Bush et al., 2005; Konrad and Eickhoff, 2010). Abnormal anatomy and dysfunction of inferior frontal and dorsolateral prefrontal cortex, frontostriatal and mesocorticolimbic networks, anterior cingulate, parieto-temporal, and cerebellar regions have been particularly highlighted (Castellanos et al., 2008; Ehlis et al., 2008; Liston et al., 2011; Makris et al., 2008; Sidlauskaite et al., 2015; Sun et al., 2012). However, others types of cognitive and emotional CTRL are involved in ADHD behaviors (Nigg and Casey, 2005) and recent investigations

concluded to a more complex relationship between executive dysfunctions and ADHD (Mattfeld et al., 2016).

Most of the ERP research on cognitive functions conducted so far in ADHD individuals has concentrated on children. Using tasks assessing cognitive processes such as attention, inhibitory control, performance monitoring, intervention effects, and ERP-energy interactions, they have identified a number of ERP abnormalities, including deficits in early components such as the N1, the N2, the P2, and mismatch negativity, and also in late components such as mainly the P3 and the slow wave (see for a review, Johnstone et al., 2013).

To date, ERP research in adults ADHD has also focused on tasks examining impulsivity/inhibitory control (Bekker et al., 2005; Ehlis et al., 2008; Fallgatter et al., 2005; Grane et al., 2016; McPherson and Salamat, 2004; Meier et al., 2012; van Rooij et al., 2015a, 2015b; Shahaf et al., 2012; Wiersema et al., 2006; Prox et al., 2007; Barry et al., 2009; Markovska-Simoska and Pop-Jordanova, 2011; Fisher et al., 2011; Köchel et al., 2012). However, most ADHD adults exhibit problem with attention. As attention precede execution, it is crucial to better understand attentional processes deficits in adults ADHD.

Attention allocation is classically explored through the use of the so-called oddball tasks that require the detection of infrequent target stimuli amongst a string of standard stimuli. This type of task especially involves selective attentional processes, defined as the ability to focus on goal-relevant events while ignoring irrelevant information. To our knowledge so far only five ERPs studies used an oddball paradigm in adult ADHD (Barry et al., 2009; Itagaki et al., 2011; Marzinzik et al., 2012; Missonnier et al., 2013; Raz, Dan, and Zysberg, 2014). Some of them reported reduced P3 amplitudes (Itagaki et al., 2011; Marzinzik et al., 2012; Raz, Dan, and

Zysberg, 2014). Others showed anomalies in components associated with early sensory-processing, i.e., increase (Barry et al., 2009) or decrease (Missonnier et al., 2013) in P2 amplitude and reduced N2 amplitude (Barry et al., 2009). Topographic differences in N1 to auditory targets, and P1, N1, P2, N2 and P3 to visual non-targets were also described (Barry et al., 2009).

However, except for one (Missonnier et al., 2013), all of these studies have exclusively concentrated their ERPs analyses on differences in mean amplitude, considering that all neuronal activity of interest is evoked by the stimulus in a time-locked fashion from trial to trial. However, single-trial analyses have proven that ERP components can not only be explained by modulation in amplitude but also largely by the partial phase resetting of ongoing activity in delimited frequency bands (Fell et al., 2004; Hanslmayr et al., 2007; Makeig et al., 2002; Mormann et al., 2005; Rousselet et al., 2007).

The used of high-density (128-channel) EEG offering increased spatial sampling, coupled with recent improved standardized weighted low-resolution electromagnetic tomography (swLORETA) today allows to reach precise spatial information (Cebolla et al. 2014, 2011; Palmero-Soler et al. 2007) and could accurately detect the anatomical substrates of the short-time cognitive processes involved in oddball paradigms.

In this study, an EEG dynamics investigations correlates of selective attentional processes in adults with ADHD will be carried out. ERPs and time–frequency measurements will be recorded during an oddball task in order to capture the event-related spectral perturbation (ERSP) and the inter-trial coherency (ITC) power and phase dynamics of single-trial EEG. Moreover, the use of high density EEG recording and swLORETA will allow identifying the cortical areas involved in the time–

frequency behaviour of the brain oscillations underlying the ERPs recorded during the task.

In combining the dynamic content analyse of EEG signals with source reconstruction, we seek to achieve a better understanding of the cortical networks underlying deficits in attentional processes in adult ADHD. This indeed represents an essential step in order to further set up efficient retraining EEG-based protocols (Gruzelier 2014; Loo, Lenartowicz, and Makeig 2015; Loo and Makeig 2012; Olbrich, Dinteren, and Arns 2015; Arns, Drinkenburg, and Leon Kenemans 2012).

In a first step, we verify that the basic processing of perception of two types of images (checkerboard and 3D-virtual tunnel) in passive condition is conserved or not in ADHD patients. In a second step, we assess and compare the effect of the oddball paradigm based on the same 3D-virtual tunnel in the control (CTRL) and ADHD groups.

EXPERIMENTAL PROCEDURES

Participants

The data were collected from twenty eight volunteers: 14 participants diagnosed with ADHD by one of the authors, neuropsychiatrist specialized and 14 healthy control subjects not diagnosed with ADHD recruited within the university by direct mails or by newspaper advertising. The average age was 38 ± 13 years for the ADHD group and 32 ± 9 years for the CTRL group. The male/female ratio was 10/4 for the ADHD group and 10/4 for the CTRL group. All participants used a voluntary consent form approved by the local ethics committee at the Brugmann Hospital in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for

experiments involving humans. Inclusion criteria for CTRL participants were no previous diagnosis of ADHD and failure to meet DSM-V criteria for adult ADHD. The participants in the ADHD group were part of the cohort of patients of the same neuropsychiatrist specialized in adult ADHD. They had been previously diagnosed with the help of the structured diagnostic interview, the Conners Adult ADHD Diagnostic Interview for DSM-IV (CAADID; Epstein et al., 2001) and the Wender-Utah Rating Scale (WURS; Wender, 1995). Ten out of the 14 participants in the ADHD group were predominantly inattentive, none of them were predominantly hyperactive/ impulsive, and 5 were of the combined subtype. Eight out of the 14 ADHD patients were medication-naïve and 6 patients were on medication (but not actually receiving treatment at the time of the recording). Exclusion criteria for both groups were a seizure disorder, head injury affecting the central nervous system, mental retardation, and sensory deficits that could interfere with behavioural performances or with electrophysiological results. Comorbid disorders are common in ADHD and were not excluded in order that the patients recruited would be typical of the normal range seen in clinic. In our ADHD group, 4 out of the 14 participants had one comorbid disorder (depression (1), anxiety (1), dysthymia (1), and bipolar disorder (1)).

Procedure

Informed written consent was first obtained from each participant. They received an explanation of the nature and duration of the study and were informed of what was expected from them. The experiment then started. Participants were first assessed with the neurophysiological testing in a single session that lasted approximately one and a half hour. Next, they were asked to complete questionnaires on demographic and medical past and present information. Finally, an evaluation of psychiatric

conditions was made with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and ADHD symptoms were investigated with the Diagnostic Interview for ADHD in adults (DIVA) (Kooij and Francken, 2010). This interview was conducted by a graduated psychologist.

Participants were instructed to abstain from taking any medication in the 48-hour period prior to testing and were asked not to use caffeine or tobacco on the morning of their testing.

Experimental paradigms

EEG was recorded during the following three tasks: (1) a neutral visual task consisting of the passive observation of a checkerboard (Fig.1A); (2) a visual perceptive task involving the viewing of a 3D virtual tunnel with a sense of virtual movement through the tunnel (Fig.1B); and (3) an oddball directional task (Fig.1 C) that required to report by pressing a button when the upward orientation (deviant stimulus) of the tunnel was presented, but not the other 3 orientations (downward, to the left or right).

For all tasks, participants looked straight ahead at the laptop screen (22.0 cm height, 30.3 cm width; refresh rate 75 Hz, resolution 800 x 600 pixels) through a form-fitting facemask and a 30 cm-long cylinder barrel (Cheron et al., 2014) to remove external visual references. Participants were asked to maintain their eyes on a green fixation dot presented centrally (Fig. 1D).

Visual Observation Tasks

Neutral visual task

Simple visual stimulations consisted of a black and white checkerboard (4.5 x 4.0 cm rectangles; black 15 lx, white 101 lx) alternating with and a gray screen (43 lx)

(Fig.1A). The stimulation frequency of this sequence was 1 Hz. The fixed inter-stimulus interval was 500 ms. The sequence (checkerboard/gray screen) was repeated 96 times.

3D tunnel visual perceptive task

Visual stimuli consisted of a 3D virtual tunnel (from 39 lx at the periphery to 74 lx close to the center) (Fig.1B) alternating with a gray screen (43 lx) with a 1 Hz frequency and 500 ms inter-stimulus interval. The tunnel with stone-textured walls (stone dimension 1.25 cm² at the periphery to 0.15 cm² close to the center) was non-stereoscopic but included perspective cues generated by the OpenGL graphic libraries (Vidal et al., 2006) with either upward, downward, to the left, or to the right orientation. The sequence (tunnel/gray screen) was presented 48 times including the four directions of the tunnel (upward, downward, to the left, to the right) each appearing 12 times. The 48-alternation sequence was presented four times. These different stimuli with a pattern contrast of about 50 % display subtended 7°(w)× 5°(h) at the eye. Thus, both foveal and parafoveal retinal fields were stimulated.

Oddball directional task

For this task, the same sequence as the previous display was presented in the same order, but instead of passive observation, the participant was asked to press a button each time (and only when) the end of the tunnel was oriented upward. When participants performed the first task they were naïve and not aware about the subsequent oddball task.

EEG recordings

Unipolar EEG recordings were performed from 128 scalp sites using a shielded electrocap against a left earlobe electrode. Eye movements were recorded

(horizontal bipolar electrooculogram; vertical unipolar recording against the common reference). Electrode impedances were kept <5 k Ω . Amplified signals (ca 11 mV, ANT DC-amplifiers, the Netherlands) were digitized (2048 Hz rate) at 16 bit resolution and notch-filtered (47.5-52.5 Hz). Off-line analysis and statistics were performed using EEGLAB software (Delorme and Makeig, 2004). Any artefactual portions of the EEG data were rejected by visual inspection. Bad channels were interpolated. Synchronous or partially synchronous artefactual activity (mostly blinks) were detected on the basis of the topographical and spectral distribution and on the time series of the independent component analysis (ICA) on continuous data.

EEG analysis

Event-related potentials

The following of the event-related potentials (ERP) components related to each task were studied: P100, N140, P220, P350 using POz electrode referenced to the left earlobe (A1). Subsequent analyses were only performed for the ERP components for which statistical differences were observed between ADHD and CTRL groups. In addition, the duration of the P100 is calculated on the time interval between the two inflection points.

Event-related spectral perturbation

Event-related desynchronization (ERD) and synchronization (ERS) were studied using EEGLABs described previously (Delorme and Makeig 2004). Briefly, for each frequency band at each frequency point the power spectrum was divided by the averaged spectral power in the pre-stimulus baseline period (-500 ms to 0 ms). Each trial contained samples from 1000 ms before to 2000 ms after the stimulus. The log₁₀-transformed of this measure allows the visualization of wider range of variation

(Grandchamp and Delorme, 2011). A color code at each image pixel indicated the reached power (in dB) at a given frequency and latency relative to the stimulation onset. Event-related perturbation is expressed in units of the percentage of the baseline. Use of \log_{10} implies that 0 (green color) is obtained for values equal to the baseline; the other values are shown in red or blue even in the pre-stimulation period.

For n trials, if $F_k(f, t)$ was the spectral estimate of trial k at frequency f and time t

$$\text{ERSP}(f, t) = \frac{1}{n} \sum_{k=1}^n |F_k(f, t)|^2 \quad (1)$$

To compute $F_k(f, t)$, the short-time Fourier transform of EEGLAB software was used providing a specified time and frequency resolution.

Inter-trial coherence

ITC is a frequency-domain measure of the partial or exact synchronization of activity at a particular latency and frequency to a set of experimental events to which EEG data trials are time-locked. This measure, also called ‘phase locking factor’, was defined by:

$$\text{ITPC}(f, t) = \left| \frac{1}{n} \sum_{k=1}^n \frac{F_k(f, t)}{|F_k(f, t)|} \right| \quad (2)$$

where $\| \cdot \|$ represents the complex norm. The ITC has values between 0 and 1, from the absence of synchronization between EEG data and the time locking events to perfect synchronization. In order to increase time resolution, the onset and termination of the ERS and ERD were measured by using wavelet transform. We used wavelet transform for complex spectro-temporal representation with Hanning-windowed sinusoidal wavelets at 1 cycles (lowest) to 12.5 cycles (highest). ERSP and ITC templates were calculated with 200 time points (-721.5 ms to 1221.5 ms), using a window of 285 samples (556.6 ms) at 97 linear spaced frequencies from 2 to

50 Hz. For the significance level of ERSP and ITC, bootstrap resampling ($p < 0.05$) was used.

The temporal accuracy ($\Delta t = \frac{1/2\pi}{\Delta f}$) was 16.3 ms. The maximal values of ERSP and ITC were measured in the same time frames of the corresponding ERP peaks.

Inverse modeling (swLORETA)

For source reconstruction, standardized weighted low resolution electromagnetic tomography (swLORETA) (Palmero-Soler et al., 2007; Cebolla et al., 2011) was used. This distributed inverse solution method derived from sLORETA (Pascual-Marqui, 2002; Pascual-Marqui et al., 2002; Wagner et al., 2004) provides spatial modeling of distinct sources of neuronal activities without any prior knowledge about the anatomical location of the generators, even in the presence of noise or when two dipoles are simultaneously active. This was realized by incorporating a singular value decomposition based lead field weighting that compensated for the varying sensitivity of the sensors to current sources at different depths (Palmero-Soler et al., 2007).

ERP source analysis

Source analysis focused on the ERP components evoked by the 3D-tunnel, because the checkerboard stimulation produced identical responses in ADHD and CTRL groups. We computed swLORETA solutions for the time peak period of the P100, N140, P220, P350 components in the two groups of participants. Briefly, swLORETA was computed using a 3D grid of 2030 voxels (5 mm spacing) representing possible sources of the signal based on probabilistic brain tissue maps provided by the Montreal Neurological Institute (Evans and Collins, 1993b), restrained to the gray matter but including the cerebellum. The grid voxels (2030 points with 5.0 mm grid

space) and recording array (128 electrodes) were placed in registration with the Collins 27 MRI (Evans and Collins, 1993b). The Boundary Element Model (BEM) was used for solving the forward problem (Geselowitz, 1967). The final coordinates (x, y, z, Talairach coordinates) we provided for labeling the corresponding brain areas were based on Talairach atlas using the ASA software, and thus identified the corresponding Brodmann areas (Lancaster et al., 2000). For the definition of cerebellar regions we used the Schmahmann et al's MRI Atlas of the Human Cerebellum (Schmahmann et al., 1999).

Statistical Analysis

To assess significance in the behavioral measure, we used one-way ANOVA test and Bonferroni's post hoc test after assessing their normality by Kolmogorov Smirnov test using Statistica 7.0 software (Statsoft, www.statsoft.com) to compare the ADHD with the CTRL group. Results were expressed as mean \pm S.D. and the differences were considered significant at $p < 0.05$. For significance in the full scalp array in the ERP, ERSP and ITC, we employed a nonparametric permutation and the Holm's method to correct for multiple comparisons (Holm, 1979). This method is provided by EEGLAB software (Delorme and Makeig, 2004).

To find the generators of the P100, N140, P220 and P350 components, we determined a threshold value for identifying statistical significance of the current density magnitude by using a nonparametric permutation test (Nichols and Holmes, (2002). The rationale for using this method was explained in detail in (Cebolla et al., 2011). In the present case, the current density for each ERP component was divided by the mean value of all voxels, giving a normalized inverse solution from which value greater than one indicates that the voxel had an activity greater than the mean. In order to use the t test as the value of merit, we subtracted one to each voxel. In

order to build the empirical distribution for the Holmes method, we randomly multiplied the value of each voxel by -1 or 1. We performed a total of 8192 t -tests for each analyzed component. The normalization process is described by the following formula:

$$J_i(t)_{normalized} = \frac{J_i(t)}{\sum_{voxel=0}^{nVoxel=2030} J_{voxel}(t)} - 1$$

where $J_i(t)$ represents the inverse solution for the i -th voxel for the time t .

We used t -test for swLORETA solutions to compare the ADHD versus the CTRL group, with a null hypothesis corresponding to the absence of between-group difference, which is equivalent to stating that the distribution of the voxel values of the groups' difference inverse solution images has a zero mean. We used the 95th percentile of the permutation distribution for the maximal statistics which defines the 0.05 level of the corrected significance threshold. In other words, we can reject the null hypothesis for any voxel with t -values of the unpermitted T image greater than the 95th percentile of the permutation distribution of the maximal statistics.

RESULTS

Behavioral measures

There was no significant difference in the average reaction time (420 ± 18 ms in ADHD vs. 428 ± 18 ms in CTRL, $p = 0.32$ $F(1, 26) = 1.03$), but a significant difference in the success rate (85.3 ± 6.6 % in ADHD vs. 90.2 ± 5.0 % in CTRL ($p < 0.03$ $F(1, 26) = 4.86$)). The latter difference was due to omission (absence of action for the

upward direction (51.7 ± 19.1 % in ADHD and 35.9 ± 20.1 % in CTRL $p < 0.04$ $F(1, 26) = 4.57$)) and not commission (no excess of action for the non-target directions).

Passive observation task

ERP analysis

Figure 2 compared the early components evoked by the presentation of the checkerboard (P100 and P220) (Fig. 2A) and by the presentation of the 3D virtual tunnel (P100, N140, P220) (Fig. 2B) in the ADHD and CTRL groups.

No statistical difference between the two groups was found for either visual stimulation. In contrast, when the 3D virtual tunnel (all directions pooled) was presented, the P350 component evoked in ADHD group was of significantly lower amplitude than in CTRL (permutation test, $p < 0.05$). The amplitude reduction was more marked in the central parieto-occipital region (POz) with a predominance on the right.

ERSP analysis

ERSP analysis corresponding to these ERPs for the checkerboard stimulation showed significant ERS in the gamma band (~ 35 Hz) between 250 and 500 ms in the parieto-occipital region in the ADHD group (Fig. 2C-E). When the 3D virtual tunnel was presented, the intensity of the ERSP recorded in the parieto-occipital region was greater than for the checkerboard showing weaker alpha-beta ERS anticipation (-150 ms to 0) during the presentation of various directional images and weaker beta ERD at the P350 latency in ADHD with respect to CTRL (Fig. 2 F-H). In contrast, as in the case of the checkerboard stimulation, a late gamma (~ 45 Hz) ERS was recorded at the latency of the P350 in the parieto-occipital region in the ADHD group (Fig. 2 F-H).

ERP generators in passive observation task

swLORETA analysis performed on the ERP data corresponding to the 128 electrodes showed that the global localization of the P100, N140, P220 and P350 components were grossly similar in ADHD and CTRL group in the passive observation condition of the 3D-virtual tunnel with only minor differences in localization and magnitude of the inverse solution (Fig. 3A). Namely, the P100 generators were bilaterally localized in the occipital lobe BA17 (-31, -84, -12); BA18 (-7, -85, 33); BA19 (-57, -11, -9) in the middle and superior temporal gyrus BA21 (63, -10, -2) and Crus I of the cerebellum (-28, -81, -24). The major difference for the P100 generation was found in the participation of the right parietal cortex BA7 (-4, -61, 58) in CTRL but not in ADHD group (Fig. 3B).

The N140 generators were localized bilaterally in the occipital lobe BA17 (15 (-15), -95, -2) and BA18 (-3 (3), -95, -6), the left middle temporal gyrus BA21 (-60, -2, -14) and the right medial frontal gyrus BA10 (6, 61, 5). These N140 generators were commonly identified in the ADHD (Fig. 3A) and CTRL groups (Fig. 3B).

P220 generator localization was not identical in the ADHD group than in CTRL. While the occipital cortex (BA18, BA19), the right inferior temporal gyrus (BA20) (55, -45, -12) and the bilateral posterior cerebellum were identified in both groups, the left middle temporal gyrus BA21 (-57, -4, -14) and the right, subgyral temporal lobe, BA37 (52, -46, -8), were only found in the CTRL group (Fig. 3A).

P350 generators were commonly localized in BA17, BA20, BA21, BA36, and posterior cerebellum in both the ADHD and CTRL groups. BA19 was additionally found in the ADHD group (Fig. 3B).

Figure 3A, B shows generators with the highest probability. Yet, comparative analysis between groups with the t-test permutation (Fig. 3C, D) highlighted

significant differences in the inverse solution corresponding to dominant generators in each group. The right parietal lobe (BA7) (20, -76, 38) contributed more to the P100 in the CTRL than ADHD group (Fig. 3C). Conversely, the left parahippocampal gyrus (BA19) (-21, -57, -2) and left premotor area (BA6) (17, -2, 55) contributed more to the P100 in the ADHD than CTRL group (Fig. 3D). The left hippocampus (-31, -28, -1) and right frontal lobe BA10 (1, 51, 5) contributed more to the N140 in the CTRL than ADHD group (Fig. 3C). In contrast, the occipital lobe (BA19) (36(-36), -77, 30), (BA18) (36,(-36), 82, -9), right frontal lobe (BA10)(12, 62, 22) and Crus I (8, -80, -27) of the right cerebellum contributed more to the N140 in the ADHD than CTRL group (Fig. 3D). The left middle temporal gyrus (BA21) (-48, 2, -20) and left inferior parietal lobe (BA40)(-47, -36, 41) contributed more to the P220 in the CTRL than ADHD group (Fig. 3C). In addition, the right frontal lobe (BA10) (5, 54, 1) contributed more to the P220 in the ADHD than CTRL group (Fig. 3D). The right frontal lobe (BA10) (10, 61, 23) contributed more to the P350 in the CTRL than ADHD group (Fig. 3C). In contrast, the left occipital Lobe (BA19)(-30, -67, -7) and the right cingulate gyrus (7, 40, 10) (BA32) contributed more to the P350 in the ADHD than CTRL group (Fig. 3D).

Oddball directional task

ERP analysis

Figure 4A-D illustrates the superimposition of the ERP traces recorded in ADHD (red) and CTRL (blue), when participants were asked to direct their attention to the direction of the 3D virtual tunnel randomly presented upward (A) (deviant condition), downward (B), to the right (D) and to the *left* (C) direction. During all conditions, the ERPs configuration was significantly different at the latency of P100 and N140 between the ADHD and the CTRL groups. While the inflection between the P100 and

P220 remained in positive values in the CTRL group (Fig. 4A-D, blue trace), a negative deflection, the N140, occurred in the ADHD group (Fig. 4A-D, red trace) giving rise to significant differences in P100 duration (29.0 ± 7.9 ms in ADHD versus 46.7 ± 11.5 ms, $p < 0.0001$) (Fig. 4A-D, horizontal blue lines) and in N140 amplitude between 110 and 150 ms ($p < 0.05$ permutation test).

We have performed the comparative analysis of the generators issued from swLORETA applied on components P100 and N140 because only these components showed a significant difference between the ADHD and CTRL groups (Fig. 4 B-D). Moreover, this analysis was carried out during the frequent conditions for two groups of participants because the number of trials was lower in the deviant condition and the same statistical differences appeared on the ERP (Fig. 4 A). These statistical comparisons showed that: (1) the left somatosensory area (BA2) (-37,-29, 29), the right parietal lobe (BA31) (14,-58, 22) and the right inferior parietal lobe (BA40) (38, -39, 41) contributed more to the P100 generators in the CTRL than in the ADHD group (Fig. 4 E), while the left frontal lobe (BA10) (-26, 39, 16) contributed more to the P100 generators in the ADHD than in CTRL group; (2) the left inferior parietal lobe (BA40) (-45, -36, 36) contributed more to the N140 generators in the CTRL than the ADHD group (Fig. 4F) while the right posterior cingulate (BA30) (11, -57, 7) (Fig. 4F) contributed more to the N140 generators in the ADHD than the CTRL group.

ERSP analysis

The ERSP analysis performed on the parieto-occipital cortex (POz) (Fig. 5A-E) during the deviant condition showed that the significant differences occurred in alpha ERS (from 100 to 220 ms) and in delta-theta ERS (from 250 to 350 ms) where these ERS were smaller in the ADHD than in CTRL group. For the frequent conditions, the only one significant difference between the two groups only occurred under the form

of a reduction of the late delta-theta ERS (from 350-600 ms) (Fig. 5A-C). The statistical distribution maps of the delta and theta oscillations in the deviant (Fig. 5E-F) and frequent (Fig. 6D-E) conditions reinforced the previous ERSP analysis performed on POz electrode. These maps indicated a stronger contribution of delta-theta oscillation recorded mainly on the right fronto-temporal scalp (Fig. 5E-F) during the deviant condition in the CTRL than in the ADHD group. A same reduction in the delta-theta oscillation was recorded in the ADHD group during the frequent condition (Fig. 6D-E) but in this case the reduction was bilaterally situated from the central to the occipital scalp.

DISCUSSION

The advantage of using a 3D virtual tunnel rather than checkerboard is that power modulation of different rhythms is expected to be stronger (Leroy et al., 2017) , which we confirm here in both ADHD and CTRL groups. EEG dynamics investigation of 3D virtual tunnel image processing showed four main differences between ADHD and CTRL: (1) significant changes in P100 duration and N140 amplitude accompanied by different source network configurations, (2) a weaker anticipative ERS in alpha and beta frequency bands, (3) a weaker ERD in beta oscillation at the P350 latency, and (4) a late gamma ERS in ADHD.

Passive observation task

Prior to the analysis of the effect of required action in the oddball paradigm the comparative study of the presentation of the two types of images (checkerboard and 3D virtual tunnel) have permitted to verify that the basic processing of perception was conserved in ADHD in passive condition. In spite of the fact that there is no external

cue to induce anticipative behaviour, we have reported stronger ERSP (alpha-beta) anticipation in the CTRL than in ADHD group. This may indicate a reduced anticipative sensibility of the ADHD subjects to endogenously expectation provided by our continuous presentation design.

ERP generators

Although the early ERPs (P100, N140, P220) do not allow distinction between the ADHD and the CTRL group, the swLORETA solution provided significant differences in the localization of the respective generators of these ERP components. Firstly, this highlighted the participation of the right parietal cortex (BA7) to the P100 only in the CTRL group. This region of the right parietal cortex is involved in visuo-spatial processing, such as mental rotation and processing of chaotic patterns stereopsis (Walter and Dassonville, 2008). This could indicate the presence of a larger network extending from BA19 to BA7 dedicated to a specific attention directed to implicit navigational image in typical participants while the network would be more restricted in the ADHD. Secondly, in the passive condition, the presentation of the 3D virtual tunnel evoked an attentional P350 in CTRL that was not present in the ADHD group. Although, the same occipito (BA17) -temporo (BA21/22, BA38) -frontal (BA10) network and the cerebellum were implicated during this period as P350 generators in the CTRL group, the absence of P350 in ADHD group may be explained by the dominance of BA10 in CTRL in comparison with the ADHD group. Conversely, BA19 was more dominant in the ADHD than CTRL group. This indicated a relatively weak contribution of the frontal cortex during the passive observation of navigational image in ADHD group as previously reported for other types of visual stimuli (Mattfeld et al., 2016).

Oddball directional task

Although the reaction time was not altered, as commonly reported (Sawaki and Katayama, 2006), the success rate was lower in the ADHD group. Surprisingly, this latter difference was not due to a lack of inhibitory control (commission errors in response to the frequent stimuli) but to the absence of action in response to the deviant stimulus. This suggests a deficit in directional recognition of implicit navigational image in adults ADHD. This would be consistent with previous evidence (Rösler et al., 2010; Das et al., 2012) that hyperactivity and impulsivity are less prominent in adulthood ADHD than in childhood ADHD (Balogh et al., 2017).

In the active condition, two main ERP components were significantly modified in the ADHD group with respect to the CTRL: the early occipital P100 and N140. P100 duration was reduced in favor of the increased amplitude of the N140 for both frequent and deviant conditions). The increased contribution of the left frontal cortex (BA10) in patients with ADHD may indicate that they mobilize more cortical activities from these part of the cortex in order to suppress excessive distractors (Vaidya and Stollstorff, 2008).

The reduced contribution of the precuneus (BA31) at the latency P100 in ADHD patients with respect to CTRL is consistent with decreased fMRI activity observed in this part of the limbic lobe during a voluntary selection process of a tone in adult ADHD (Karch et al., 2014). The reduced contribution of the somatosensory cortex (BA2) at the latency of P100 may be related to morphological alteration (Li et al., 2015) and or compensatory process (Duerden et al., 2012). The increased contribution of the posterior cingulate (BA30) to the emergence of N140 in ADHD group may be related to increased attentional (Hahn et al., 2007) and cognitive (Buckner et al., 2008) demands of this region for the accomplishment of the oddball visual task. This observation indicates an early difference in the generators involved

in the recognition of a directional image between ADHD and CTRL groups. The possibility that visuo-vestibular conflict may also influence the present results merits to be explored in the future.

The N140 corresponds to the classical N1 component of the visual evoked potential (Hopf and Mangun, 2000) also considered as the early directing-attention negativity recorded after the presentation of the visual cue in the contingent negative variation paradigm of Arjona et al., (2014). Overall, a clinical alteration in ERP studies was seen as a global decrease of all the evoked components. For example, when the P300 emerged during an auditory oddball paradigm it was preceded by a N140-like component which its amplitude increased in parallel to the P300 amplitude when the subjects were active in place of passive (Lugo et al., 2016). In contrast, the amplitude of both components were smaller in patients with locked-in syndrome (Lugo et al., 2016). However, as in the present study, it was reported that the N140 amplitude was independently modulated from the P300 amplitude (Fig. 5 of Sole Puig et al., 2016). In this later cue/no-cue experiment demonstrating the possible contribution of eye vergence movement during orienting attention, the N175 amplitude increased while the P300 decreased. Moreover, this study showed that the time and strength of eye vergence coincide with the onset and strength of an evoked positivity which peaked just before 200 ms (Fig. 7 of Sole Puig et al., 2016). As it was reported by the same group (Solé Puig et al., 2015) an alteration in vergence modulation in children with ADHD, we can say that the N175 increase could be related to eye vergence control in ADHD reflecting a defect in cognitive processing of sensory information.

Compared to controls during deviant condition, ADHD patients showed a decrease of the ERS alpha on left parieto-occipital scalp from 100 to 220 ms followed by a decrease of the ERS delta-theta on the right fronto-temporal scalp from 250 to 350

ms. As frontal theta activity reflects activation of neural networks involved in the attention to target stimuli (Deiber et al. 2007; Missonnier et al., 2013) and to directional recognition (Ekstrom et al., 2005), this theta alteration revealed a decrease in neural network activation implicated in visual navigation attention in ADHD. In contrast, during the latter stage of information processing both groups exhibited the same alpha-beta ERD indicating that the recruitment of the global activities related to these rhythms are similar. This points also on the fact that the rhythmic alterations are not due to a general decrease of the arousal in the ADHD subjects. The early decrease of parieto-occipital alpha ERS suggests a difference in top-down modulation in ADHD group (Leroy et al., 2017). Although the P350 and late evoked positivity (<400 ms) were not different in ADHD with respect to control, the ERSP analysis highlighted two significant differences in ERS theta depending of the action or the disengagement of attentional processes which necessitate successful inhibition (Greer et al., 2017). The delta-theta ERS preceding the action and the ERS theta accompanying the inhibition of action were both decreased in ADHD group indicating the implication of delta-theta in executive function (De Blasio and Barry, 2013; Harper, Malone, and Bernat, 2014) more specifically during a directional virtual task (Bohbot et al., 2017).

Our findings further clarify the notion that the early cortical stages of visual processing are compromised in adults with ADHD, inducing the emergence of different ERPs generators and EEG dynamics. Considering that classical tools for ADHD diagnosis are based on qualitative clinical observation and interview possibly biased by subjectivity, EEG analysis is an additional objective tool that might contribute to diagnosis. This may also open the possibility to use electrophysiological

characterization of EEG dynamics as the basis for future neurofeedback or brain stimulation therapies.

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Figure 1

Overview of the three different stimulation paradigms and experimental settings.

Paradigm 1: passive directional task; checkerboard images (A) were compared to 3D-tunnel (B) (four directions randomly presented, (Left, Right, Up, Down)) intermixed with uniform gray images. Each visual item was presented for 500 ms. 96 and 192 presentations were used for the checkerboard and the 3D-tunnel, respectively. Paradigm 2: Oddball directional task; the same sequence of four directions randomly 3D-tunnel was presented but the subject was asked to press a

button each time the end of the tunnel was oriented upwards (Condition Deviant). The subject is equipped with an EEG-cap and looks straight-ahead through a form fitting facemask connected through a cylindrical tunnel to laptop screen centred on the line of gaze at a distance of 30 cm from the eyes.

Figure 2

Superimposition of the event-related potentials (grand average, $n = 14$ ADHD and $n = 14$ CTRL) evoked by the checkerboard (A) and the 3D-tunnel (B) presentation in ADHD group (red traces) and CTRL (blue traces) recorded at the POz electrode. The grey vertical bar to presentation 3D tunnel (B) represents the statistical significance of P350 components difference between the two groups ($p < 0.05$, permutation test).

Event-related spectral perturbation (ERSP) evoked by checkerboard (left side) (C-E) or 3D-tunnel stimulation (right side) (F-H) (grand average, $n = 14$ ADHD and $n = 14$ CTRL) recorded at the POz electrode. The third columns (E, H) represent the statistical significance (permutation with Holms, $p < 0.05$).

The topography at right represents the statistical map (permutation with Holms test $p < 0.05$) between the two groups at 3D-tunnel stimulation.

Figure 3

swLORETA sources obtained for P100 (3D-virtual tunnel), N140, P220 and P350 event-related potentials (ERP) components (A,B). Nonparametric statistical maps calculated on all subjects for the 3D-virtual tunnel stimulation in relation to P100, N140, P220 and P350 for the CTRL group compared to the ADHD (C) and for ADHD group compared to the CTRL group (D). The white arrows point to the significant and respective ERP generators corresponding to Brodmann areas (BA) and specific

regions of the cerebellum named in accordance to the Atlas of Human Cerebellum of (Schmahmann et al., 1999)(see details in the main text).

Figure 4

Superimposition of the event-related potentials (grand average, $n = 14$ ADHD and $n = 14$ CTRL) evoked by the 3D-tunnel presentation according to directions; Up (A), Down (B), Left (C), Right (D) in ADHD group (red traces) and CTRL (blue traces) recorded at the POz electrode. The grey vertical bars represent the statistical significance of N140 components (A-D) and P350 components (B) difference between the two groups ($p < 0.05$, permutation test). The horizontal blue lines indicate the duration of P100 in the CTRL group.

swLORETA sources, nonparametric statistical maps calculated on all subjects for the 3D Tunnel stimulation in relation to P100 component (E) and to N140 component (F) in frequent condition for the CTRL group and ADHD group.

Figure 5

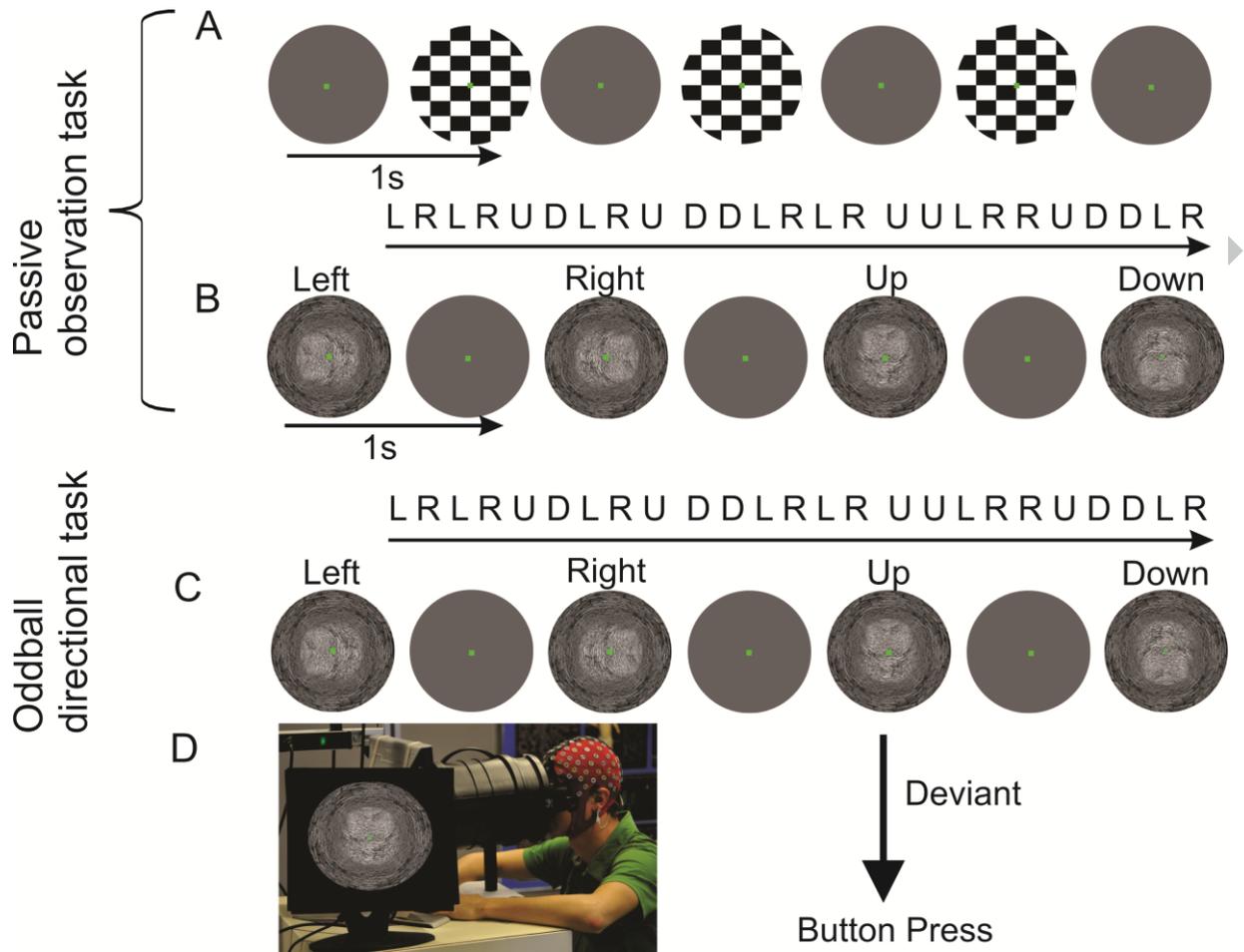
Effects of deviant condition (Up direction) in the 3D-tunnel presentation (grand average, $n = 14$ subjects). A-C: Event-related spectral perturbation in POz electrode (top line) evoked by the Up direction between CTRL group (A) and ADHD group (B) showing a significant (permutation with Holms test $p < 0.05$) theta and alpha ERS (C). D-F: Topography of the alpha (D) theta oscillation (E) and delta oscillation (F) during the deviant condition. The third column represents the statistical map (permutation with Holms test $p < 0.05$).

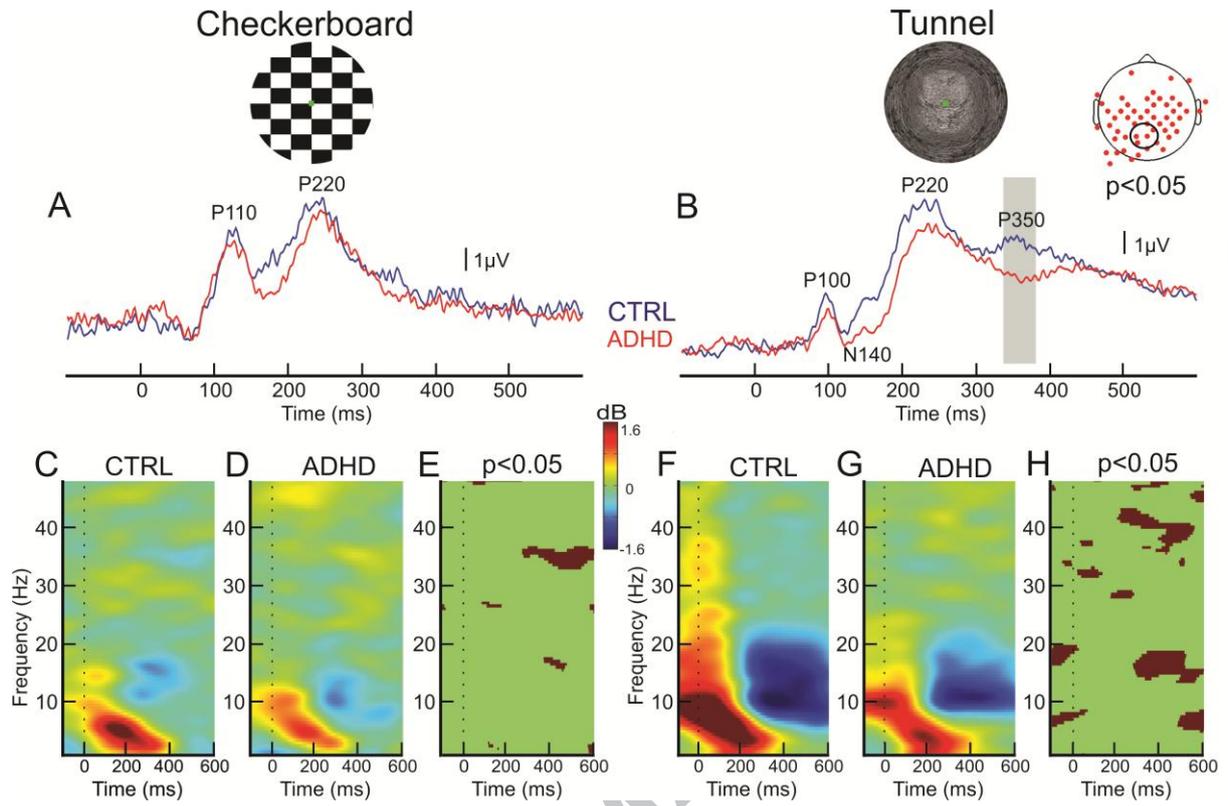
Figure 6

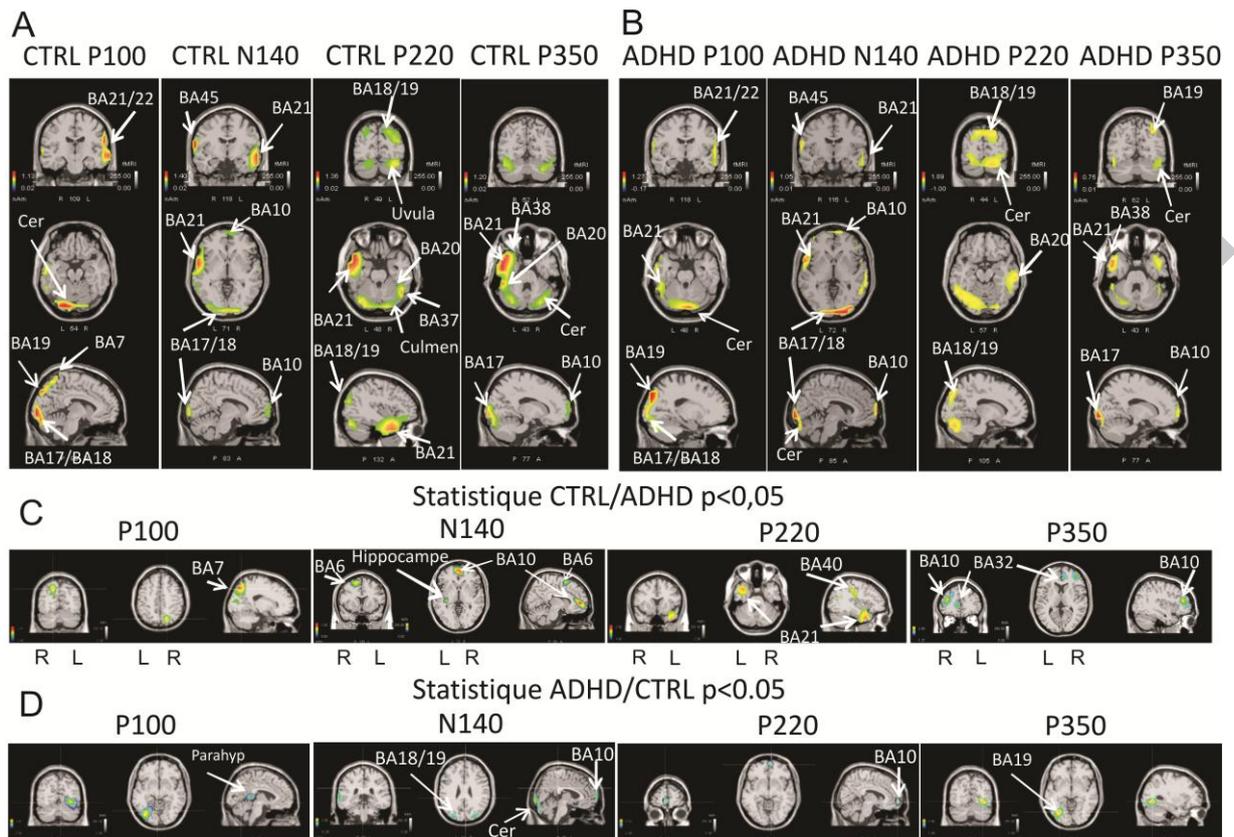
Effects of frequent condition (Down, Left, Right directions) in the 3D-tunnel presentation (grand average, $n = 14$ subjects). A-C: Event-related spectral

perturbation in POz electrode (top line) evoked by the Down, Left, Right directions between CTRL group (A) and ADHD group (B) showing a significant (permutation with Holms test $P < 0.05$) theta ERS (C). D-E: Topography of theta oscillation (D) and delta oscillation (E) during the frequent condition. The third column represents the statistical map (permutation with Holms test $p < 0.05$).

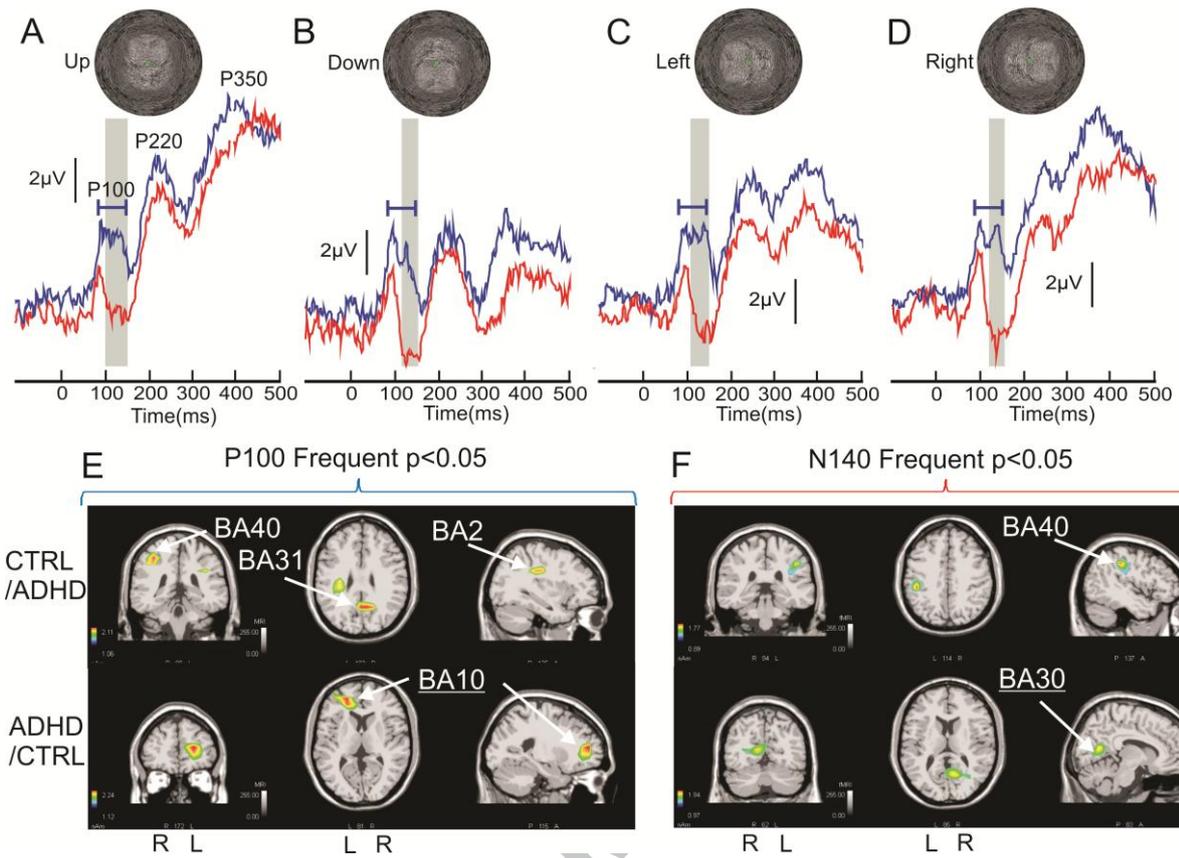
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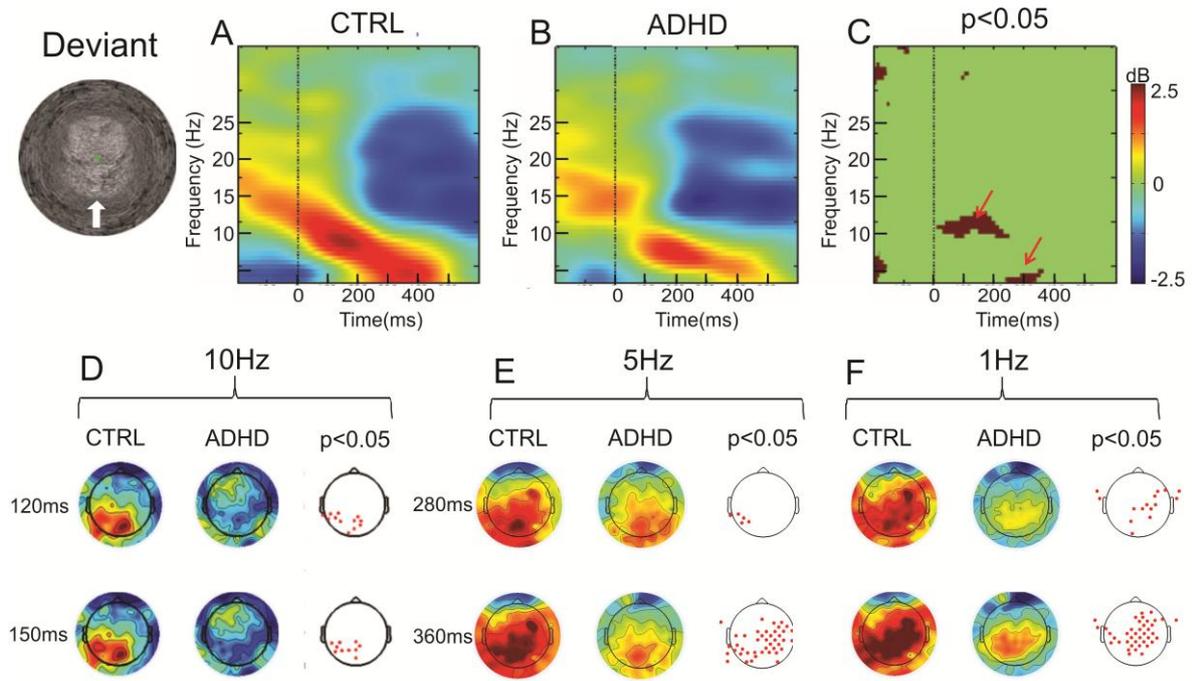


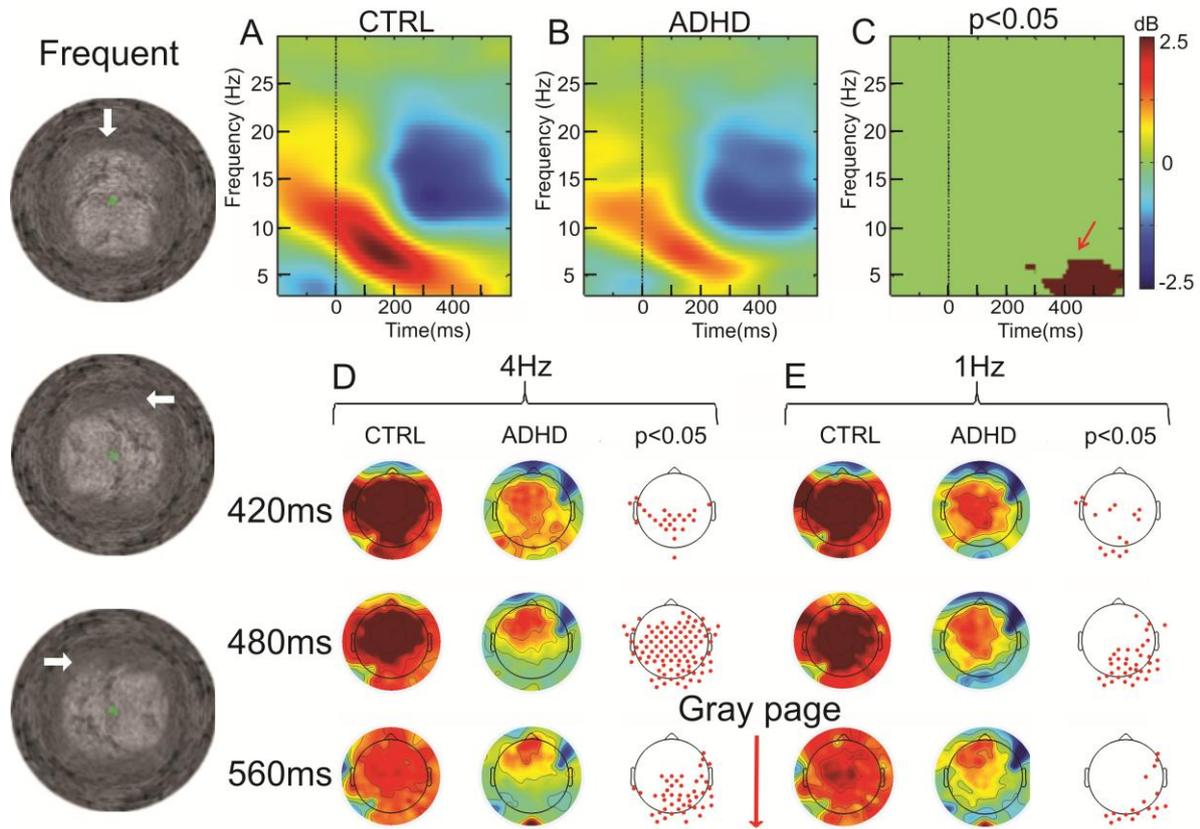




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Highlights

- In a new oddball paradigm using navigational images P100 duration was reduced and N140 amplitude increased in ADHD
- Alteration of the event-related potentials generators of the earlier visual processing in ADHD
- The left BA2, BA31 and BA40 contributed more to the P100 generators in control than in ADHD
- The left BA10 contributed more to the P100 and the BA30 contributed more to the N140 in ADHD.
- Weaker anticipative ERS in alpha and beta frequency bands in ADHD

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