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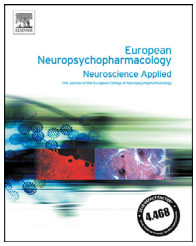

From self-induced to perceived errors - A generalized over-monitoring activity in obsessive-compulsive disorder

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Abstract
Well-functioning error monitoring of the inner and outer environments is essential for adaptively altering behavior, while malfunction characterizes conditions such as obsessive-compulsive disorder (OCD). The underlying brain processing is manifested as Error-Related Negativity (ERN) signal elicited following error comission, and Perceived Error Related Theta Activity (PERTA) signal elicited following detection of discrepancy in the environment. Yet, while enhanced ERN was repeatedly demonstrated in OCD patients and was found to be potentiated among their unaffected first degree relatives, no comparable observations were reported with regard to PERTA. We recorded EEG activity while OCD patients, OCD patients' siblings (Family), and healthy controls (HC) performed computerized tasks. For the examination of ERN we used the Stroop task and for the examination of PERTA we presented correct and incorrect mathematical equations. Increased ERN (0–120 ms post response) was observed in both the OCD and Family groups, but only the OCD patients' signal significantly differed from that of HC's. Similarly, modified PERTA activity was observed in both the OCD and Family groups in the N1 peak (65–125 ms post perceived error), but only for the OCD group this activity significantly differed from that of HC. Both ERN and PERTA's N1 are fast occurring peaks, which suggests that OCD is associate with a constantly over-activated detection system that monitors the inner

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and outer environment and reacts promptly following detection of a mistake. Furthermore, the modified but non-significantly different activity of the Family group suggests that the pathological condition evolves in vulnerable individuals with neuronal predisposition.

1. Introduction

Obsessive–Compulsive Disorder (OCD) is a chronic and disabling disorder that affects approximately 1–3% of the population and causes marked distress and significant functional impairments (DSM5, 2013; Leckman et al., 2010; Ruscio et al., 2010; Weissman, 1998). Although there is considerable heterogeneity regarding the content of obsessions and compulsions, the main symptoms dimensions converge to symmetry\ordering, contamination\cleaning, taboo thoughts\checking, and hoarding (DSM5, 2013; Leckman et al., 2010; Mataix-Cols et al., 2005; Pauls et al., 2014). Common to all these dimensions is the feeling that some flaw must be corrected, and OCD participants often report a distressing sense of incompleteness until things look, feel, or sound "just right" (Coles et al., 2005).

According to the DSM-5 (DSM5, 2013), compulsions are typically performed in response to obsessions, with the aim of reducing the distress triggered by them. However, as 'Not Just Right' experience and pervasive doubts are core features of OCD (Ghisi et al., 2010; Lazarov et al., 2014), compulsions can also be triggered by perceived flaws in the external environment that arouse the urge to react (Coles et al., 2005). While the former state is thought to represent an affective-cognitive process, the latter may represent an over-activation of a general monitoring system (Mesika et al., 2014). Accumulating evidence from imaging studies of OCD participants suggest that, in response to self-induced mistakes ($_{SI}$Mistakes), there is over-activation of a specific monitoring system that is most pronounced in the anterior cingulate cortex (ACC) (Brem et al., 2012; Endrass et al., 2010; Falkenstein et al., 2000). For example, ACC hyperactivity has been consistently reported in OCD participants during tasks that include the commission of a mistake, such as Stop-Signal, Flanker, or Stroop (Chamberlain et al., 2005; Hajcak et al., 2005; Hajcak and Simons, 2002; Saxena et al., 2001; Tzur and Berger, 2007b; Yeung et al., 2004). During these tasks, electroencephalogram (EEG) can detect an Error-Related Negativity (ERN) signal, which is considered to originate in the ACC and elicited whenever a subject makes a mistake (Fitzgerald et al., 2005; Luu and Tucker, 2001; Weinberg et al., 2015).

Although theories of ERN functional significance are under debate, it is usually considered as a trigger for behavioral adjustment aimed to improve performance and prevent future errors (Riesel et al., 2011). Notably, apart from being enhanced in OCD participants (Fitzgerald et al., 2010, 2005; Gehring et al., 1993, 2000; Hajcak and Simons, 2002; Luu et al., 2003; Yeung et al., 2004), ERN was also found to be potentiated among their unaffected first degree relatives (Carrasco et al., 2013; Riesel et al., 2011). In addition, studies in healthy subjects have also identified activity elicited by *perceived* erroneous information (e.g., viewing misspelled words or wrong equations such as $1+3=5$) (Jost et al., 2004; Núñez-Peña and Honrubia-Serrano, 2004; Szűcs and Csépe, 2005). Notably, activity following perceived mistakes ($_{P}$Mistake) shares the same scalp distribution (over the medial prefrontal cortex; mPFC), brain source localization (ACC), and theta band frequency (4–8 Hz) that characterize the classic error negativity (Ne) or error related negativity (ERN) found for self-induced errors, or from the feedback response negativity (FRN) found after feedback to erroneous responses (Cohen et al., 2007; Luu et al., 2004; Mesika et al., 2014).

Specifically, the ERN signal peaks 50–150 ms post response (Gehring et al., 1993; Hajcak et al., 2005), while Perceived Error-Related Theta Activity (PERTA) has three distinct peaks that can be detected 100–400 ms post stimulus (Mesika et al., 2014).

Considering that OCD is characterized with over-monitoring (Chamberlain et al., 2005; Coles et al., 2005; Fitzgerald et al., 2005; Hajcak and Simons, 2002) and increased ERN, individuals with OCD are also expected to demonstrate increased PERTA activity. However, to the best of our knowledge, PERTA activity has not yet been investigated in OCD participants. In the attempt to further elucidate this phenomenon, we compared the evoked ERN and PERTA of OCD participants (OCD group), their unaffected siblings (Family group), and healthy controls (HC).

1.1. Methods

The study was performed at Chaim Sheba Medical Center, Israel (2012–2014), and the protocol was approved by the local Institutional Review Board and the Israeli Ministry of Health. All participant underwent demographic and clinical assessments and completed two different computerized tasks while EEG activity was recorded.

1.2. Participants

The study included 31 OCD participants, 17 of their siblings, and 31 HC. Participants were recruited via newspapers and internet advertisements, and from the outpatient program at Chaim Sheba Medical Center. OCD candidates were initially screened with a short telephone interview and then using elaborated clinical interview conducted by a psychiatrist or a psychologist. The clinical interview included a structured diagnostic interview for DSM-IV (SCID) (Spitzer et al., 1992), neurological examination, neurological disorders history, the Raven test for IQ estimation (Raven and Court, 1998), and the Hamilton Depression Scale (HADR) (Hamilton, 1960). Additionally, the Yale-Brown Obsessive-Compulsive Scale (YBOCS) (Goodman et al., 1989) was administered to all OCD and Family candidates. The inclusion criteria for OCD participants were: Right-handed, 18 – 65 years old, DSM-IV diagnosis of OCD established by a senior

psychiatrist using SCID, and a score of $\geq$ 20 in the YBOCS (10 items). Exclusion criteria were other Axis-I psychopathology, neurological disorders, or a current depressive episode. Inclusion criteria for the Family and HC groups were right-handed and 18 - 65 years old, while exclusion criteria were any diagnosed Axis-I psychopathology or prescribed medications for Axis-I disorders. All participants read and signed an informed consent form.

2. Computerized tasks

The Stroop (Golden, 1978) and Equation (Tzur and Berger, 2007a) tasks were administered using E-Prime software (Psychology Software Tools, Inc.) on a 17-inch computer screen using a response pad with four keys. During the tasks, EEG was recorded using the ASA lab EEG system (A.N.T. Enschede, Netherlands), with a 32 channels cap (Waveguard) and two Electrooculography (EOG) channels. Electrode's impedances were kept below 10 KΩ, and all channels were average referenced. Data were collected at the rate of 250 samples per second and digitized with a 24-bit AD converter.

2.1. Stroop task

The words 'red', 'green', 'yellow' and 'blue' were presented (in Hebrew) with their respective color (congruent condition), or in one of the three other colors (incongruent condition). Participants were instructed to press the key associated with the color of the word while ignoring the word's meaning. The task comprised 10 blocks of 80 trials (800 total trials), with each block initiated by the subject. Each trial started with the presentation of a fixation cross for 1000 ms, followed by the Stroop stimulus. The visual stimulus stayed in view for 2000 ms or until a key-press. Random inter-trial intervals (ITIs; 200/400/600 ms) were used in order to reduce a monotonous task rhythm.

In order to increase the rate of $_{SI}$Mistakes, the key-color association was altered prior to the initiation of each block, and participants were allowed 10 practice trials to adapt for that new arrangement.

2.2. Equation task

Participants were presented with 360 trials (plus 10 practice trials) of simple arithmetic problems (addition or subtraction), which were followed by an equal number of either correct or incorrect ($_{P}$Mistake) solutions. As the magnitude of PERTA was shown to depend on the salience of the violation, with larger conflict/mismatch eliciting stronger activity [33], the incorrect solution condition included two possible levels of deviation, appearing with equal probability. For example, for the problem "1 + 2 =", the incorrect solution could be either small ($_{P}$Mistake$_{S}$; e.g., "4″), or large ($_{P}$Mistake$_{L}$; e.g., "8"). Equations including identical operands (e.g., 3 + 3, 4 + 4) were excluded. The trials were presented in random order in four blocks (45 correct and incorrect trials in each block). Each trial began with a fixation point (500 ms), followed by an equation (1500 ms), then a black screen (600 ms), and ended with a solution (1500 ms). Random inter-trial intervals (ITIs; 200/400/600 ms) were used in order to reduce a monotonous task rhythm.

2.3. EEG analysis

All EEG analyzes were performed using EEGLAB toolbox for Matlab (Delorme and Makeig, 2004). Continuous EEG data were filtered using 1-100 Hz band-pass and 50 Hz notch. EEG data were segmented (2-s epochs) into trials that were time-locked to the participants' response during the Stroop task or to the time of solution presentation during the Equation task. The segmented data were manually inspected and noisy segments or channels were removed. Subsequently, the data were decomposed using infomax-Independent Component Analysis (ICA), and eye blinks and horizontal eye movements were excluded. Second manual inspection was then performed and residual artifacts were removed. Excluded channels were replaced with spherical interpolation of the neighboring channels values, and data were re-referenced to the average.

For the Stroop task, data were divided into response type (Correct/$_{SI}$Mistake), and ERN was computed as the power difference between the two types. Since most of the mistakes were made within the incongruent trials (93%), the analysis was carried out solely for this condition. In addition, the mean power was converted to decibel (dB), and event-related spectral perturbation (ERSP) and inter-trial coherence (ITC) analyzes were conducted. In order to determine the same time window of the ERN signal for all groups, we calculated a combined ERN of the OCD, Family and HC as a general group, which resulted in a time window of 0-120 ms post response.

For the Equation tasks, data were gathered according to conditions (Correct/ $_{P}$Mistake$_{S}$ / $_{P}$Mistake$_{L}$) and filtered for theta band at a time window ranging between 0 and 400 ms post solution presentation. We then converted the mean theta power from the Cz, FC1, FC2 and Fz electrodes to decibel (dB) (Gehring et al., 2000; Hajcak et al., 2005; Hajcak and Simons, 2002; Tzur and Berger, 2007b) and calculated Event-Related Potential (ERP) for each condition. Additionally, we employed a wavelet Analysis (spectral wavelet analysis decomposition) and performed a trial-wise baseline correction (using the −300 to 0 ms range). Finally, we converted the mean theta power to decibel (dB) (Gehring et al., 2000; Hajcak et al., 2005; Hajcak and Simons, 2002), and ERSP and ITC analyses were conducted. In order to determine the same time windows for the different PERTA peaks, an adaptive mean was calculated for the N1, P2 and N3 components of all groups combined, and analysis was conducted in a time window of 60 ms around the mean peak value (30 ms before and 30 ms after the peak).

2.4. Statistical analyses

Data analysis was performed using the STATISTICA software, version 12 (StatSoft, Tulsa, OK). For ERN analysis, EEG power was analyzed using a one-way ANOVA with Group (OCD, Family, and HC) as independent variables, and ERN ($_{SI}$Mistake minus Correct EEG responses) as the dependent

Table 1 Demographic characterization and clinical measures. HADR - Hamilton Depression Scale; YBOCS - Yale-Brown Obsessive-Compulsive Scale; SRI – Serotonin reuptake inhibitor.

Assessments\group	OCD	Family	HC
Sample size	31	17	31
Female\Male	15/16	8/9	14/17
Age	32±2.7	29±3.1	34 ±2.1
Raven IQ	37±6.1	36±5.9	46±6.2
HAMD-21	9 ± 1.3	6 ± 1.2	5 ± 1.9
YBOCS	26±1.3*	6 ± 2.2	-
Medications	Escitalopram: 13 Fluoxetine: 8 Fluvoxamine: 3 Sertraline: 7	-	-

* Indicates statistical significance of $p < 0.05$.

variable. For PERTA analysis, EEG power was analyzed using a mixed-model ANOVA with Group (OCD, Family, and HC) as a between subjects independent variables, Response type (Correct / $_{P}$Mistake$_{S}$ / $_{P}$Mistake$_{L}$) as within subject independent variables, and theta band dB mean power as the dependent variable. Significant results were further analyzed using Tukey post-hoc test. All data are presented as mean ± SEM.

3. Results

3.1. Demographic and clinical characterization

Demographic and clinical measures of the participants are presented in Table 1. The three groups did not differ with respect to gender, age, IQ or HAMD scores, but the OCD group had higher YBOCS score in comparison to the Family group [t(36)=4.53 $p = 0.01$].

3.2. Self-induced mistakes in the Stroop task

We excluded from the analysis subjects who had less than 8 $_{SI}$Mistakes (Pontifex et al., 2010) (6 OCD, 2 Family, and 6 HC), so that the ERN analysis included data from 25 OCD, 15 Family, and 25 HC participants. The groups did not differ in their rates of mistakes (11 ± 1.5%, 9 ± 2.1% and 9 ± 2.5%, respectively; $F(2,62) = 0.59$, $p = 0.92$). Leven's test revealed no statistical difference between the group's variances ($p > 0.05$).

Fig. 1 illustrates the mean EEG power during Correct and $_{SI}$Mistake responses of the groups.

ERN analysis ($_{SI}$Mistake-Correct responses) revealed a significant ERN difference between the groups [$F(2,62) = 3.07$, $p = 0.04$]. Tukey post hoc analysis revealed increased ERN in the OCD compared to the HC participants ($p = 0.03$), but not to the Family participants ($p = 0.32$; Fig. 2) groups. The Family and the HC groups did not differ between them ($p = 0.25$).

Further analysis revealed no significant interactions with group for ERSP [$F(2,62) = 1.05$, $p = 0.35$] or ITC [$F(2,62) = 0.75$, $p = 0.47$], but did reveal main effects for condition ([$F(1,62)=31.4$, $p = 0.01$] and [$F(1,62) = 25.5$ $p = 0.01$], respectively) such that all groups demonstrated increased ERSP and ITC during the $_{SI}$Mistake condition.

3.3. Perceived mistakes in the Equation task

PERTA analysis was conducted for all participants (31 OCD, 17 Family, and 31 HC). As can be seen in Fig. 3, response to the different solution types in the theta band was characterized by three peaks, N1 (65–125 ms), P2 (150–210 ms), and N3 (230–290 ms).

Statistical analysis of N1 (Figure 4a) revealed a significant Group X Condition interaction [$F(4, 148) = 2.53$, $p = 0.03$], and post hoc analysis revealed that the OCD group was the only one to exhibit increased activity during the larger error ($_{P}$Mistake$_{L}$) compare to the Corrects solution trials ($p = 0.02$). In addition, there was a significant main effect of group [$F(2, 74) = 3.05$, $p = 0.05$], and post hoc analysis revealed overall increased activity in the OCD group in comparison to both the Family and HC groups ($p = 0.03$). During the P2 and N3 peeks no interaction effect with group was observed ([$F(4148) = 0.48$, $p = 0.74$] and [$F(4148) = 0.74$, $p = 0.56$], respectively), but a main effect of Condition emrged ([$F(2148) = 35.4$, $p < 0.001$], and [$F(2148) = 30.3$, $p < 0.001$], respectively) such that all groups exhibited

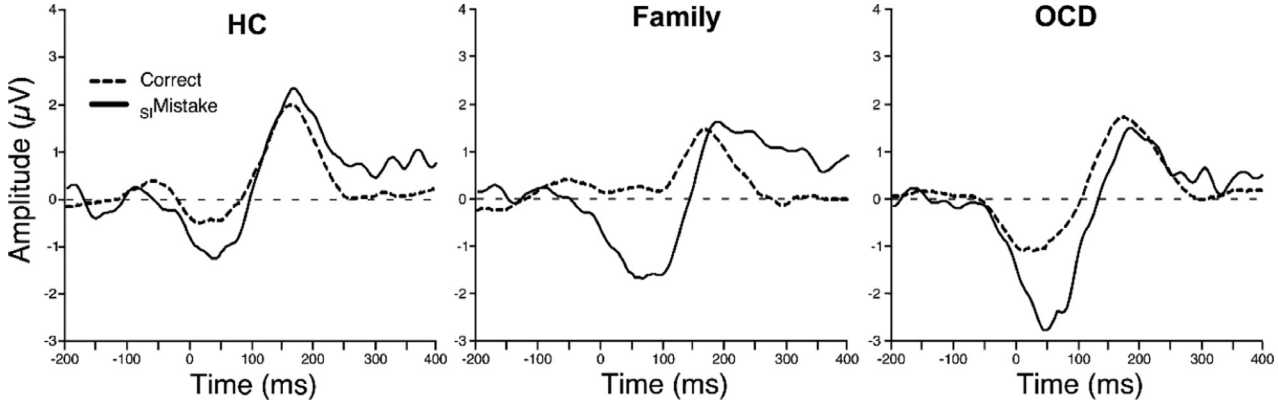

Fig. 1 Mean power during Correct and $_{SI}$Mistake responses in the Stroop task as recorded from the Cz electrode in the different groups.

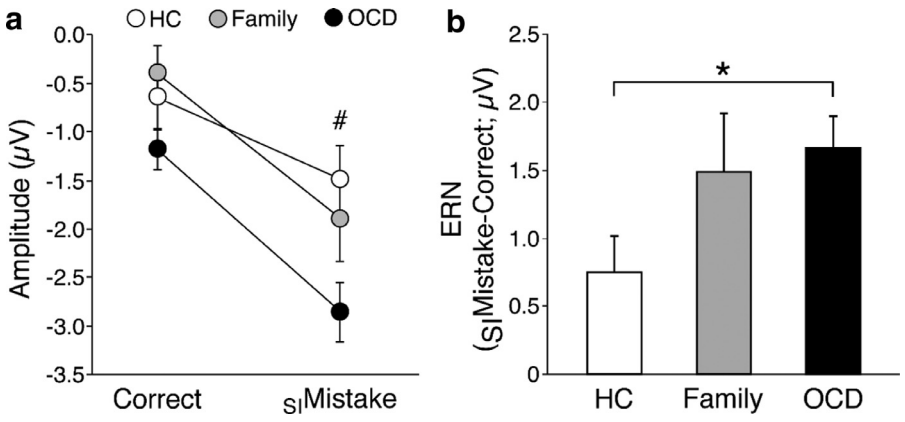

Fig. 2 ERN responses of the OCD, Family and HC groups in the Stroop task. (a) Amplitude of the Responses in the Correct and $_{SI}$Mistake trails. (b) ERN, calculated as the amplitude of the response in $_{SI}$Mistakes trials minus the amplitude of the response in Correct trials. $^{*}p < 0.05$ between OCD and HC.

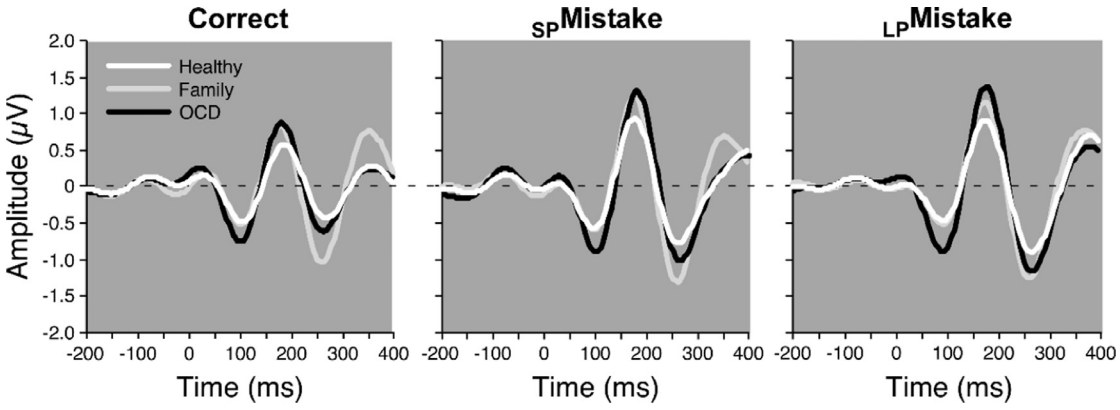

Fig. 3 Responses of the OCD, Family and HC groups to presentation of the different solutions in the Equation task.

increased activity during Mistakes trials in comparison to Correct trials. Finally, analysis of $_{P}$Mistake$_{L}$ - Correct EEG responses revealed that the OCD group exhibited increased activity during the N1 peak as compared to both control groups [$F(2,74) = 3.65$, $p = 0.03$]. Tukey post hoc analysis revealed a significant difference between OCD and HC participants ($p = 0.02$) but not between the OCD and the Family groups ($p = 0.42$), or between the Family group and HC ($p = 0.63$). These differences were not observed during P2 [$F(2,74) = 0.646$, $p = 0.52$] and N3 [$F(2,74) = 1.05$, $p = 0.35$] peaks (Fig. 4b).

A wavelet analysis revealed no power differences between the groups [$F(4146) = 0.52$, $p = 0.73$] during the N1 peak. However, ITC analysis during N1 peak revealed main effect of group [$F(2,73) = 4.24$, $p < 0.01$], and planned comparison revealed statistically significant increased ITC activity in the OCD participants in comparison to HC ($p = 0.03$) and Family ($p < 0.01$) participants. No differences were found between the HC and Family groups ($p = 0.2$; Fig 5). ITC analysis also revealed a main effect for Condition during the P2 and N3 peeks ([$F(2146) = 13.7$, $p < 0.001$] and [$F(2, 146) = 7.7$, $p < 0.001$], respectively), in which all the groups exhibited increased coherence during the Mistakes trials in comparison to Correct trials.

4. Discussion

The present study is the first to explore both self-induced and perceived error monitoring in OCD. As expected, we found differences in the ERN and PERTA responses between OCD participants and controls, whereby OCD participants exhibited a modified early response (~100 ms) to both kinds of errors, suggesting pathological sensitivity to errors. This excessive reaction to errors/discrepancies is consistent with the constant feeling of "not just right" and the persistent attempts to set order in the inner and outer environments that characterize OCD (Coles et al., 2003). Our results are also in line with the cybernetic model of OCD (Pitman, 1987) which proposes that the core problem in OCD is a mismatch between perceptual inputs and internal reference signals (i.e., expectations), and with the violation of expectation theory (Tzur and Berger, 2007b) stating that the mismatch between expected and actual outcomes is reflected as ERN and PERTA signals. Notably, these signals are manifested as theta oscillations over the mPFC and ACC areas, which were found to be centrally involved in error monitoring, action-outcome learning, negative affect appraisal, and goal-directed behaviors (Cavanagh and Shackman, 2015; Cavanagh et al., 2012; Etkin et al., 2011; Wessel et al., 2012).

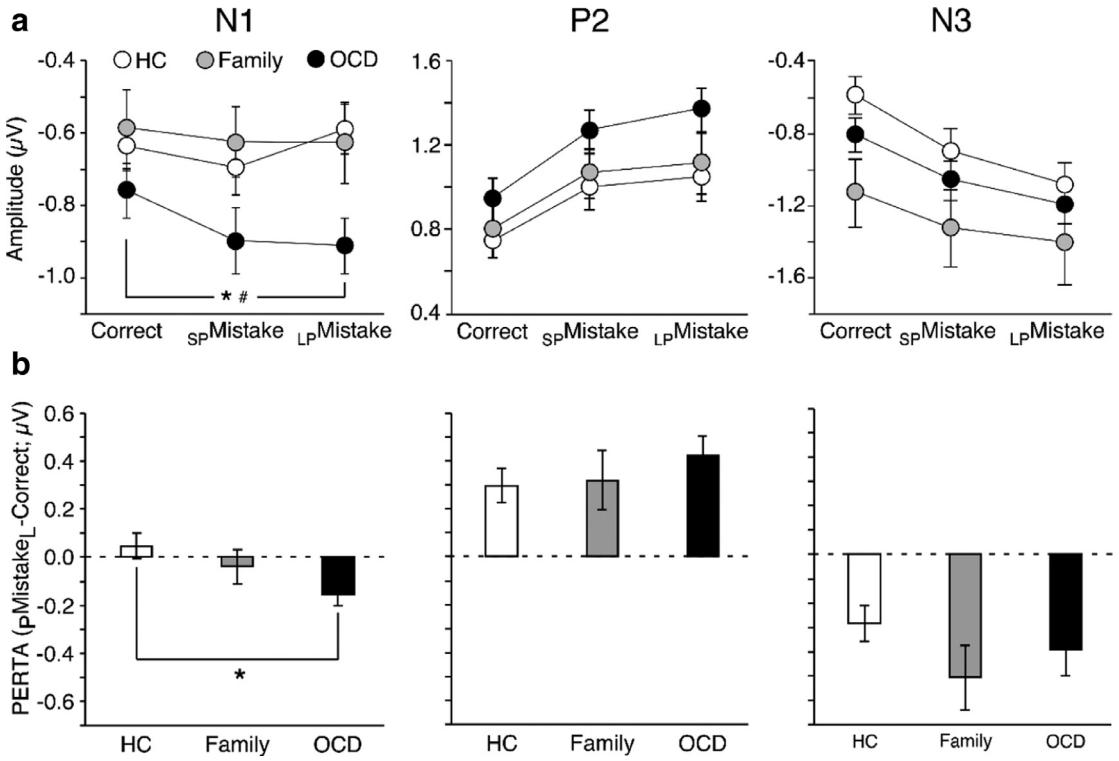

Fig. 4 PERTA responses of the OCD, Family, and HC groups in the Equation task. (a) Amplitude of the different peaks in the Correct, $_{SP}$Mistake, and $_{LP}$Mistake trails. (b) PERTA, calculated as the amplitude of the response in $_{LP}$Mistake trials minus the amplitude of the response in Correct trials for each peak. $^{*}p < 0.05$ between the OCD and Control groups; $^{\#}p < 0.05$ between Correct and $_{LP}$Mistake responses of the OCD group.

These findings support the postulation of an automatic brain process that is elicited at early stages of processing, before the comprehensive processing of the stimulus is completed, and like the Ne/ERN, signals that "something is wrong." (Mesika et al., 2014). OCD participants' PERTA was further associated with enhanced ITC during the N1 peak in both Correct and $_{P}$Mistake solutions. Computed within a single EEG trial, ITC reflects the temporal and spectral synchronization within EEG and the extent to which underlying phase-locking occurs (Lachaux et al., 1999). As such, ITC provides a direct measure of cortical synchrony (Makeig et al., 2004), considered to be a fundamental mechanism involved in information processing and critical for feature-binding and other cognitive processes (Palva et al., 2005; Tass et al., 1998). Notably, increased theta oscillations and ITC over the mPFC following negative feedback were found to be associate with increased communication between the mPFC and the lateral PFC (Kerns, 2006; Kerns et al., 2004), possibly reflecting monitoring and adjusting of behavior according to outcomes (Cavanagh and Shackman, 2015). When combined with repeated post-error adjustments, which take place following both types of error detection (Lavro and Berger, 2015), our results may suggest that repetitive and stereotyped behaviors (i.e., compulsions) represent attempts to reduce OCD patients' overreaction to errors.

Previous findings have identified increased ERN in first degree family members of OCD participants compare to HC (Carrasco et al., 2013). However, this population is expected to be heterogenic and thus it is not surprising that we failed to find significant differences between our Family group and the HC or OCD groups. This null finding should be qualified, however, considering the small sample size of the Family sample. Nevertheless, during both the ERN and PERTA's N1 and P2, the Family group demonstrated intermediate responses consistent with a predisposition to OCD.

4.1. Study limitation

Our study has several limitations. First, based on previous studies (e.g., Chamberlain et al., 2008) we have recruited to the Family group only unaffected siblings of our OCD cohort. Unfortunately, due to lack of compliance, this resulted in a relatively small number of participants and low statistical power for detecting differences between this group and the two other subject groups. Further studies are needed in order to examine whether PERTA signal is indeed a familial trait in OCD. Second, the computerized tasks that were used to elicit the ERN and PERTA signals may involve cognitive processes other than error monitoring (e.g., detecting a signal, calculating an equation, etc.), and future studies should confirm our results with additional approaches (e.g., a task that contains erroneous verbal content such as spelling mistakes). In addition, as modified ERN was also detected in individuals suffering from anxiety (Hajcak et al., 2003), this variable should have been assessed for all groups. Finally, only the OCD group was administered

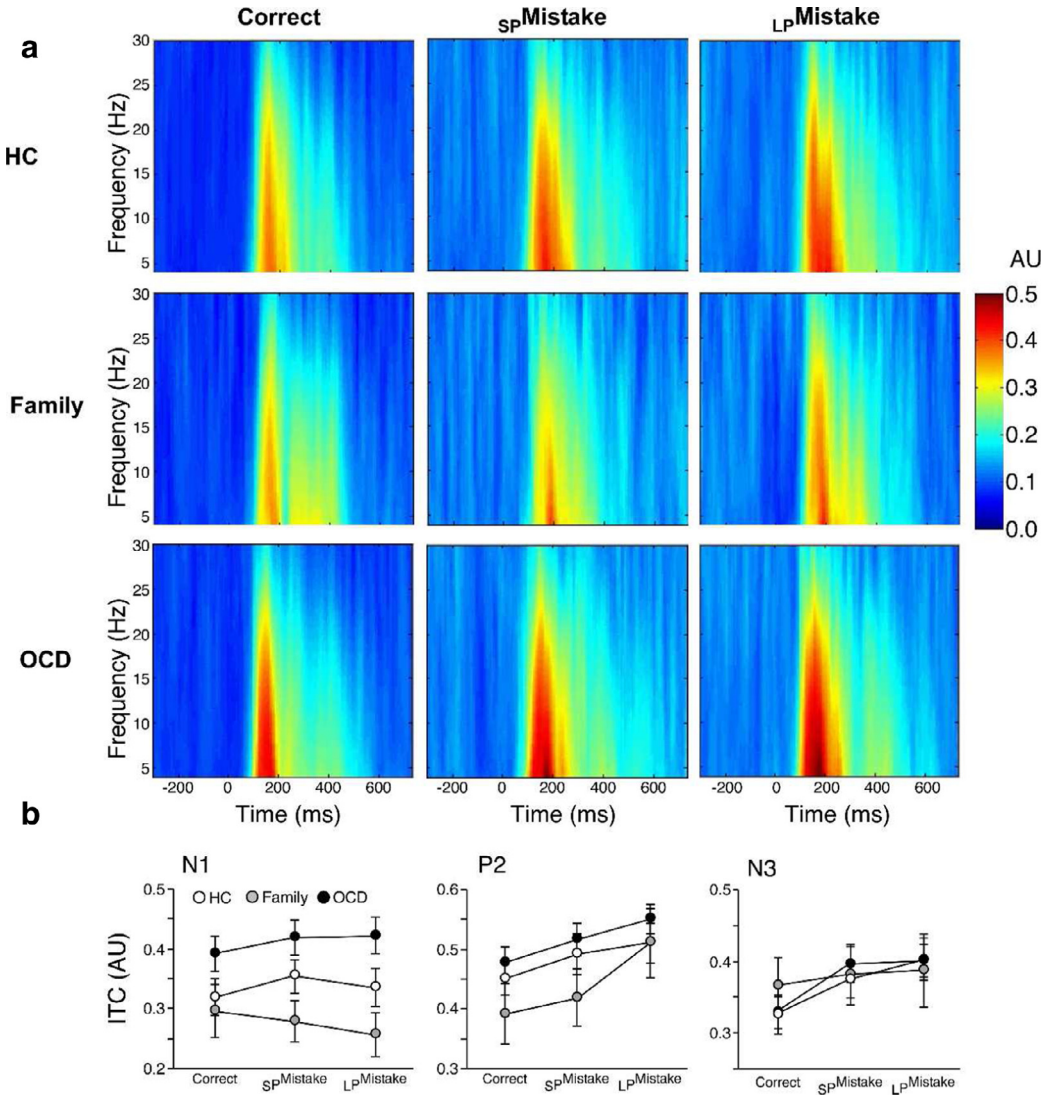

Fig. 5 Inter-trial coherence in the Equation task. (a) Wavelets representing ITC of the different groups in the different conditions during the N1 peak of the PERTA response. (b) Mean ± SEM of the ITC of the different groups in the different conditions during the N1, P2, and N3 peaks.

medications, which might affect relevant brain processes and consequently our results. This is especially true with regard to the PERTA signal, as the ERN signal was found not to be influenced by medications (Stern et al., 2010).

Taken together, our results suggest that OCD is associate with heightened alertness to mistakes. Notably, our study shows that this hyper-alertness is not restricted to actions nor to any OCD-relevant content (e.g., contamination, morality, responsibility) but rather to the mere detection of discrepancies from expectations. Future studies may determine if the combination of ERN and PERTA can be used as a biomarker of OCD, as the specificity of the ERN alone to OCD is challenged similar findings in anxiety and affective disorders (Endrass and Ullsperger, 2014).

Declaration of competing interest

The authors declare no conflict of interests

CRediT authorship contribution statement

L. Carmi: Conceptualization, Writing - original draft, Formal analysis. **U. Alyagon:** Methodology, Formal analysis. **N. Barnea-Ygael:** Visualization, Formal analysis. **J. Zohar:** Conceptualization, Writing - original draft. **A. Zangen:** Conceptualization, Writing - original draft. **R. Dar:** Conceptualization, Writing - original draft.

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