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Activating attachment memories affects Default Mode Network in a non-clinical sample with perceived dysfunctional parenting: an EEG functional connectivity study

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Abstract

Dysfunctional parenting constitutes a factor of psychopathological vulnerability affecting development both at neurobiological and psychological level. The default mode network (DMN), a large scale network for brain functional integration, is supposed to play a crucial role in those psychological functions altered by dysfunctional parenting. Here we investigate electroencephalography DMN functional connectivity in relation to perceived dysfunctional parenting (PDP) in a non-clinical sample. We hypothesized that participants with high PDP would exhibit decreased DMN connectivity after the activation of attachment memories. Our results support this hypothesis: participants with high PDP showed a decrease of theta connectivity between left temporoparietal junction and right anterior cingulate cortex after the activation of attachment memories, and, compared to participants with low PDP, showed a decrease of delta connectivity in the same brain areas. We interpret these decreased DMN connectivity in participants with high PDP as the "neurophysiological signature" of the impaired ability to mentalize their own relational experiences with significant others after the activation of early attachment memories. Thus, the activation of attachment memories in individuals exposed to dysfunctional parenting could lead to a transitory failure of functional brain connectivity and consequent disturbance of high integrative mental functions, such as emotional regulation and mentalization.

Keywords: Attachment, Default mode network, Dysfunctional parenting, Electroencephalography, Functional connectivity, Mentalization

Introduction

Dysfunctional parenting, such as very low care, emotional abuse and high overprotection, has been compared to others forms of child maltreatment [1-5]. Consistently, a significant and increasing body of evidence suggests that dysfunctional and/or neglectful parenting, like other forms of early relational trauma, is one of the major risk factor and negative prognostic cause for almost all psychiatric disorders [6-9]. Indeed, regardless of specific diagnosis, it has been reported that dysfunctional parenting constitutes a factor of psychopathological vulnerability affecting development both at neurobiological and psychological level [2, 6-8, 10-13]. Among the most common psychopathological consequences related to dysfunctional parenting there are emotive disorders and dysregulation [14, 15], alterations in inhibitory control and executive functions [10], cognitive and consciousness disturbances [2, 16, 17], self identity and self agency alterations [18, 19], mentalization dysfunctions [5, 20], relational problems and low social competence [21, 22]. Some scholars have hypothesized that a significant amount of these psychopathological disturbances have in common a lack of mental integration produced by dysfunctional parenting [2, 16, 23, 24].

Under a neurobiological point of view it has been supposed that the default mode network (DMN), a crucial large scale network for brain functional integration [25-27], plays an important role in those psychological functions altered by dysfunctional parenting [28-31]. Consistently, the DMN and its subcomponents alterations are frequently reported in people with dysfunctional parenting and other forms of child maltreatment [8, 12].

One of the most intriguing issue in this area is that clinical observations and empirical research data lead to consider that some of these disturbances, such as emotive and behavioural dysregulation, dissociative symptoms, mentalization disruption, relational problems, are not stable symptoms, but may emerge when triggered by socio-emotional stimuli like the activation of early attachment memories [16, 24, 32]. According to attachment theory and its subsequent clinical applications, the automatic and implicit (i.e., unconscious) activation of attachment relational memories in

individuals with histories of neglect or maltreatment in childhood could trigger disintegrative psychopathological process that leads to typical psychopathology related to dysfunctional parenting [2, 23, 24].

For this reason the aim of the present study was to investigate electroencephalography DMN functional connectivity in relation to the quality of the perceived dysfunctional parenting (PDP), i.e. the self-reported experiences of neglect, abuse and/or overprotection within the relationships with one's parents [33-35], both in resting state (RS) and after the activation of attachment memories using the Adult Attachment Interview as a trigger (AAI) [36, 37] in a non-clinical sample. Based on empirical data and clinical grounds, we hypothesized that participants with PDP, compared to participants without PDP, would exhibit decreased DMN connectivity after the activation of attachment memories.

Materials and Methods

Participants

Participants were 50 students (fourteen men, mean age: 22.62 ± 2.41 years) recruited through advertisements posted in the university. The enrollment lasted from October 2017 to May 2018. Study participants contributed voluntarily and anonymously after providing informed consent. They did not receive payment or any other compensation (i.e., academic credit). Inclusion criteria were: age between 18 and 30 years, both genders. Exclusion criteria were: history of psychiatric disease and/or neurologic diseases; head trauma; left handedness; assumption of Central Nervous System active drugs in the two weeks prior to assessment. A checklist with dichotomous items was used to assess inclusion/exclusion criteria and socio-demographic data.

After receiving information about the aim of the study, all participants provided a written consent to participate in the study that was performed according to the Helsinki declaration standards. The research was approved by the European University's ethic review board.

Procedure

After providing the written informed consent, all participants were administered the Measure of Parental Style (MOPS) [38] and the Brief Symptom Inventory (BSI) [39]. Furthermore, in order to identify the presence of past and/or current psychiatric disorders, during the intake visit, participants were asked screening questions according to a checklist prepared for a previous study [40].

On a separate day from the self-report assessment, all participants underwent the Adult Attachment Interview (AAI) [37], a semi-structured interview able to activate the attachment system by the retrieval of childhood emotional and relational memories of past attachment experiences [37, 41]. Rigorous psychometric testing and meta-analyses of the AAI demonstrate stability and discriminant and predictive validity in both clinical and nonclinical populations [42, 43]. In the present study, the AAI was used as "trigger stimulus" of the attachment behavioral system. Indeed, previous studies demonstrated that the AAI is able to alter psychophysiological parameters related to the emotion regulation of people with different attachment styles [36, 44, 45] and to modify the cortical functional connectivity related to the retrieval of early attachment memories in both healthy and clinical subjects [16].

Trained clinical psychologists (LP) administered the AAI in a quiet and comfortable room. EEG recordings were performed before (Pre-AAI condition) and immediately after (i.e., about 8-10 minutes for each participant) the interview (Post-AAI condition). The interviews lasted on average one hour and 30 minutes.

Questionnaire

The MOPS [38] is the redefined version of the Parental Bonding Instrument [46] and it is composed by 30 items which separately investigate mother' (15 items) and father' (15 items) parental styles. Items are scored on a 4-point Likert scale (from "not true at all" to "extremely true") and grouped in three dimensions for each parent, confirmed through principal components analysis

123 [38]: indifference, over-control, and abuse. Higher scores reflect higher self-reported experiences of
124 neglect, abuse and/or overprotection during the first 16 years of life. The MOPS has been used
125 extensively in clinical research [9, 34, 47] and it was developed to overcome some negative aspects
126 (e.g., low clarity of several items) of the original version [9]. Satisfactory psychometric properties
127 have been reported in the original validation study [38]. Furthermore, good cross-cultural adaptation
128 has been observed [48, 49]. In the present research, the Italian version of the scale has been used
129 [48] and the Cronbach's alpha in the present sample was 0.88 for the 30-item MOPS total scores.
130 The BSI [39] is the short version of the Symptom Checklist-90R [50] and it is composed by
131 53 items evaluating a broad range of psychological symptoms during the past seven days. Items are
132 scored on a 4-point Likert scale ranging from 0 (not at all) to 4 (extremely) and grouped in 9
133 primary symptom dimensions: somatization, obsession-compulsion, interpersonal sensitivity,
134 depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. A measure of
135 general level of psychopathology, the global severity index (GSI), is also calculated using the sums
136 for the nine symptom dimensions (higher scores reflects more self-reported symptoms). The BSI is
137 widely used in clinical research and it is characterized by good psychometric properties [51]. In the
138 present study, the Italian version of the scale was used [52] and the Cronbach's alpha in the present
139 sample was 0.94 for the GSI.
140
141 *EEG recordings*
142 Resting State (RS) EEG was recorded using the Micromed System Plus digital EEGraph
143 (Micromed© S.p.A., Mogliano Veneto, TV, Italy) in the European University EEG Lab, with each
144 participants sitting in a comfortable armchair, with his/her eyes closed, in a quiet, semi-darkened
145 silent room for 5 minutes. In order to avoid alcohol and or caffeine effects on EEG data,
146 participants were asked to refrain from drinking alcohol and caffeine for 4 to 6 hours immediately
147 before their EEG recordings.

EEG recordings included 31 standard scalp leads, positioned according to the 10-20 system (recording sites: Fp1, AF3, F3, FC1, C3, CP1, P3, PO3, O1, F7, FC5, T3, CP5, T5, Fz, Cz, Pz, Fp2, AF4, F4, FC2, C4, CP2, P4, PO4, O2, F8, FC6, T4, CP6, T6), and the Electrocardiography (ECG). The reference electrodes were placed on the linked mastoids. Impedances were kept below 5KΩ before starting the recording and checked again at the end of the experimental recording. Sampling frequency was 256 Hz; A/D conversion was made at 16 bit; pre-amplifiers amplitude range was ±3200 and low-frequency pre-filters were set at 0.15 Hz. The following band-pass filters were used: HFF= 0.2 Hz; LFF= 128 Hz. In the present study the following frequency bands was considered: delta (0.5–4 Hz); theta (4.5–7.5 Hz); alpha (8–12.5 Hz); beta (13–30 Hz); gamma (30.5–60 Hz).

Details about artifact rejection have been described elsewhere [40]. Briefly, visual artifact rejection (e.g., cap adjustment) was firstly performed on the raw EEG trace. These segments were removed, and then independent component analysis (ICA) was applied to EEG recordings to identify and remove non-cerebral artifacts (i.e., eye and muscular movements, cardiac pulses) before data analysis. Although it has been reported that ICA correction may affect EEG connectivity [53], correcting artifacts using this procedure is widely used in EEG phase synchronization studies [54-56]. Furthermore, several reports [54-56] documented no significant modifications of EEG coherence data after ICA correction.

The minimum length of the artifact-free EEG recording included in the analysis was 180 seconds (even if not consecutive) for each participant for each condition (i.e., pre-AAI and post-AAI).

Connectivity analysis

All EEG analysis were performed using the exact Low Resolution Electromagnetic Tomography software (eLORETA), a validated tool for localizing brain electric activity based on multichannel surface EEG recordings [57]. The eLORETA software is characterized by a satisfactory localization agreement with different multi-modal imaging techniques, and it is a

suitable tool for DMN assessment [58]. The connectivity analysis were performed using the lagged phase synchronization formula [59]. This algorithm has been widely used to assess EEG functional connectivity, and it is characterized by several advantages (e.g., it is resistant to non-physiological artifacts) [59]. Although functional magnetic resonance imaging (fMRI) is commonly used to investigate the functional connectivity of DMN, recent studies have shown that EEG is also suitable for investigating the functional properties of this network.

According to previous EEG connectivity studies [29, 30, 40, 60], in order to evaluate functional connectivity in the DMN, 12 Regions of Interest (ROIs) were selected (Figure 1) and the 'single nearest voxel' option (i.e., each ROI consisted of a single voxel, the closest to each seed) was chosen (detailed DMN Montreal Neurological Institute and Talairach coordinates can be found in [40]). Briefly, the "ROI-maker#2 method" available in the eLORETA software has been selected and, starting from 42 Brodmann Areas (BAs) in each hemisphere provided by the software [61], 12 ROIs were defined according Thatcher et al. [58].

The eLORETA calculated the lagged phase synchronization values between all these ROIs (i.e., 144 connections) and the source reconstruction algorithm [57].

Statistical analysis

In order to reveal groups of subjects with high and low PDP (i.e., PDP+ and PDP- groups), a Two Step Cluster Analysis procedure was performed using MOPS sub-scales scores. Cluster solutions was assessed using Schwarz's Bayesian Criterion (BIC) as clustering criterion [62]. Chi-squared tests ($\chi 2$), and Mann–Whitney's U tests were used to investigate differences between clusters, respectively for dichotomous and dimensional variables.

EEG connectivity analysis was performed using the eLORETA software. Between and within comparisons were performed for each frequency band. Specifically the following statistical comparisons were performed: i) Pre-AAI PDP+ vs Pre-AAI PDP-, ii) Post-AAI PDP+ vs Pre-AAI PDP+, iii) Post-AAI PDP- vs Pre-AAI PDP-, iv) Post-AAI PDP+ vs Pre-AAI PDP-. All

comparisons were performed using the statistical non-parametric mapping (SnPM) methodology provided by the eLORETA software (i.e, a Fisher's permutation test) [63]. In order to avoid family-wise type-I errors, the non-parametric randomization procedure (supplied by the eLORETA software), was performed for the correction of multiple comparison [63]. For all comparisons, the eLORETA software provides experimental values of T, corresponding to a significance of $p< 0.01$ and $p< 0.05$.

Finally, Spearman's *rho* correlation coefficients were reported as measures of associations among MOPS subscales scores, GSI, and any significant EEG connectivity data observed in the between comparisons. Cluster Analysis, Chi-squared tests, Mann–Whitney's U tests, correlation analyses were performed using IBM SPSS Statistics for Windows, version 23.0. The use of nonparametric tests was chosen because none of the present variables were normally distributed (Shapiro–Wilk test, $p< 0.05$).

Results

The Two Step Cluster Analysis procedure indicated a 2-group solution (BIC change= −36.01; Ratio of distance measures= 3.38). 34 % of the sample (N= 17) was included in the first cluster, and 66 % (N= 33) was included in cluster 2. Compared to individuals included in cluster 2 (i.e., PDP- group), subjects included in cluster 1 (i.e., PDP+ group) had significantly higher scores in all PDP sub-subscales. Thus, cluster 1 is mostly characterized by individuals reporting higher PDP. Furthermore, compared to the individuals with low PDP, those with high PDP had a significantly higher scores in the GSI and in all BSI subscales, with the exception of interpersonal sensitivity, phobic anxiety and psychoticism subscales. Detailed bivariate analyses are listed in Table 1.

EEG recordings suitable for the analysis were obtained for all participants. Qualitative visual evaluation of the EEG recordings, performed by a trained neurophysiologist, showed no relevant modifications of the background rhythm frequency (e.g., epileptic discharges).

Furthermore, no relevant modifications of EEG signal (e.g., evidence of sleepiness) during the recordings were detected. The average time analyzed for the present sample was 283 ± 14 sec and 276 ± 15 respectively for cluster 1 and cluster 2 subjects in pre-AAI condition and 291 ± 12 sec and 277 ± 19 in post-AAI condition.

Connectivity results

In the between-groups comparison (PDP+ vs PDP-) for the Pre-AAI condition, the thresholds for significance were T= ±2.73 corresponding to $p< 0.05$, and T= ±3.19 corresponding to $p< 0.01$. In this condition, no significant modifications were observed between groups (Figure 2; Panel A).

In the within-group comparison (Post-AAI vs. Pre-AAI) for the PDP+ group, the thresholds for significance were T= ±3.99 corresponding to $p< 0.05$, and T= ±4.63, corresponding to $p< 0.01$. In this comparison, significant modifications were observed in the theta frequency (Figure 3; Panel A). Compared to Pre-AAI condition, PDP+ individuals showed in Post-AAI condition a decrease of theta connectivity between left Temporoparietal Junction (TPJ; ROI 11) and right Anterior Cingulate Cortex (ACC; ROI 8) (T= -4.09, $p= 0.037$). No significant differences were observed in the other frequency bands, although a significant trend was observed between left TPJ and right ACC also in the delta band (T= -3.76, $p= 0.08$).

In the within-group comparison (Post-AAI vs. Pre-AAI) for the PDP- group, the thresholds for significance group were T= ±3.54 corresponding to $p< 0.05$, and T= ±4.03, corresponding to $p< 0.01$. In this comparison, significant modifications were observed in the alpha frequency band (Figure 3; Panel B). Compared to Pre-AAI condition, PDP- individuals showed in Post-AAI condition an increase of alpha connectivity between right TPJ (ROI 12) and both right and left Posterior Cingulate Cortex (PCC; ROI 6 and ROI 5) (respectively T= 3.56; $p= 0.047$ and T= 3.71; $p= 0.030$). No significant differences were observed in the other frequency bands

In the between-groups comparison (PDP+ vs PDP-) for the Post-AAI condition, the thresholds for significance were T= ±2.92 corresponding to $p< 0.05$, and T= ±3.47 corresponding to

$p < 0.01$. Significant modifications were observed in the delta band (Figure 3; Panel B). Compared to PDP- individuals, PDP+ participants showed a decrease of delta connectivity between left TPJ (ROI 11) and right ACC (ROI 8) (T= -3.29; $p = 0.018$). No significant differences were observed in the other frequency bands.

Association among EEG functional connectivity data, MOPS and GSI scores

MOPS total score was negatively related with the strength of delta connectivity between left TPJ and right ACC (*rho*= -0.28; $p = 0.048$). Furthermore, the strength of delta connectivity observed after the AAI between left TPJ and right ACC was negatively related with both maternal indifference (*rho*= -0.36; $p = 0.010$) and maternal over-control (*rho*= -0.33; $p = 0.020$) sub-scale. Although GSI was positively related with all MOPS sub-scales, no significant correlation was observed between EEG connectivity data and psychopathological score. Detailed correlations are reported in Table 2.

Discussion

The a priori hypothesis of the present study was that participants with high PDP (i.e., PDP+ group), compared to participants with low or without PDP (i.e., PDP- group), would exhibit decreased DMN connectivity after the activation of attachment memories. Our results support this hypothesis. Indeed, after the activation of attachment memories triggered by the AAI, PDP+ participants (within-group comparison) showed a decrease of theta connectivity between left TPJ and right ACC. Furthermore, after the administration of the AAI, compared to PDP- participants, PDP+ individuals showed a decrease of delta connectivity in the same brain areas (i.e., left TPJ and right ACC). Consistently with our hypothesis, these connectivity modifications were observed exclusively after the activation of early attachment memories as no significant DMN connectivity differences were detected in the between-groups comparison before the administration of the AAI.

277 Our results are in line with previous studies reporting DMN alterations in people with
278 dysfunctional parenting and other forms of early relational adverse experiences [8, 12]. The DMN is
279 thought to be involved in several higher-order integrative mental functions such as self-
280 consciousness, self-processing and episodic memory [58, 64] that are supposed to be impaired by
281 dysfunctional parenting. This network has been conceptualized as a distributed and dynamic brain
282 system composed by a set of interacting hubs and subsystems with specific functions [26, 27].
283 Specifically, the dorsal medial subsystem, which includes several brain areas such as the TPJ and
284 dorsal medial prefrontal cortex, has been associated with mentalization, social cognition as well as
285 with semantic/conceptual processing. Conversely, the medial temporal subsystem, which involves
286 anatomical regions such as hippocampal formation, the retrosplenial cingulate cortex and ventral
287 medial prefrontal cortex, has been related with autobiographical thought, episodic memory and
288 contextual retrieval. Finally, the midline hubs of the DMN, namely the mPFC, the rostral anterior
289 cingulate and the posterior cingulate cortex, are involved across a wide range of self-related
290 processes integrating the dorsal medial and medial temporal subsystem [26, 27].
291 Therefore, taking into account DMN related functions and processes as well as the type of
292 mental processes elicited by the AAI, we may speculate that the decreased DMN connectivity
293 observed between left TPJ and right ACC in the PDP+ participants is the "neurophysiological
294 signature" of the impaired ability to mentalize their own relational experiences with significant
295 others after the activation of early attachment memories.
296 Indeed, the role of both left and right TPJ and of the ACC in mentalization [i.e., the ability to
297 attribute mental states to oneself and to others and to understand that others have mental states
298 independent from one's own; see for example 65, 66, 67] is widely recognized in the literature [68-
299 70].
300 Our interpretation is also strengthened by the increase of DMN connectivity between right TPJ and
301 both right and left PCC observed in PDP- participants after the administration of the AAI. The PCC
302 is considered the crucial node of the DMN [71] and it is involved in several emotion and cognitive

processing [72], with critical relevance in maintaining a sense of self-consciousness and self-referential thoughts during RS [73]. It is also interesting to note that PDP- participants showed increased connectivity in the alpha frequency band, which is considered to be positively related to DMN activity as well as with spontaneous self-referential processes, such as mentalization [25]. Therefore, this result seems to support our interpretation according to which during the AAI participants are induced to mentalize their own relational experiences, presumably activating a set of self-related processes such as episodic and autobiographical memories.

Taken together, our results support both clinical observations and experimental results according to which the alterations associated with PDP are not stable symptoms but may emerge when triggered by early attachment relational memories [16, 23, 32]. These results seem to be also partially consistent with MRI studies indicating that early-life adversity may be associated with structural alterations in brain white matter, specifically in the cingulate cortex [11]. According to our data, it is possible to hypothesize that, in individuals with early adverse relational experiences, the structural connectivity deficit becomes functionally evident and clinically symptomatic when the system is overloaded by affective and cognitive attachment related stimuli. Moreover, although it was not among the goals of the present research, future work could investigate whether and to what extent the attachment style can influence the DMN functional connectivity. In fact, the same adverse experiences can lead to very different development paths and the possibility that different attachment styles may be associated with different patterns of alteration of functional connectivity cannot be excluded in principle.

Another result rising from this study is the usefulness of MOPS in detecting the psychopathological vulnerability related to the early relational adverse experiences. In our opinion, MOPS based screening could be useful in the clinical practice where the clients report their own perception of parental way to protect and control, and combined with EEG connectivity seems to be a useful and reliable tool to improve our understanding on the psychopathological processes underlying PDP.

In spite of our interesting results, the study has some limitations that should be considered. Firstly, the sample size is limited, which may affect the generalizability of the results. Furthermore, our sample included mostly female participants, and previous studies showed sex differences in EEG brain activity during RS condition [74].

Secondly, we have investigated PDP and psychopathology using self-report measures, which are known to be potentially affected by social desirability. Thirdly, we used scalp EEG recordings, which have an intrinsic limit in space resolution. Finally, we have investigated DMN functional connectivity after AAI, which make our interpretations specific to the activation of attachment memories. It is possible that others not-related attachment triggers (e.g., viewing negative emotional facial expressions) may be associated with different DMN alterations in high PDP individuals. Although these ideas are purely hypothetical, they might be useful in guiding future research.

Despite these limitations, to the best of our knowledge, this is the first study which investigated the association between DMN EEG functional connectivity and PDP both in RS and after the activation of attachment memories. In conclusion, our results seem to support the hypothesis according to which the activation of attachment memories in individuals exposed to dysfunctional parenting and other forms of early relational adverse experiences could lead to a transitory failure of functional brain connectivity and consequent disturbance of high integrative mental functions. These transitory alterations might explain, even partially, the emergence of some typical psychopathological symptoms such as emotional dysregulation, dissociative symptoms, inhibitory control and executive functions disturbances, self identity and self agency and mentalization impairments [10, 16, 23, 24]. Therefore, our result also highlights the possibility of developing new therapeutic approaches focused on the self neuro-modulation, such as alpha/theta neurofeedback, which may increases mentalization and DMN EEG connectivity [60].

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Reference

[1] N. Draijer, W. Langeland, Childhood trauma and perceived parental dysfunction in the etiology of dissociative symptoms in psychiatric inpatients, Am J Psychiatry 156 (3) (1999) 379-385.

[2] L. Dutra, J.F. Bureau, B. Holmes, A. Lyubchik, K. Lyons-Ruth, Quality of early care and childhood trauma: a prospective study of developmental pathways to dissociation, J Nerv Ment Dis 197 (6) (2009) 383-390.

[3] M.H. Teicher, J.A. Samson, Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes, Am J Psychiatry 170 (10) (2013) 1114-1133.

[4] B. Farina, G. Liotti, Does a dissociative psychopathological dimension exist? A review on dissociative processes and symptoms in developmental trauma spectrum disorders, Clin Neuropsychiatry 10 (1) (2013) 11-18.

[5] F.J. Infurna, C.T. Rivers, J. Reich, A.J. Zautra, Childhood trauma and personal mastery: their influence on emotional reactivity to everyday events in a community sample of middle-aged adults, PLoS One 10 (4) (2015) e0121840.

[6] A.R. Lima, M.F. Mello, J. Mari Jde, The role of early parental bonding in the development of psychiatric symptoms in adulthood, Curr Opin Psychiatry 23 (4) (2010) 383-387.

[7] M.H. Teicher, J.A. Samson, C.M. Anderson, K. Ohashi, The effects of childhood maltreatment on brain structure, function and connectivity, Nat Rev Neurosci 17 (10) (2016) 652-666.

[8] E.J. McCrory, M.I. Gerin, E. Viding, Annual Research Review: Childhood maltreatment, latent vulnerability and the shift to preventative psychiatry - the contribution of functional brain imaging, J Child Psychol Psychiatry 58 (4) (2017) 338-357.

[9] R. Icick, S. Lauer, L. Romo, G. Dupuy, J.P. Lepine, F. Vorspan, Dysfunctional parental styles perceived during childhood in outpatients with substance use disorders, Psychiatry Res 210 (2) (2013) 522-528.

[10] P. Pechtel, D.A. Pizzagalli, Effects of early life stress on cognitive and affective function: an integrated review of human literature, Psychopharmacology (Berl) 214 (1) (2011) 55-70.

[11] P.E. Lutz, A. Tanti, A. Gasecka, S. Barnett-Burns, J.J. Kim, Y. Zhou, G.G. Chen, M. Wakid, M. Shaw, D. Almeida, M.A. Chay, J. Yang, V. Lariviere, M.N. M'Boutchou, L.C. van Kempen, V. Yerko, J. Prud'homme, M.A. Davoli, K. Vaillancourt, J.F. Theroux, A. Bramoulle, T.Y. Zhang, M.J. Meaney, C. Ernst, D. Cote, N. Mechawar, G. Turecki, Association of a History of Child Abuse With Impaired Myelination in the Anterior Cingulate Cortex: Convergent Epigenetic, Transcriptional, and Morphological Evidence, Am J Psychiatry 174 (12) (2017) 1185-1194.

[12] N.S. Philip, L.H. Sweet, A.R. Tyrka, L.H. Price, R.F. Bloom, L.L. Carpenter, Decreased default network connectivity is associated with early life stress in medication-free healthy adults, Eur Neuropsychopharmacol 23 (1) (2013) 24-32.

[13] J.R. Measelle, J. David, J.C. Ablow, Increased levels of inflammation among infants with disorganized histories of attachment, Behav Brain Res 325 (Pt B) (2017) 260-267.

[14] E.C. Dunn, K. Nishimi, S.H. Gomez, A. Powers, B. Bradley, Developmental timing of trauma exposure and emotion dysregulation in adulthood: Are there sensitive periods when trauma is most harmful?, J Affect Disord 227(2018) 869-877.

[15] S. Kench, H.J. Irwin, Alexithymia and childhood family environment, J Clin Psychol 56 (6) (2000) 737-745.

[16] B. Farina, A.M. Speranza, S. Dittoni, V. Gnoni, C. Trentini, C.M. Vergano, G. Liotti, R. Brunetti, E. Testani, G. Della Marca, Memories of attachment hamper EEG cortical connectivity in dissociative patients, Eur Arch Psychiatry Clin Neurosci 264 (5) (2014) 449-458.

[17] E. McCrory, S.A. De Brito, E. Viding, Research review: the neurobiology and genetics of maltreatment and adversity, J Child Psychol Psychiatry 51 (10) (2010) 1079-1095.

[18] E.A. Carlson, T.M. Yates, L.A. Sroufe, Dissociation and the Development of the Self. In: P. Dell, J.A. O'Neil (Eds.), Dissociation and Dissociative Disorders: DSM-V and beyond, Routledge, New York, 2009, pp. 39-52.

[19] S. Pallini, A. Alfani, L. Marech, F. Laghi, Unresolved attachment and agency in women victims of intimate partner violence: A case-control study, Psychol Psychother 90 (2) (2017) 177-192.

[20] M. Brune, S. Walden, M.A. Edel, G. Dimaggio, Mentalization of complex emotions in borderline personality disorder: The impact of parenting and exposure to trauma on the performance in a novel cartoon-based task, Compr Psychiatry 64(2016) 29-37.

[21] A. van Dijke, J.A.B. Hopman, J.D. Ford, Affect dysregulation, psychoform dissociation, and adult relational fears mediate the relationship between childhood trauma and complex posttraumatic stress disorder independent of the symptoms of borderline personality disorder, Eur J Psychotraumatol 9 (1) (2018) 1400878.

[22] G. Attili, P. Vermigli, A. Roazzi, Children's social competence, peer status, and the quality of mother-child and father-child relationships: A multidimensional scaling approach, Eur Psychol 15 (1) (2010) 23-33.

[23] G. Liotti, B. Farina, Painful Incoherence: The Self in Borderline Personality Disorder. In: M. Kyrios, R. Moulding, M. Nedeljkovic, S.S. Bhar, G. Doron, M. Mikulincer (Eds.), The self in understanding and treating psychological disorders, Cambridge University Press, Cambridge, 2016, pp. 169-178.

[24] R. Meares, The Dissociation Model of Borderline Personality Disorder, Norton Professional Books, New York, 2012.

[25] G.G. Knyazev, EEG correlates of self-referential processing, Front Hum Neurosci 7(2013) 264.

[26] J.R. Andrews-Hanna, The brain's default network and its adaptive role in internal mentation, Neuroscientist 18 (3) (2012) 251-270.

[27] J.R. Andrews-Hanna, J. Smallwood, R.N. Spreng, The default network and self-generated thought: component processes, dynamic control, and clinical relevance, Ann N Y Acad Sci 1316(2014) 29-52.

[28] P. Qin, G. Northoff, How is our self related to midline regions and the default-mode network?, Neuroimage 57 (3) (2011) 1221-1233.

[29] C. Imperatori, G. Della Marca, R. Brunetti, G.A. Carbone, C. Massullo, E.M. Valenti, N. Amoroso, G. Maestoso, A. Contardi, B. Farina, Default Mode Network alterations in alexithymia: an EEG power spectra and connectivity study, Sci Rep 6(2016) 36653.

[30] B. Farina, G. Della Marca, G. Maestoso, N. Amoroso, E.M. Valenti, G.A. Carbone, C. Massullo, A. Contardi, C. Imperatori, The Association among Default Mode Network Functional Connectivity, Mentalization, and Psychopathology in a Nonclinical Sample: An eLORETA Study, Psychopathology 51 (1) (2018) 16-23.

[31] X. Xie, S. Mulej Bratec, G. Schmid, C. Meng, A. Doll, A. Wohlschlager, K. Finke, H. Forstl, C. Zimmer, R. Pekrun, L. Schilbach, V. Riedl, C. Sorg, How do you make me feel better? Social cognitive emotion regulation and the default mode network, Neuroimage 134(2016) 270-280.

[32] B. Vai, L. Sforzini, R. Visintini, M. Riberto, C. Bulgarelli, D. Ghiglino, E. Melloni, I. Bollettini, S. Poletti, C. Maffei, F. Benedetti, Corticolimbic Connectivity Mediates the Relationship between Adverse Childhood Experiences and Symptom Severity in Borderline Personality Disorder, Neuropsychobiology 76 (2) (2017) 105-115.

[33] M.V. Torrado, S.S. Ouakinin, L. Bacelar-Nicolau, Alexithymia, Emotional Awareness and Perceived Dysfunctional Parental Behaviors in Heroin Dependents, Int J Ment Health Addiction 11 (6) (2013) 703-718.

[34] K. Fletcher, G. Parker, A. Bayes, A. Paterson, G. McClure, Emotion regulation strategies in bipolar II disorder and borderline personality disorder: differences and relationships with perceived parental style, J Affect Disord 157(2014) 52-59.

[35] K. Otani, A. Suzuki, Y. Matsumoto, T. Shirata, Link of negative core beliefs about the self with perceived dysfunctional parenting, Psychiatry Res 270(2018) 715-719.

[36] M. Dozier, R.R. Kobak, Psychophysiology in attachment interviews: converging evidence for deactivating strategies, Child Dev 63 (6) (1992) 1473-1480.

[37] C. George, N. Kaplan, M. Main, Adult Attachment Interview Protocol, (3rd ed). University of California at Berkekey, 1996.

[38] G. Parker, J. Roussos, D. Hadzi-Pavlovic, P. Mitchell, K. Wilhelm, M.P. Austin, The development of a refined measure of dysfunctional parenting and assessment of its relevance in patients with affective disorders, Psychol Med 27 (5) (1997) 1193-1203.

[39] L.R. Derogatis, N. Melisaratos, The Brief Symptom Inventory: an introductory report, Psychol Med 13 (3) (1983) 595-605.

[40] C. Imperatori, B. Farina, M. Adenzato, E.M. Valenti, C. Murgia, G.D. Marca, R. Brunetti, E. Fontana, R.B. Ardito, Default mode network alterations in individuals with high-trait-anxiety: An EEG functional connectivity study, J Affect Disord 246(2019) 611-618.

[41] G. Liotti, Trauma, dissociation and disorganized attachment: three strands of a single braid, Psychother Theor Res Pract Train 41(2004) 472-486.

[42] M.J. Bakermans-Kranenburg, M.H. Van IJzendoorn, A psychometric study of the Adult Attachment Interview: Reliability and discriminant validity, Dev Psychol 29 (5) (1993) 870-879.

[43] P. Ravitz, R. Maunder, J. Hunter, B. Sthankiya, W. Lancee, Adult attachment measures: a 25-year review, J Psychosom Res 69 (4) (2010) 419-432.

[44] M.D. Beijersbergen, M.J. Bakermans-Kranenburg, M.H. van Ijzendoorn, F. Juffer, Stress regulation in adolescents: physiological reactivity during the adult attachment interview and conflict interaction, Child Dev 79 (6) (2008) 1707-1720.

[45] G.I. Roisman, J.L. Tsai, K.H. Chiang, The emotional integration of childhood experience: physiological, facial expressive, and self-reported emotional response during the adult attachment interview, Dev Psychol 40 (5) (2004) 776-789.

[46] G. Parker, H. Tupling, L.B. Brown, A parental bonding instrument, Br J Med Psychol 52 (1) (1979) 1-10.

[47] S. Beshai, P. Parmar, Trait mindfulness may buffer against the deleterious effects of childhood abuse in recurrent depression: A retrospective exploratory study, Clin Psychol 23 (1) (2018) 1-11.

[48] A. Picardi, L. Tarsitani, A. Toni, A. Maraone, V. Roselli, E. Fabi, F. De Michele, I. Gaviano, M. Biondi, Validity and reliability of the Italian version of the Measure of Parental Style (MOPS), J Psychopathol 19 (1) (2013) 54-59.

[49] F.L. Baeza, M.A. Caldieraro, D.O. Pinheiro, M.P. Fleck, Translation and cross-cultural adaptation into Brazilian Portuguese of the Measure of Parental Style (MOPS)--a self-reported scale--according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recommendations, Rev Bras Psiquiatr 32 (2) (2010) 159-163.

[50] L. Derogatis, The SCL-90-R Manual, Clinical Psychometric Research Unit. Johns Hopkins University School of Medicine, Baltimore, MD., 1977.

[51] L.R. Derogatis, K.L. Savitz, The SCL-90-R, Brief Symptom Inventory, and Matching Clinical Rating Scales. In: M.E. Maruish (Ed.), The use of psychological testing for treatment planning and outcomes assessment Lawrence Erlbaum Associates Publishers, Mahwah, NJ, US, 1999, pp. 679-724.

[52] D. De Leo, G.B. Frisoni, R. Rozzini, M. Trabucchi, Italian community norms for the Brief Symptom Inventory in the elderly, Br J Clin Psychol 32 (Pt 2)(1993) 209-213.

[53] N.P. Castellanos, V.A. Makarov, Recovering EEG brain signals: artifact suppression with wavelet enhanced independent component analysis, J Neurosci Methods 158 (2) (2006) 300-312.

[54] X. Li, R. Ma, L. Pang, W. Lv, Y. Xie, Y. Chen, P. Zhang, J. Chen, Q. Wu, G. Cui, Y. Zhou, X. Zhang, Delta coherence in resting-state EEG predicts the reduction in cigarette craving after hypnotic aversion suggestions, Sci Rep 7 (1) (2017) 2430.

[55] M. Moazami-Goudarzi, J. Sarnthein, L. Michels, R. Moukhtieva, D. Jeanmonod, Enhanced frontal low and high frequency power and synchronization in the resting EEG of parkinsonian patients, Neuroimage 41 (3) (2008) 985-997.

[56] J.W. Kam, A.R. Bolbecker, B.F. O'Donnell, W.P. Hetrick, C.A. Brenner, Resting state EEG power and coherence abnormalities in bipolar disorder and schizophrenia, J Psychiatr Res 47 (12) (2013) 1893-1901.

[57] R.D. Pascual-Marqui, C.M. Michel, D. Lehmann, Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain, Int J Psychophysiol 18 (1) (1994) 49-65.

[58] R.W. Thatcher, D.M. North, C.J. Biver, LORETA EEG phase reset of the default mode network, Front Hum Neurosci 8(2014) 529.

[59] R.D. Pascual-Marqui, D. Lehmann, M. Koukkou, K. Kochi, P. Anderer, B. Saletu, H. Tanaka, K. Hirata, E.R. John, L. Prichep, R. Biscay-Lirio, T. Kinoshita, Assessing interactions in the brain with exact low-resolution electromagnetic tomography, Philos Trans A Math Phys Eng Sci 369 (1952) (2011) 3768-3784.

[60] C. Imperatori, G. Della Marca, N. Amoroso, G. Maestoso, E.M. Valenti, C. Massullo, G.A. Carbone, A. Contardi, B. Farina, Alpha/Theta Neurofeedback Increases Mentalization and Default Mode Network Connectivity in a Non-Clinical Sample, Brain Topogr 30 (6) (2017) 822-831.

[61] R.D. Pascual-Marqui, Review of Methods for Solving the EEG Inverse Problem, Int J Bioelectromagn 1 (1) (1999) 75-86.

[62] M. Pompili, M. Innamorati, Z. Rihmer, X. Gonda, G. Serafini, H. Akiskal, M. Amore, C. Niolu, L. Sher, R. Tatarelli, G. Perugi, P. Girardi, Cyclothymic-depressive-anxious temperament pattern is related to suicide risk in 346 patients with major mood disorders, J Affect Disord 136 (3) (2012) 405-411.

[63] T.E. Nichols, A.P. Holmes, Nonparametric permutation tests for functional neuroimaging: a primer with examples, Hum Brain Mapp 15 (1) (2002) 1-25.

[64] R.L. Buckner, J.R. Andrews-Hanna, D.L. Schacter, The brain's default network: anatomy, function, and relevance to disease, Ann N Y Acad Sci 1124(2008) 1-38.

[65] M. Adenzato, M. Brambilla, R. Manenti, L. De Lucia, L. Trojano, S. Garofalo, I. Enrici, M. Cotelli, Gender differences in cognitive Theory of Mind revealed by transcranial direct current stimulation on medial prefrontal cortex, Sci Rep 7(2017) 41219.

[66] M. Tettamanti, M.M. Vaghi, B.G. Bara, S.F. Cappa, I. Enrici, M. Adenzato, Effective connectivity gateways to the Theory of Mind network in processing communicative intention, Neuroimage 155(2017) 169-176.

[67] M. Adenzato, F. Garbarini, The *As If* in cognitive science, neuroscience and anthropology: a journey among robots, blacksmiths and neurons, Theory Psychol 16 (6) (2006) 747-759.

[68] A. Ciaramidaro, M. Adenzato, I. Enrici, S. Erk, L. Pia, B.G. Bara, H. Walter, The intentional network: how the brain reads varieties of intentions, Neuropsychologia 45 (13) (2007) 3105-3113.

[69] R.N. Spreng, R.A. Mar, A.S. Kim, The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis, J Cogn Neurosci 21 (3) (2009) 489-510.

[70] A. Abu-Akel, S. Shamay-Tsoory, Neuroanatomical and neurochemical bases of theory of mind, Neuropsychologia 49 (11) (2011) 2971-2984.

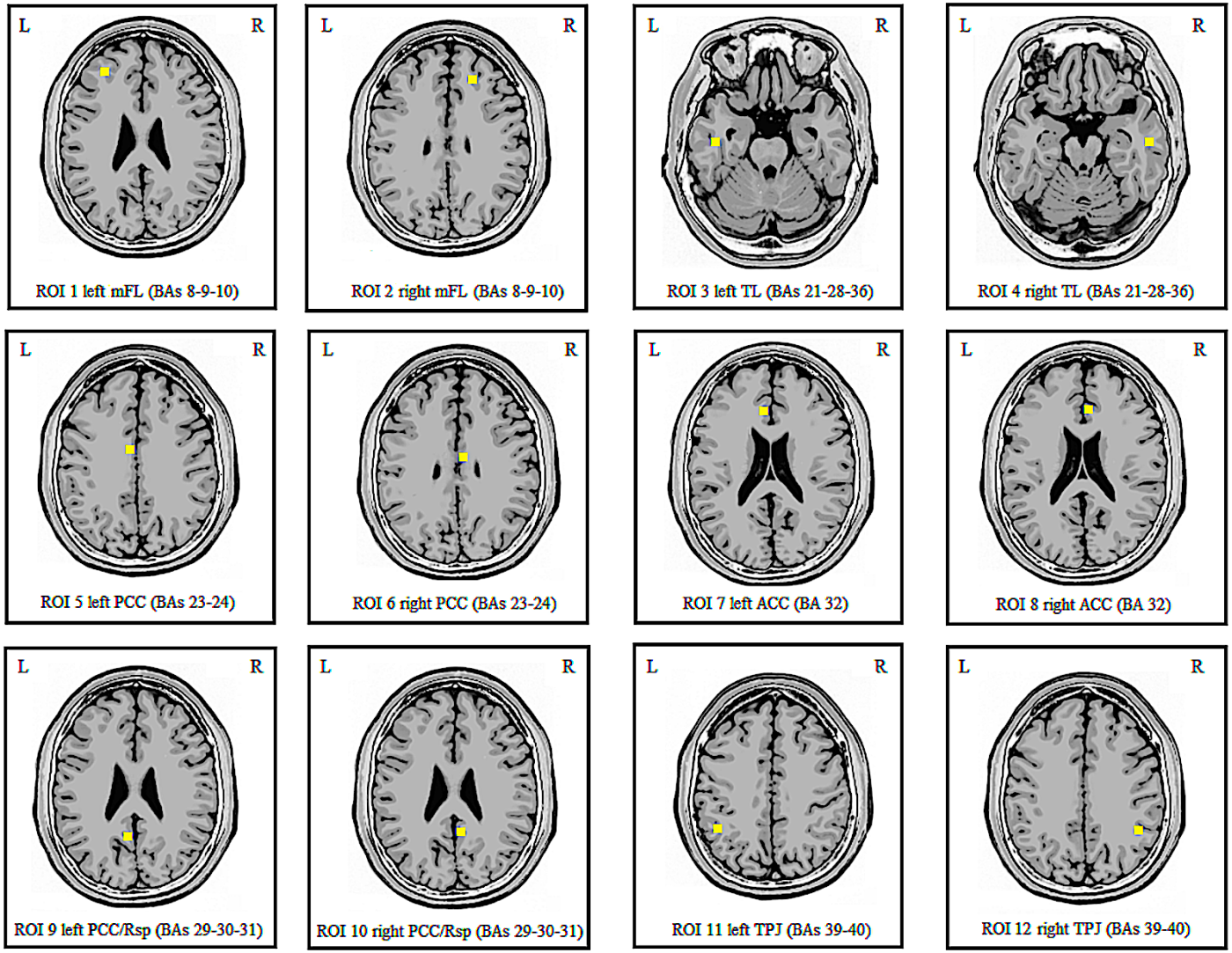
[71] R. Leech, S. Kamourieh, C.F. Beckmann, D.J. Sharp, Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control, J Neurosci 31 (9) (2011) 3217-3224.

[72] B.A. Vogt, D.M. Finch, C.R. Olson, Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions, Cereb Cortex 2 (6) (1992) 435-443.

[73] P. Fransson, G. Marrelec, The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis, Neuroimage 42 (3) (2008) 1178-1184.

[74] F. Miraglia, F. Vecchio, P. Bramanti, P.M. Rossini, Small-worldness characteristics and its gender relation in specific hemispheric networks, Neuroscience 310(2015) 1-11.

559 **Legend to figure 1.** Axial view of the Default Mode Network regions of interest.



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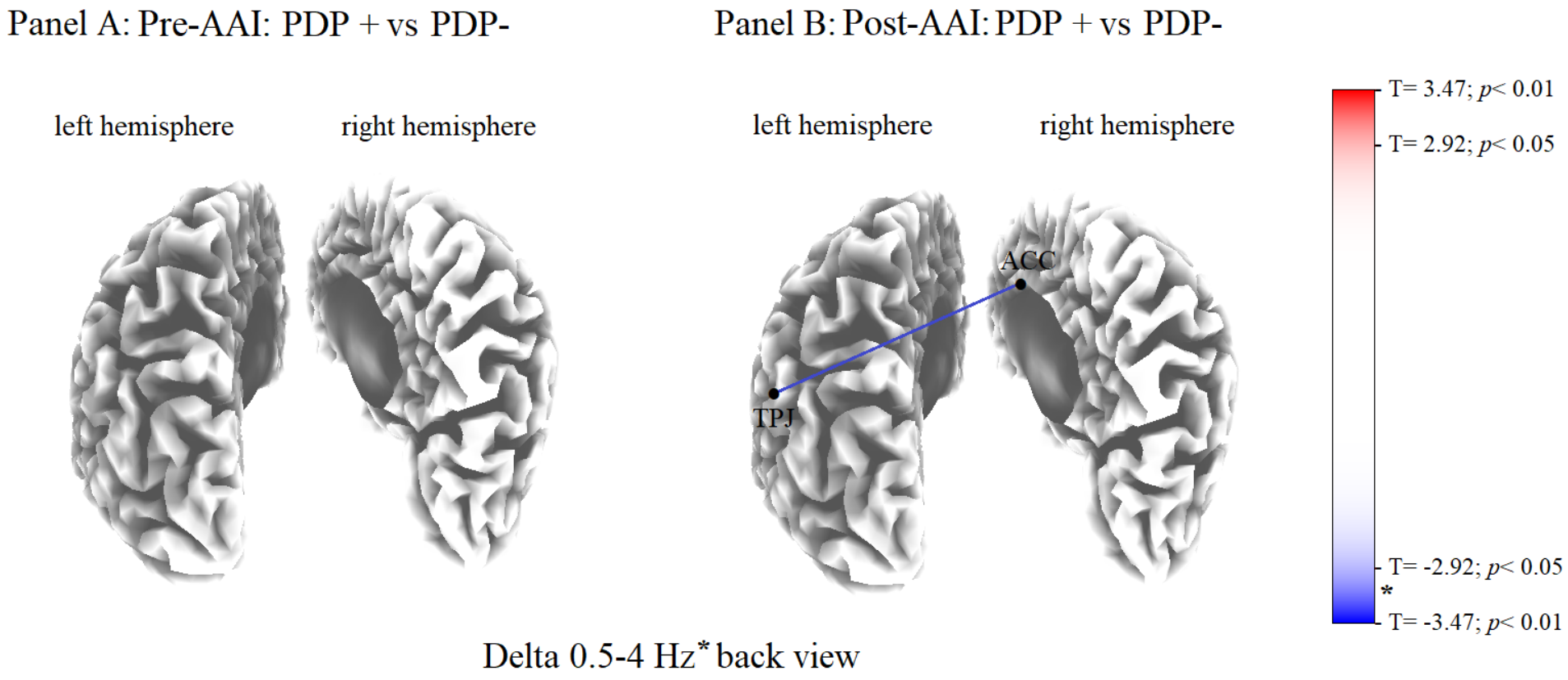
561 Abbreviation:L= left; R= right; ROI= region of interest; mFL= medial Frontal Lobe; BA (Brodmann area); TL= Temporal Lobe; PCC= Posterior Cingulate cortex; ACC=
562 Anterior Cingulate Cortex; PCC/Rsp= Posterior Cingulate/Retrosplenial cortex; TPJ= temporo-parietal junction

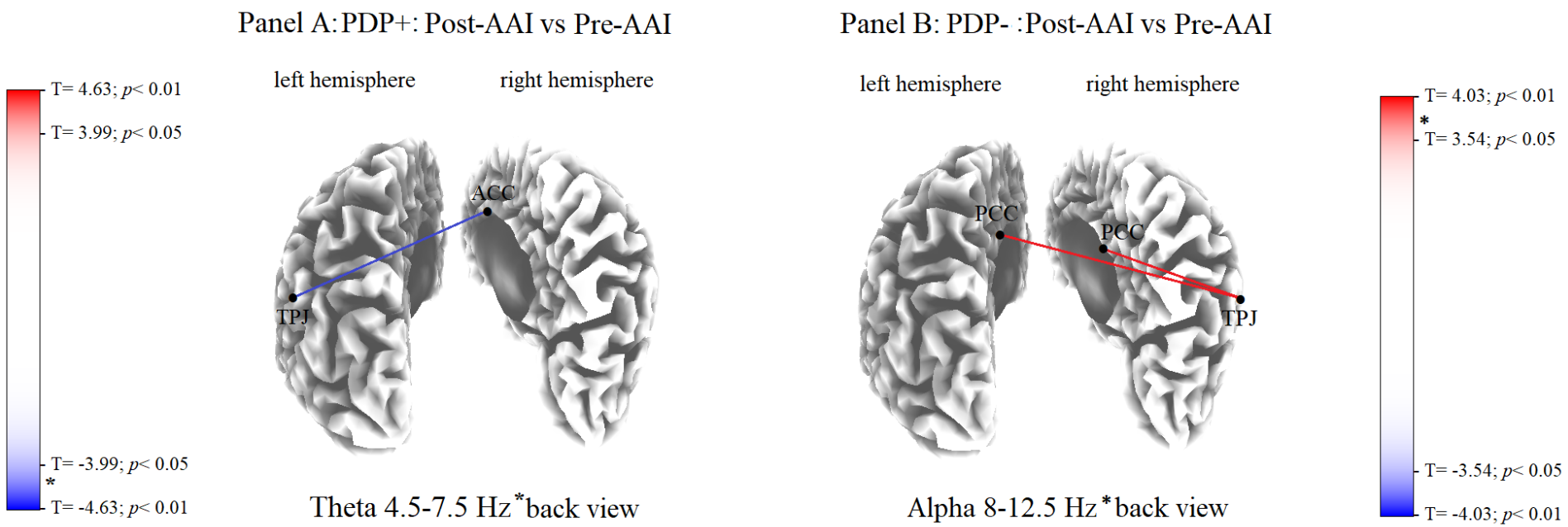
Legend to figure 2. Results of the eLORETA between comparisons of EEG functional connectivity in the delta bands. Panel A: PDP+ vs PDP- in Pre-AAI condition; Panel B: PDP+ vs PDP- in Post-AAI condition. Blue lines indicate connections presenting a significant decrease of EEG functional connectivity. Red lines would indicate increase of EEG functional connectivity (not present). Threshold values (T) for statistical significance (corresponding to $p< 0.05$ and $p< 0.01$) are reported in the right side of the figure. In this comparison, significant modifications (*) were observed in the Post-AAI condition. Compared to PDP- individuals, PDP+ subjects showed a decrease of delta connectivity between left TPJ and right ACC.



Abbreviations: AAI= Adult Attachment Interview; PDP+= high perceived dysfunctional parenting group; PDP-= low perceived dysfunctional parenting group; TPJ= temporoparietal junction; ACC= anterior cingulate cortex

Legend to figure 3.

Results of the eLORETA within comparisons (pre-AAI vs post-AAI) of EEG functional connectivity in PDP+ and PDP- group, respectively for theta and alpha band. Panel A: Post-AAI vs Pre-AAI for PDP+ group; Panel B: Post-AAI vs Pre-AAI for PDP- group. Blue lines indicate connections presenting a significant decrease of EEG functional connectivity. Red lines indicate connections presenting an increase of EEG functional connectivity. Threshold values (T) for statistical significance (corresponding to $p< 0.05$ and $p< 0.01$) are reported in the right and left side of the figure, respectively for PDP+ and PDP- group. In this comparisons, significant modifications were observed for both PDP+ (*) and PDP- group (*). Compared to Pre-AAI condition, PDP+ individuals showed in Post-AAI condition a decrease of theta connectivity between left TPJ and right ACC. Conversely, compared to Pre-AAI condition, PDP- individuals showed in Post-AAI condition an increase of alpha connectivity between right TPJ and both right and left PCC.



Abbreviations:

AAI= Adult Attachment Interview; PDP+= high perceived dysfunctional parenting group; PDP-= low perceived dysfunctional parenting group; TPJ= temporoparietal junction; ACC= Anterior Cingulate Cortex; PCC= Posterior Cingulate Cortex

590 Table 1. **Bivariate analyses**

Variables	**Cluster 1 (PDP+) (N = 17)**	**Cluster 2 (PDP-) (N = 33)**	**Test Statistics**	***p* =**
Age – M ± DS	22.59 ± 2.90	22.64 ± 2.16	$U = 265$	0.748
Educational level (years) – M ± SD	15.71 ± 1.65	15.44 ± 1.84	$U = 249$	0.624
Women - N (%)	13 (76.5)	23 (69.7)	$\chi^2_1 = 0.26$	0.613
MOPS total score – M ± DS	40.65 ± 15.81	9.47 ± 6.32	$U = 0.05$	**< 0.001**
MOPS sub-scales				
Maternal indifference – M ± DS	5.59 ± 5.72	0.94 ± 1.50	$U = 89$	**< 0.001**
Maternal over-control – M ± DS	7.94 ± 2.79	3.39 ± 2.18	$U = 57.5$	**< 0.001**
Maternal abuse – M ± DS	6.24 ± 4.63	0.94 ± 1.48	$U = 57$	**< 0.001**
Paternal indifference – M ± DS	8.47 ± 5.63	1.13 ± 1.34	$U = 43.5$	**< 0.001**
Paternal over-control – M ± DS	5.18 ± 2.38	2.53 ± 2.34	$U = 113$	**< 0.001**
Paternal abuse – M ± DS	7.24 ± 3.82	0.44 ± 0.88	$U = 22.5$	**< 0.001**
BSI-GSI – M ± DS	0.95 ± 0.66	0.56 ± 0.68	$U = 143.5$	**0.005**
Somatization – M ± DS	0.86 ± 0.72	0.44 ± 0.63	$U = 172$	**0.024**
Obsession-Compulsion – M ± DS	1.40 ± 0.86	0.81 ± 0.90	$U = 153$	**0.009**
Interpersonal Sensitivity – M ± DS	0.94 ± 0.88	0.57 ± 0.70	$U = 203$	0.106
Depression – M ± DS	0.98 ± 0.75	0.62 ± 0.79	$U = 170$	**0.023**
Anxiety – M ± DS	1.21 ± 0.82	0.75 ± 0.87	$U = 168$	**0.021**
Hostility – M ± DS	0.98 ± 0.99	0.46 ± 0.67	$U = 186.5$	**0.049**
Phobic Anxiety – M ± DS	0.47 ± 0.72	0.25 ± 0.61	$U = 238$	0.324
Paranoid Ideation – M ± DS	1.01 ± 0.75	0.49 ± 0.79	$U = 138$	**0.003**
Psychoticism – M ± DS	0.76 ± 0.71	0.48 ± 0.71	$U = 194$	0.071

Abbreviations:
PDP+= high perceived dysfunctional parenting group; PDP-= low perceived dysfunctional parenting group; SD = standard deviation; MOPS= Measure of Parental Style; BSI-GSI = Brief Symptom Inventory-Global Severity Index;

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Table 2. Values of Spearman's *rho* correlation coefficient among EEG connectivity data, MOPS and BCSL-GSI scores in all sample (N = 50). Significant correlations are indicated by stars (*).

	MOPS Total	Maternal indifference	Maternal over-control	Maternal abuse	Paternal indifference	Paternal over-control	Paternal abuse	GSI	Delta ROIs 11-8
MOPS total	-								
Maternal indifference	0.78**	-							
Maternal over-control	0.83**	0.57**	-						
Maternal abuse	0.81**	0.73**	0.72**	-					
Paternal indifference	0.79**	0.60**	0.52**	0.59**	-				
Paternal over-control	0.70**	0.38**	0.58**	0.41**	0.41**	-			
Paternal abuse	0.80**	0.51**	0.52**	0.64**	0.66**	0.60**	-		
GSI	0.55**	0.51**	0.46**	0.46**	0.42**	0.34*	0.36*	-	
Delta ROIs 11-8	-0.28*	-0.36*	-0.33*	-0.26	-0.13	-0.08	-0.22	-0.26	-

Abbreviations: ROIs= Regions of interest; MOPS= Measure of Parental Style; = Global Severity Index;
* $p < 0.05$; ** $p < 0.01$