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Short Communication

Altered cellular immune reactivity in traumatized women with and without major depressive disorder

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ABSTRACT

Alterations of the hypothalamic-pituitary-adrenal (HPA) axis such as altered glucocorticoid receptor sensitivity and increased immune reactivity might contribute to the pathogenesis of major depressive disorder (MDD). Exposure to adverse childhood experiences (ACE) precipitates vulnerability to MDD and might be associated with endocrine and immune alterations in the disorder.

In order to disentangle the effects of ACE and MDD, we recruited 87 women: n = 23 with MDD and ACE as determined by clinical interview and questionnaires (Structured Clinical Interview for DSM-IV, Early Trauma Inventory, Childhood Trauma Questionnaire), n = 24 with MDD without ACE, n = 21 with ACE but no current or lifetime MDD, and n = 26 healthy women without either MDD or ACE. Glucocorticoid signaling and mitogen-stimulated proliferation were analyzed *ex vivo* in peripheral blood-derived mononuclear cells. Additionally, mRNA expression of the glucocorticoid and the mineralocorticoid receptor (GR / MR) was assessed.

Peripheral GR sensitivity as well as GR and MR expression levels were not significantly different between groups. Women with ACE showed an increased immune response after mitogen stimulation independent of the presence of MDD.

Our results provide evidence for a functionally altered *ex-vivo* immune response in cell cultures from women with a history of ACE. Thus, ACE might contribute to the pathogenesis of MDD through inflammatory pathways.

1. Introduction

Alterations of the hypothalamic-pituitary-adrenal (HPA) axis such as altered glucocorticoid receptor sensitivity and increased immune reactivity might contribute to the pathogenesis of major depressive disorder (MDD) (Pariante, 2017). Exposure to adverse childhood experiences (ACE) enhances the risk to develop MDD later in life and is itself associated with changes in HPA axis function (Mandelli et al., 2015; Anacker et al., 2014). Indeed, a growing body of evidence suggests a close interplay among ACE, inflammation and altered HPA axis signaling in the pathogenesis of later life mental disorders (Nusslock and Miller, 2016; Baumeister et al., 2016; Fernandez et al., 2016; Geiger et al., 2018). This is not surprising as HPA axis signaling has a strong impact on neuronal and immune cells (Vyas et al., 2016).

It has been hypothesized that in patients with MDD altered GR functioning such as GR resistance leads to a reduced feedback sensitivity of the HPA axis followed by enhanced circulating cortisol in blood (Pariante and Lightman, 2008; Holsboer, 2000). Additionally, GR resistance might reduce the regulatory effects of corticoids on immune cell activity (Pariante, 2017). Traditional measures of HPA axis feedback sensitivity include *in vivo* stimulation paradigms such as the dexamethasone suppression test. Additionally, there are several, methodologically different *ex vivo* strategies that measure peripheral glucocorticoid receptor (GR) sensitivity, for example in peripheral blood-derived mononuclear cells (PBMCs) (Rohleder et al., 2010; Heuser et al., 1994; Leistner and Menke, 2018). In MDD, a large body of evidence suggests an overall reduced central and peripheral GR sensitivity (Pariante, 2017; Leistner and Menke, 2018), yet findings in other "stress-related" psychiatric conditions and findings from different methodological approaches are equivocal (Leistner and Menke, 2018).

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Table 1
Demographical data and statistical comparison (chi-square test for categorical / ANOVA for continuous data) for the subsample.

	MDD- / ACE– (n = 26)	MDD + / ACE- (n = 24)	MDD + / ACE + (n = 23)	MDD- / ACE + (n = 21)	p-value
Age (mean/SD)	32 (11)	37 (10)	33 (11)	35 (12)	0.38
Smoker (yes/no)	6/20	8/16	11/12	5/16	0.45
BMI	21 (3)	23 (4)	22 (3)	23 (3)	0.12
Years of education (mean/SD)	12 (1)	11 (1)	11 (2)	11 (1)	0.39
Cell culture data (yes/no)	22/4	20/4	18/5	12/9	0.11
mRNA data (yes/no)	23/3	22/2	22/1	21/0	0.41
CTQ sum score (mean/SD)	28 (3)	47 (14)	63 (16)	66 (20)	< .001
ETI sum score (mean/SD)	23 (42)	378 (368)	648 (494)	719 (340)	< .001
MADRS score (mean/SD)	1 (1)	30 (7)	33 (6)	3 (2)	< .001
Use of oral contraceptives (yes/no)	7/19	8/16	8/15	5/16	0.83
Use of antidepressant medication (yes/no)	0/26	6/18	6/17	0/21	0.002
Lymphocytes [cells/nl]	1.98 (0.67)	2.33 (0.62)	1.79 (0.43)	2.08 (0.49)	0.01
Lymphocytes [%]	33.2 (8.6)	33.5 (7.4)	31.4 (7.8)	33.2 (9.0)	0.81
Monocytes [cells/nl]	0.45 (0.14)	0.52 (0.13)	0.47 (0.14)	0.51 (0.14)	0.33
Monocytes [%]	7.5 (1.5)	7.7 (2.3)	8.2 (1.3)	7.8 (1.6)	0.62
pro-inflammatory cytokines:	5.36 (12.02)	0.64 (2.11)	0.85 (2.16)	1.33 (2.97)	0.62
IL-6 [ng/ml]	5.51 (12.03)	2.73 (3.95)	3.14 (3.89)	9.81 (27.68)	0.69
TNF-a [ng/ml]					

Importantly, different *ex vivo* methods have been used to characterize peripheral GR sensitivity and responsiveness to proinflammatory stimuli, including stimulation of PBMCs with mitogens or lipopolysaccharides (LPS). Subsequent determination of cellular proliferation rates in the presence of glucocorticoids, but also cytokine expression or prostaglandine synthesis have been investigated and found to be altered in MDD (Leistner and Menke, 2018; Lisi et al., 2013).

A well-known risk factor for MDD is a history of ACE. Besides having a strong impact on brain development (McEwen and Gianaros, 2011), ACE are associated with long-lasting neurobiological changes, including alterations in HPA axis function such as enhanced endocrine reactivity (Heim et al., 2010; Cattaneo et al., 2015), which - in part - overlap with those alterations seen in MDD (Heim et al., 2008). While a recent report by Koenig and colleagues has demonstrated increased hair cortisol levels in women with ACE in an FKBP5 genotype dependent manner (Koenig et al., 2018), there are several studies suggesting an overall increased central as well as peripheral GR sensitivity in traumatized individuals (Rohleder et al., 2010; Leistner and Menke, 2018; De Bellis and Zisk, 2014).

Another intriguing overlap between MDD, ACE and HPA axis signaling is inflammation. Elevated low-grade pro-inflammatory signaling is frequently found in MDD and is related to more severe, treatment refractory subtypes of MDD (Pariante, 2017). ACE are also associated with altered immune function (Baumeister et al., 2016; Fernandez et al., 2016; Geiger et al., 2018; Schury and Kolassa, 2012; Pace et al., 2012). Thus, a dysfunctional immune response might be an important mechanistic link between ACE and MDD later in life.

In this study, we sought to systematically analyze *ex vivo* GR sensitivity and mitogen-stimulated proliferation in women with MDD with and without ACE, and in healthy women with and without ACE. Particularly, we assessed *ex vivo* GR signaling by means of a lymphocyte proliferation test using a non-radioactive assay protocol (Regen et al., 2017). GR sensitivity, including cellular immune response as part of the assay's underlying principle, was assessed in cell cultures derived from healthy women with and without ACE and depressed women with and without ACE. Furthermore, GR and mineralocorticoid receptor (MR) mRNA expression was measured qualitatively in unstimulated cells.

We hypothesized a reduced peripheral GR sensitivity by means of glucocorticoid inhibition of lymphocyte proliferation, as well as reduced GR and MR mRNA expression in patients with MDD. These effects should be most pronounced in those patients with a history of ACE. As a consequence of GR resistance, we furthermore expected an increased mitogen stimulated immune response in MDD and ACE.

2. Materials and methods

2.1. Participants

The sample represents a subsample from a previously published study (Wingenfeld et al., 2017), which was conducted at two study centers. The here presented data include those participants, who were recruited at the Dept. of Psychiatry at the Charité, Campus Benjamin Franklin and *via* public posting in Berlin as blood samples were only collected in this subgroup. Our subsample included 26 healthy women who had never had any mental disorder and did not report sexual or physical abuse (healthy controls; MDD - / ACE -), 25 women with MDD and ACE (MDD + / ACE +), 25 women with MDD without ACE (MDD + / ACE -) and 22 women with ACE but no current or lifetime MDD (MDD - / ACE +). ACE was defined as repeated sexual or physical abuse at least once a month over one year or more before age of 18. All participants underwent a clinical assessment, including the Structured Clinical Interview for DSM-IV axis I and II to validate psychiatric diagnoses. To assess childhood trauma, the German versions of the Early Trauma Inventory (ETI) (Bremner et al., 2000) and the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1998) were used. Healthy participants with and without ACE were free of any current psychiatric disorder. MDD patients met DSM-IV diagnosis of current major depressive episode. Exclusion criteria for the MDD groups were post-traumatic stress disorder, schizophrenia, schizoaffective disorder, bipolar disorder, depressive disorder with psychotic features, anorexia, and lifetime alcohol or drug dependence. Table 1 provides an overview of the patient demographic data. Further exclusion criteria for all participants were CNS diseases or severe somatic diseases, metabolic or endocrine diseases, autoimmune diseases, current infections, or pregnancy and a body mass index (BMI) higher than 30. For technical reasons, PBMC cell cultures were not available from all participants (see Table 1). The study took place at the Department of Psychiatry, Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin. All participants provided written informed consent. Healthy control participants and outpatients received monetary remuneration (€200) for their participation. The study was approved by the local ethics committee.

2.2. Procedures

2.2.1. PBMC isolation

Participants arrived at the laboratory at 8 a.m. after an overnight fast for blood collection. Each participant provided a total volume of

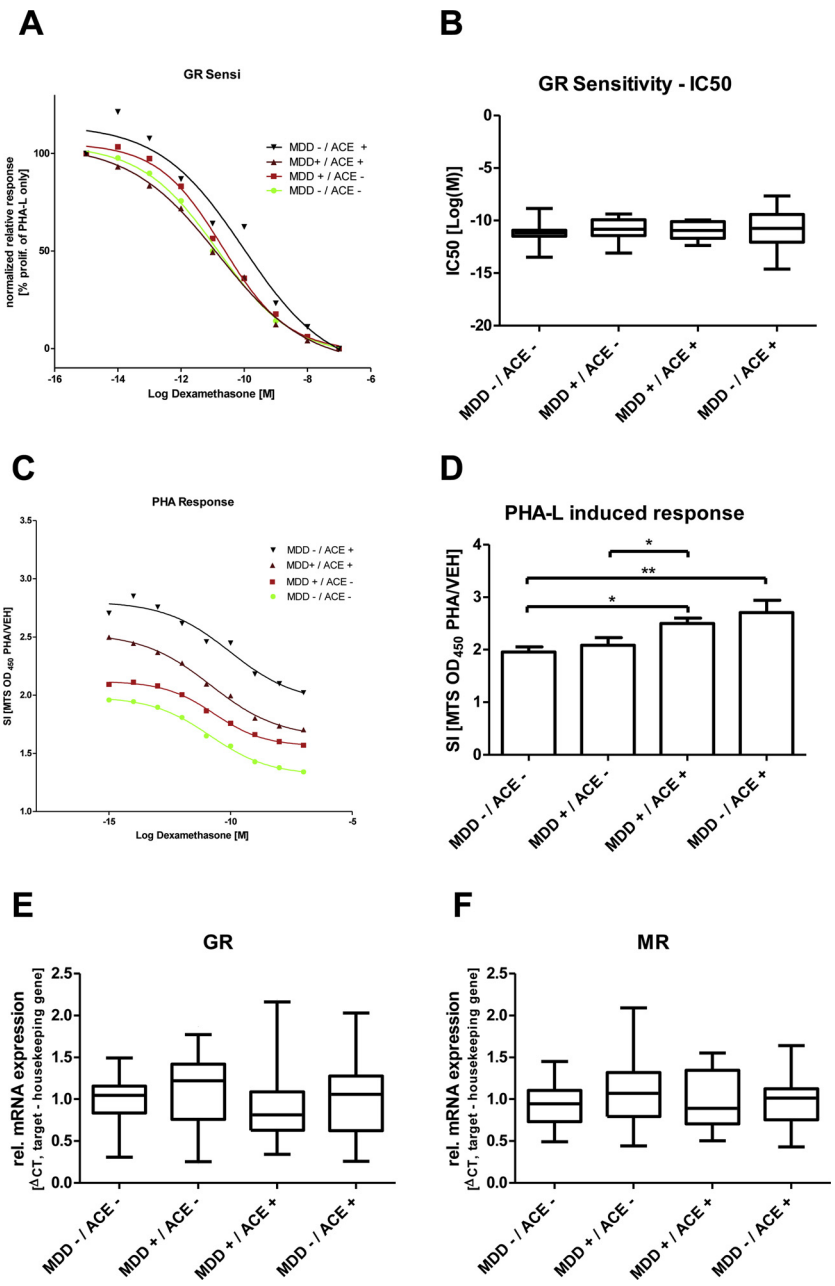

Fig. 1. Glucocorticoid receptor sensitivity and mitogen-induced proliferative response of peripheral blood-derived mononuclear cells. Fig. 1 (A) demonstrates top- and bottom-normalized lymphocyte proliferation upon stimulation with PHA-L in the presence of increasing concentrations of dexamethasone. ANOVA of IC50-values (B) did not reveal any main effect of group ($F = 0.45$, $p = 0.72$). Comparison of raw stimulation indices between all groups (C) indicates increased response to PHA-L stimulation for cells derived from patients with a history of ACE (MDD - / ACE + and MDD + / ACE +). When comparing SI values in the absence of DEX, ANOVA revealed a significant main effect of group (D; means +/- SEM, $F = 5.9$, $p = 0.001$). Post hoc analysis indicates significantly increased proliferative response in cells from women with a history of trauma (MDD - / ACE + and MDD + / ACE +) compared to healthy controls (MDD - / ACE -; ANOVA with Tukey's post-test, * $p < 0.05$, ** $p < 0.01$) mRNA expression of MR (E) and GR (F) were not significantly altered between groups (GR: $F = 0.535$, $p = 0.659$; MR: $F = 573$; $p = 0.635$).

40 ml of peripheral venous blood for PBMC isolation. Blood was collected using specialized heparinized cell separation collection tubes using a principle based on a FICOLL™ gradient centrifugation strategy (BD CPT™ heparin tubes, BD Biosciences). Tubes are evacuated and contain layers of separating gel and a FICOLL™ solution. PBMCs were isolated according to the manufacturer's instructions (see supplement for details), washed, resuspended in RPMI 1640 Medium (Biochrom AG Berlin), containing 10% FCS (Biochrom), 1% Penicillin/Streptomycin (10,000 U / 10 mg per ml; Biochrom), and 2-Mercaptoethanol (143 mM; Sigma-Aldrich), counted and seeded at a density of 10,000 cells per well into a flat-bottom 96-well-plate.

2.2.2. GR sensitivity assay

The assay followed previously published methods (Regen et al., 2017). A detailed description of the methodology as well as assay performance is included in the supplemental materials. In brief, the assay measures the ability of lymphocytes to undergo proliferation following mitogenic stimulation with phytohemagglutinine-L (PHA-L; 1 µg/ml), which is a nonspecific, plant-derived mitogen. In parallel, a glucocorticoid (Dexamethasone) is added at different concentrations in order to stimulate the GR, which results in inhibition of proliferation.

2.2.3. Gene expression analysis of glucocorticoid and mineralocorticoid receptor

Gene expression in unstimulated PBMCs was qualitatively assessed by real-time reverse-transcription polymerase chain reaction (PCR). Total RNA was extracted from 10^6 cells using TRIzol® reagent (Invitrogen), for details see supplement S1. For qPCR amplification of glucocorticoid (GR-), mineralocorticoid (MR-) receptor and GAPDH housekeeping gene-specific transcripts we used gene-specific primers as specified in the supplement, with SYBR Green I fluorescence monitoring for template quantification on an Abi StepOne amplifier (Applied Biosystems, Foster City, USA). Expression level were assessed using the double-delta-CT method.

2.2.4. Statistical analyses

Demographic and clinical data were investigated with analyses of variances (ANOVA) or Chi^2 test using SPSS (IBM SPSS Statistics 22). Cell culture data were pre-analyzed using GraphPad Prism™ statistical software version 5.04 (GraphPad Software, La Jolla, USA).

For all cell culture data, curve-fitting analyses followed a "log (inhibitor) *vs.* response four parameter variable slope" nonlinear regression analysis. For evaluation of GR-sensitivity, IC50 values of each dataset were computed in GraphPad Prism™ based on the results of the nonlinear regression analysis. Cellular mitogen-stimulated proliferation was assessed by comparing the stimulation indices (SI-values) from the average values of the first data point of the GR sensitivity assay in the absence of Dexamethasone.

All cell-culture data were subsequently analyzed for group differences using ANOVA. In case of significant effects Bonferroni post-hoc test were computed.

3. Results

3.1. Sample characteristics

The groups did not differ in age, years of education, smoking status, and body mass index (Table 1). None of the healthy controls (MDD - / ACE -) and none of ACE-only group (MDD - / ACE +) took any psychotropic medication. MDD + / ACE + patients did not differ in medication intake from MDD + / ACE - patients. Women with a history of ACE had significantly higher trauma-related ratings compared to patients without a history of ACE, yet patients with a history of ACE did not differ from MDD + / ACE + patients with respect to trauma-related ratings. MDD patients with and without a history of ACE did not differ in depression severity. Patients with MDD had higher depression rating scores compared to women without MDD.

3.2. GR sensitivity

Fig. 1 A demonstrates top- and bottom-normalized inhibitor-response curves for patient-specific cell cultures stimulated with PHA-L and treated with dexamethasone at increasing concentrations. Peripheral GR sensitivity, as assessed by comparing the IC50-values for dexamethasone inhibition of mitogen-induced proliferation in patient-derived lymphocyte cultures was compared between groups by ANOVA. Statistical analysis revealed no significant effect of group (Fig. 1B; $F = 0.452$, $p = 0.716$).

3.3. Cellular immune response

Fig. 1C demonstrates the distribution of the non-normalized raw data of the inhibitor-response curves and depicts group differences in the gross proliferative (immune) response. Average PHA-L induced response, as measured by quantification of the mitogenic response of cells in the absence of dexamethasone, is depicted in Fig. 1D. ANOVA revealed a significant main effect of group ($F = 5.91$, $p < 0.001$). Post hoc analysis demonstrates significantly increased proliferation in cell cultures from the MDD - / ACE + ($p < 0.01$) and MDD + / ACE + groups ($p < 0.05$) compared to cells from healthy controls. Immune response in women with MDD + / ACE + was also significantly higher compared to women with MDD + / ACE - ($p < 0.05$).

3.4. GR / MR mRNA expression

mRNA expression of GR and MR in mononuclear cells, as quantified by qPCR and analyzed by ANOVA, was not significantly different between the four groups (GR: $F = 0.535$, $p = 0.659$; MR: $F = 573$; $p = 0.635$). Furthermore, GR/MR ratio did not differ between groups ($F = 0.119$, $p = 0.95$).

4. Discussion

We found an increased proliferation rate of PBMCs in women with ACE, regardless of comorbid MDD. Neither childhood trauma nor depression had an effect on *ex vivo* GR sensitivity. There were also no main effects of group on GR and MR expression as assessed by quantification of mRNA expression levels in patient-specific PBMCs.

We observed a significantly increased immune response in cell cultures from women with a history of ACE, regardless of current MDD. This finding is well in line with the notion of long-lasting changes in immune reactivity after ACE (Baumeister et al., 2016; Schury and Kolassa, 2012) and with enhanced low-grade pro-inflammatory signaling in MDD (Pariante, 2017). Interestingly, MDD patients without ACE did not show this increased immune response. Thus, ACE might be especially associated with an inflammatory pathogenesis (phenotype) of MDD (Cattaneo et al., 2015). Our findings demonstrate an increased immune response even in traumatized, phenotypically healthy women. Thus, an elevated immune response might reflect a vulnerability factor for the development of mental illness. With respect to the mechanism underlying the proliferative response that was measured in our approach, it is noteworthy that altered mitochondrial bioenergetic functioning may underlie the observed effects. Interestingly, mitochondrial bioenergetic functioning has been reported to be reduced in MDD patients (Rossignol et al., 2014), and increased in women with a history of ACE, as assessed by the CTQ (Boeck et al., 2016). The observed increased immune responsiveness in traumatized women could serve as a putative "biotype of early traumatization" and possibly be used as a tool for further investigation of underlying mechanisms of trauma-associated biological signatures. Our findings of an increased immune response in ACE are also in line with findings in individuals with PTSD (Rohleder et al., 2010; Sommershof et al., 2009; Gola et al., 2013; Grassi-Oliveira et al., 2017). Furthermore, there is some evidence that treatment resistance to antidepressants is associated with elevated low-grade pro-inflammatory signaling (Carvalho et al., 2013).

In contrast to our hypothesis, we observed no significant group effects in GR sensitivity. However, the finding of an unaltered GR sensitivity adds to results from our prior study with the same cohort on *in vivo* measurement of HPA axis feedback sensitivity. Using the combined DEX/CRH test, we did not find significant differences in cortisol response between healthy controls and participants with MDD and/ or ACE (Spitzer et al., 2018). Previous research reported variable effects of trauma and depression on GR sensitivity, including *ex vivo* and *in vivo* approaches. While women with ACE exhibit rather increased GR sensitivity, GR sensitivity seems to be decreased in patients with MDD (Rohleder et al., 2010; Leistner and Menke, 2018; Rohleder et al., 2004). However, in women with atypical depression an increased, rather than decreased HPA axis feedback sensitivity has been reported (Levitan et al., 2002), suggesting a more complicated picture in MDD. Notably, our sample of healthy traumatized women was free of any psychiatric disorder and was also physically healthy. Thus, these women might reflect a resilient sample in terms of psychopathology and HPA axis alterations.

Contrary to our hypothesis, we did not find significant group effects on MR or GR expression. However, the literature remains controversial and there are several other studies, which did not reveal altered number or binding capacity of GR, despite functional changes in the glucocorticoid signaling pathway (Pariante and Miller, 2001). There are only very few studies on MR function in MDD, suggesting alterations especially in treatment-resistant (Juruena et al., 2013) and older patients (Otte et al., 2015). To the best of our knowledge, no study investigated MR function in individuals with ACE. However, in a previous study we did not see alterations in MR (and GR) sensitivity in a sample of patients with borderline personality disorder, which was characterized by a high prevalence of childhood trauma (Fischer et al., 2015).

There are also several limitations of our study. Given the small sample size and the inclusion of women only in the present study, our

findings should now be validated in a larger cohort with male and female participants and possibly including additional characterization of the *ex vivo* cell culture response with respect to potential genetic and epigenetic modulators, that have been reported to mediate GR sensitivity (Rohleder et al., 2010; Heuser et al., 1994; de Kloet et al., 2007; Menke et al., 2016). Furthermore, both ACE and MDD are associated with an increased risk for metabolic syndrome, but only individuals with a BMI < 30 were included. This might have reduced the between-group contrast. Another methodological limitation concerns the use of fetal calf serum. The serum was from a single batch, yet effects of the serum on cell culture parameters cannot be excluded. It would have been interesting to investigate individuals with emotional abuse but without sexual and/or physical abuse to differentiate the impact of trauma type. Additionally, we did not asses chronic and traumatic stress in adulthood as well as personality traits, which might be an important mediator in terms of possible risk and resilience factors for the immunological response to environmental challenges (Vedhara et al., 2015; Luchetti et al., 2014).

In sum, our results provide evidence for a functionally altered *ex-vivo* immune response in cell cultures from women with a history of ACE. Thus, ACE might contribute to the pathogenesis of MDD through inflammatory pathways.

Conflict of interest

Dr. Otte has received honoraria fees for lectures from Lundbeck and Servier and has received compensation as a member of the scientific advisory board from Lundbeck and Neuraxpharm. Dr. Wingenfeld, Dr. Kuehl, Dr. Schultebraucks, Dr. Hellmann-Regen and Dr. Spitzer, report no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2018.10.023.

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