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Short communication

Markers of neuroinflammation influence measures of cortical thickness in bipolar depression

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ABSTRACT

We tested if peripheral levels of cytokines and chemokines associate to grey matter volumes, cortical thickness and fMRI neural responses to a moral valence decision task in bipolar patients. ICAM1 and CCL4 negatively correlated with cortical thickness in Inferior Temporal Gyrus, and sCD25 in Parahippocampal Gyrus. TNF-α, Interleukine-8, and CCL2 correlated positively with cortical thickness in the Anterior Cingulate Cortex, and with lower BOLD responses to negative stimuli. Markers of immune activation are associated with measures of brain structural and functional integrity in bipolar depression.

1. Introduction

Mood-congruent negative biases in emotional processing with altered neural responses, connectivity in fronto-limbic networks (Vai et al., 2014), reduced cortical grey matter (GM) volumes (Wise et al., 2016) and cortical thickness (CT) (Hibar et al., 2018), have been associated with Bipolar Disorder (BD), and suggested to parallel and contribute to illness outcomes.

Cortico-limbic regions show lower cell density in BD (Drevets et al., 1998), but pathophysiological explanations are lacking. Peripheral markers of activated inflammatory response in BD have been associated with increased risk of illness (Padmos et al., 2008), disrupted white matter microstructure (Benedetti et al., 2016b), and treatment outcome (Benedetti et al., 2017).

We now investigated the effect of a panel of inflammation-related cytokines, chemokines, and cell adhesion proteins, on GM CT, volumes, and fMRI neural responses during a moral valence attribution task in bipolar depression.

2. Methods

For detailed methods see Supplementary materials.

We studied 26 BD type I inpatients affected by a depressive episode, without psychotic features, and 24 healthy controls (HC).

Eleven cytokines/chemokines were measured using the bead-based Luminex system: Tumor Necrosis Factor-α (TNF-α), Interferon-γ (IFN-γ), Interleukin-6 and 8 (IL-6), IL-8, C-X-C Motif Chemokine 10 (CXCL10), Interleukin-2 receptor-α (IL-2Ra-sCD25), chemokine (C-Cmotif) ligand 2 and 4 (CCL2-CCL4), Pentraxin-related protein (PTX3); cell adhesion proteins: Intercellular Adhesion Molecule 1 (ICAM1), Vascular Adhesion Molecule 1 (VCAM1).

MRI studies were performed on a 3.0-Tesla scanner (Gyroscan Intera, Philips, The Netherlands). Data were analyzed with Statistical Parametric Mapping 12, Computational Atlas Toolbox 12, separately in HC and patients. Whole brain results were Family-wise error (FWE) corrected for multiple comparisons $p < 0.05$. Age, sex, ongoing lithium treatment, and imipramine equivalent doses were treated as nuisance covariates.

We searched whole-brain CT and volumes for the effect of each analyte. To test whether CT could be related to the content of brain tissue water, we compared CSF volume in patients with an age-matched sample of 26 HC, and correlated CSF volume with inflammatory markers and CT. CSF volumes were adjusted by dividing raw CSF volumes to total intracranial volume of each subject and multiplying for 100.

During fMRI, participants rated the moral valence of positive and negative adjectives (Benedetti et al., 2007). At first-level, the neural

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Table 1
Clinco demographic characteristics of the sample.
(average ± standard deviation).

	BD (n = 26)	HC (n = 23)	T, p
Age (years)	47.96 ± 13	27.5 ± 9.96	6.20, 0.00
Onset (year)	33.15 ± 12.95	–	
Duration (years)	14.50 ± 8.4	–	
Sex	M = 21 F = 38	M = 8 F = 15	0.64, 0.42
Depressive episodes	7.44 ± 6.04	–	
Manic episodes	3.76 ± 5.09	–	
Medication load	125.87 ± 112.75	–	
IDSC[a]	32.28 ± 10.86	–	

[a] Inventory of depressive symptomatology.

correlates of inhibiting negative stimuli were isolated with a double-subtraction contrast. At second level, individual contrasted images were entered as dependent variables, with inflammation markers as linear regressors.

3. Results

Clinico-demographic characteristics of the sample are resumed in Table 1. We do not report on analytes (SupplTable1) or brain differences between patients and HC because of the significant age difference and multicollinearity between age and group. Multiple regressions showed significant effects on CT and neural responses in patients (Fig. 1 SupplTables 2 and 3) but not in HC. No effects were found on brain volumes.

Negative associations were detected for sCD25 in Right Inferior Temporal Gyrus, ICAM-1 in Left Parahippocampal Gyrus, CCL4 in Right Parahippocampal Gyrus. In addition, we found a positive association of TNF-α, IL-8, and CCL2 with CT in Right Anterior Cingulate Cortex (rACC). BD patients had higher adjusted CSF volumes compared to HC ($p < 0.001$), but CSF did not associated with serum analytes or CT.

TNF-α inversely correlated with neural response during the inhibition of negative stimuli in bilateral dorsomedial PFC and OFC, right cuneus and postcentral gyrus, left dorsolateral PFC and precentral gyrus. IL-8 associated with lower responses in right dorsomedial PFC.

4. Discussion

In patients, but not in HC, serum levels of inflammatory markers associated with CT and neural responses in regions involved in cognitive generation of affect, in regulating autonomic responses to stressful

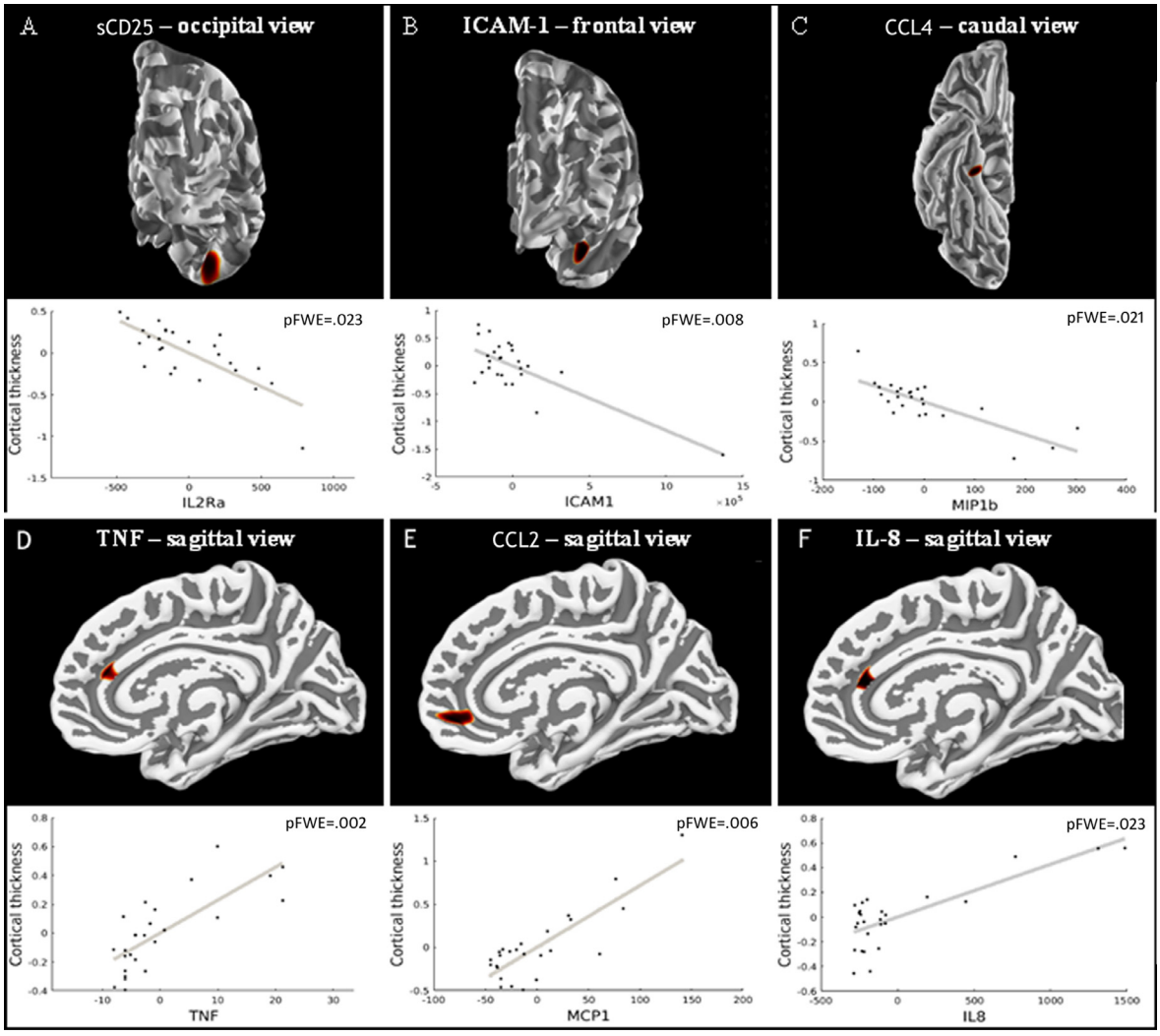

Fig. 1. Brain area where an effect of inflammatory markers has been observed and regression plots showing the direction of the effect. 1A: occipital view of the right hemisphere showing the cluster affected by sCD25. 1B: frontal view of the left hemisphere showing the cluster affected by ICAM-1. 1C: caudal view of the left hemisphere showing the cluster affected by CCL4. 1D: sagittal view of the left hemisphere showing the cluster affected by TNF-α. 1E: sagittal view of the right hemisphere showing the cluster affected by CCL2. 1F: sagittal view of the right hemisphere showing the cluster affected by IL-8. For visualization purposes we used $p < 0.001$ uncorrected images.

events, and in assigning emotional valence to internal and external stimuli (Pizzagalli, 2011).

Serum levels of sCD25, ICAM-1, and CCL4 showed an inverse correlation with CT in brain regions known to be characterized by thinning in BD (Rimol et al., 2012). CCL4 is involved in the recruitment of Natural Killer, dendritic, and regulatory T cells (Bystry et al., 2001; Maurer and von Stebut, 2004). sCD25 contributes to the maturation of regulatory T cells (Breunis et al., 2003). ICAM-1 contributes to T cells' activation and migration to the site of inflammation, and is highly expressed in the cortex of depressed patients (Thomas et al., 2004).

TNF-α, IL-8 and CCL2 positively correlated with CT in rACC, a key brain area for emotional and cognitive control, dysfunctional and disrupted in BD (Drevets et al., 1998). TNF-α can exert a direct cytotoxic effect on neurons (Olmos and Llado, 2014), and induce IL-8, which increases expression of cellular death mediators (Thirumangalakudi et al., 2007). CCL2, also inducible by TNF, regulates the migration of T cells, Natural Killers, and monocytes (Deshmane et al., 2009), and CCL2 gene polymorphisms have been associated with BD (Altamura et al., 2010). Increased intra- and extracellular water (swelling) could account for these effects on CT, but the detected increase of CSF in patients was unrelated to cytokine levels.

In agreement with our previous studies (Benedetti et al., 2016a, 2017), TNF-α and IL-8 also associated with lower differential neural responses to negative stimuli in frontal regions involved in cognitive and emotional functions and decision making. It can now be hypothesized that TNF-α and IL-8 could exert their detrimental role by influencing structure and function of prefrontal GM.

Small sample size, age difference, and medication status limit the generalizability of the results. Replications in larger, and independent samples are needed to test this hypothesis and confirm this finding.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.01.009.

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