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THE EFFECT OF EARLY TRAUMA ON SUICIDAL VULNERABILITY DEPENDS ON FRONTO-INSULAR SULCATION

Running title : Trauma, prefrontal sulcation and suicide

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ABSTRACT

Improving our understanding of pathophysiology of suicidal behavior (SB) is an important step for prevention. Assessment of suicide risk is based on socio-demographic and clinical risk factors with a poor predictivity. Current understanding of SB is based on a stress-vulnerability model whereby early-life adversities are predominant. SB may thus result from a cascade of developmental processes stemming from early-life abuse and/or neglect. Some cerebral abnormalities, particularly in fronto-limbic regions, might also provide vulnerability to develop maladaptive responses to stress, leading to SB. We hypothesized that SB is associated with interactions between early trauma and neurodevelopmental deviations of the frontal and insular cortices. We recruited 86 euthymic women, including 44 suicide attempters (history of depression and SB) and 42 affective controls (history of depression without SB). The early development of prefrontal cortex (PFC) and insula was inferred using three-dimensional MRI-derived regional sulcation indices, which are indirect markers of early neurodevelopment. The insula sulcation index was higher in emotional abused subjects; among those patients, PFC sulcation index was reduced in suicide attempters, but not in affective controls. Such findings provide evidence that SB likely traced back to early stages of brain development in interaction with later environmental factors experienced early in life.

KEYWORDS : brain sulcation, early adversity, insula, prefrontal cortex, suicide

1. INTRODUCTION

Each year, one million individuals commit suicide worldwide. Improving our understanding of suicidal behavior (SB) pathophysiology and our ability to predict and prevent this disorder have become a priority. However, the current assessment of suicide risk is based on socio-demographic and clinical risk factors that show poor predictivity (Chan et al. 2016). Therefore, it is important to better understand the pathogenesis and pathophysiology of SB, an important step to develop a multilevel risk assessment approach that integrates biomarkers associated with SB.

The current understanding of SB is based on a stress-vulnerability model whereby some individuals are at higher risk of committing suicide in stressful situations (Mann 1998). An important subgroup of individuals with SB are exposed to early-life adversities. In these individuals, SB may result from a cascade of developmental processes stemming from early-life abuse and/or neglect. Indeed, early stress adversely affects the nature and trajectory of brain development (Pechtel and Pizzagalli 2011). For instance, cortical thickness (CT) in left insula and right orbitofrontal cortex is significantly reduced in maltreated young people compared with healthy controls (Lim et al. 2018). Interestingly, these regions are also known to play a role in SB (van Heeringen and Mann 2014).

It has also been suggested that some cerebral abnormalities, particularly in fronto-limbic regions, might provide vulnerability to develop maladaptive responses to stress, leading to acute psychiatric illness or episodes and adverse psychosocial events (van Heeringen and Mann 2014). For instance, CT is reduced predominantly in ventrolateral and dorsolateral prefrontal cortex (PFC) in patients with depression and high risk of SB compared with patients with depression without high risk of SB (Wagner et al. 2011). Moreover, CT is reduced

in frontoparietal regions and insula of patients with depression and thoughts of death(Taylor et al. 2015). CT in the right ventrolateral PFC is decreased in euthymic subjects with history of mood disorders and suicide attempts compared with non-attempters and healthy controls. Moreover, PFC CT has been associated with history of childhood maltreatment Ding et al. 2015).

However, it is difficult to conclude whether such CT alterations are the cause or the consequence of the maladaptive response to stress. Indeed, CT is a brain anatomy feature which is a neuroplasticity marker that captures the dynamic interplay between brain maturation and adaptive processes (Giedd and Rapoport 2010, (Zatorre et al. 2012). Therefore, it cannot provide information on early neurodevelopmental alterations that might favor maladaptive responses to future early-life adversity and consequently increase the risk of SB. Cortical sulcation, an indirect marker of early brain development, might provide such early neurodevelopmental information. Cortical sulcation, a developmental process that take place from the 10th gestational week (Chi et al. 1977), is a very complex process, involving factors at different scales, including genetic, cellular and mechanical factors (Zilles et al. 2013, (Ronan and Fletcher 2015, (Borrell 2018, (Kroenke and Bayly 2018, (Foubet et al. 2019, (Van Essen 2020). The cortical sulcation, which is intrinsically related to the brain functional organization (Welker 1988), might enable increases in cortical surface area while limiting accompanying increases in axonal wiring costs(Klyachko and Stevens 2003). Cortical folding morphology has been quantitatively investigated in neuroimaging studies by assessing the degree of “gyrification” (i.e. by measuring the normalized gyral surface) (Armstrong et al. 1995) or of “sulcation” (i.e. by measuring the normalized surface of the cortex buried in the sulci)(Cachia et al. 2008). In adults, the global and regional sulcal indices (Cachia et al. 2008), which reflects the extent of burying of the whole cortex and of specific cortical regions, is considered an

indirect retrospective marker of these early developmental processes (Zilles et al. 2013). Interestingly, the global sulcation index in the right hemisphere is reduced in patients with treatment-resistant depression (Penttila et al. 2009). Moreover, in two large and independent samples (Penttila et al. 2009, (Sarrazin et al. 2018), PFC sulcation index was increased in, a subgroup of patients in whom neurodevelopmental alterations might play a major role (Sigurdsson et al. 1999, (Arango et al. 2014).

Altogether, previous clinical and brain imaging studies provide converging evidence that early-life adversity might interact with neurodevelopmental factors and increase suicide risk. In this study, we aimed at testing the hypothesis of the involvement of the interaction between early trauma and fronto-limbic sulcation in SB risk.

2. MATERIALS and METHODS

2.1 Participants

Eighty-six euthymic women were recruited among the outpatients of the Department of Emergency Psychiatry & Post-Acute Care, Montpellier Academic Hospital, France: 44 suicide attempters (SA) (i.e. individuals with past history of major depressive episode and suicide attempts) and 42 affective controls (AC) (i.e. individuals with past history of major depressive episode, but no personal history of suicide attempts). A suicide attempt was defined as any act carried out with some intent to die. Patients who met the inclusion criteria were then interviewed in person by a psychiatrist. Inclusion criteria were: being a 18 to 65-year-old woman; history of major depressive episode with/without history of suicide attempt; Caucasian; right-handed (assessed with the Edinburgh scale); euthymic at the time of the MRI scan (Hamilton Depression Rating Scale score <7 and Young Mania Rating Scale score <7).

Exclusion criteria were: lifetime history of severe head trauma, central nervous system disorder, schizophrenia, and history of alcohol or drug abuse or dependence in the last 12 months.

The local Ethics Committee (CPP Sud Méditerranée IV, CHU Montpellier) approved the study protocol that was carried out in accordance with the ethical guidelines of the French National Ministry of Health, Labor and Welfare, and the Declaration of Helsinki. Study participants provided written informed consent.

2.2 Clinical assessment

Participants underwent a standardized interview by a psychiatrist to determine the depression score and to assess the absence of manic or psychotic symptoms, according to the DSM-IV criteria using the Mini-International Neuropsychiatric Interview, version 5.0.0. During this interview, a psychiatrist administered the French version of the National Adult Reading Test (NART) to estimate the verbal IQ. Impulsivity was assessed with the Barrat Impulsivity Scale (BIS-10) (Bayle et al. 2000), and anger dimensions with the State-Trait Anger Expression Inventory (STAXI) (Forgays et al. 1997). History of childhood maltreatment was assessed using the self-report Childhood Trauma Questionnaire (CTQ) that evaluates the frequency, intensity, and type of trauma (Bernstein et al. 1994). The questionnaire (five subscales) assesses five types of childhood trauma: emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse. Participants rate the CTQ items using a 1–5-point scale, from “never true” to “very often true.” Each CTQ subscale includes five items; responses range from 5 (no maltreatment) to 25 (severe maltreatment). Higher scores indicate higher levels of childhood trauma. The cut-off scores for moderate-severe exposure were set at ≥ 15 for emotional neglect, ≥ 10 for physical neglect, ≥ 13 for emotional abuse, ≥ 10 for physical abuse, ≥ 8 for sexual abuse. All psychotropic treatments (name, daily dose) during the last 24h before MRI data acquisition (reflecting usual treatment for the last months) were recorded. The medication load

taking into account dosage and duration of antidepressants as well as presence of other psychotropic was calculated for each patient (Sackeim 2001).

2.4. MRI data acquisition

MRI data were acquired at the Neuroradiology Department - I2FH (Institut d'Imagerie Fonctionnelle Humaine, Academic Hospital of Montpellier) using a 1.5T MRI system (MAGNETOM AVANTO, Siemens, Erlangen, Germany) equipped with a standard 12-channel receive-only head coil. A three-dimensional (3D) magnetization-prepared, rapid acquisition gradient echo (MP-RAGE) sequence was obtained for each participant with the following parameters: TR = 2100 ms, TE = 4.1ms, IR = 1100 ms, 15° flip angle, PAT = 2, aligned with the corpus callosum, voxel-size 0.98 x 0.98 x 1mm, 160 transversal slices.

2.5. MRI data analysis

Raw T1 images were processed using with the Morphologist toolbox using BrainVISA 4.5 software with standard parameters (<http://brainvisa.info>) that allows the automatic segmentation (Mangin et al. 2004) and labeling of cortical sulci (Perrot et al. 2011). Such fully automated approach avoids operator-related biases and is suitable for the analysis of large samples. This approach has been used in studies on schizophrenia (Cachia et al. 2008, (Penttila et al. 2008, (Gay et al. 2013) and depressive disorders (Penttila et al. 2009, (Penttila et al. 2009, (Sarrazin et al. 2018).

2.5.1. Brain segmentation

An automated pre-processing step was implemented to skull strip the T1 MRI images and segment the brain tissues. No spatial normalization was applied to overcome potential bias that may result from sulcus shape deformations caused by warping. The cortical folds were automatically segmented throughout the cortex from the skeleton of the gray

matter/cerebrospinal fluid mask, with the cortical folds corresponding to the crevasse bottoms of the “landscape”, the altitude of which is defined by its intensity on the MRI images. This provides a stable and robust sulcal surface definition that is not affected by variations in cortical thickness or gray matter/white matter contrast (Mangin et al. 2004) due to aging or treatment, for instance. A brain mask was used to estimate the brain outer surface for each subject following an isotropic closing procedure of the sulcal outer surface. The surface area of the resulting envelope that swaddles the brain surface (referred to as ‘hull’) was computed for the left and right hemisphere of each subject. For each participant, images at each processing step were visually checked. No gross segmentation error (e.g. cortical ribbon thinning, gyrus or sulcus missing) was detected.

2.5.2. Sulcal labeling

Cortical folds were then converted to a graph-based representation of the cortex containing information on shape (area, depth and length) and spatial organization (position and orientation) (Mangin et al. 1995). Sulci were then automatically recognized using a Bayesian probabilistic model that provides the probability of each sulcus presence at any cortex position (Perrot et al. 2011). This recognition step, using a previously validated procedure with a mean accuracy rates of 86%, resulted in labeled sulci graphs for each hemisphere for each subject, and did not require any manual intervention.

2.5.3. Sulcal morphometry

Analysis of cortical sulcation was based on 3D mesh-based regional sulcal indices (r-SI) that reflect the degree of regional cortical burying (Cachia et al. 2008). The r-SI is defined as the ratio between the sum of the areas of the cortical folds included in the region of interest and the total outer cortex area (i.e. hull area) (Cachia et al. 2008). Hence, a $r-SI = 0$ zero indicates a totally smoothed cortical surface. Such sulcal indices are slightly different from the gyrification

index (GI), which is the ratio of the gyral contour length to the outer exposed surface (Zilles et al. 1988), and embodies additional information (included in the gyral contour length) related to the cortex thickness and sulcal opening. Moreover, the classical GI captures the shape of the cortical folds, which are complex 3D structures, from measures on two-dimensional MRI slices (Zilles et al. 1988). Conversely, SI are based on measures derived from a 3D reconstruction of the sulcal surface.

The regional mean cortical thickness, related to the laminar organization of the cerebral cortex and reflecting cortical plasticity (Rakic 2009, (Zatorre et al. 2012), was estimated for each region of interest.

2.6. Statistical analysis

This study focused on three pre-selected brain regions that cover the lateral and medial parts of prefrontal cortex (PFC) and the insula, and have been repeatedly associated with suicide (van Heeringen and Mann 2014). First, for each cortical region, a mixed-design repeated measures linear model was used with hemisphere ('Left' vs. 'Right') as intra-individual factor, age as covariate, and mood disorder subtype ('bipolar' vs. 'unipolar') and clinical group (SA vs. AC) as categorical factor to identify the cortical regions associated with SB. Then, the possible effect of early trauma was investigated by adding to the previous model five factors derived from the five CTQ dimensions (Bernstein et al. 1994): physical abuse, emotional neglect, physical neglect, sexual abuse, and emotional abuse. To increase the statistical power, the five dimensions were dichotomized in two-level factors ('absence/low' vs 'moderate/severe'), using standard cut-offs (see details in the 'Clinical assessment' section).

Group-comparisons of quantitative [Mean \pm SD] and qualitative [N (%)] demographic and clinical data were based on bilateral Student's t and Chi2 tests, respectively.

Statistical significance was probed with Pillai's F tests in the linear models. A two-tailed p value <0.05 was considered significant. All statistical analyses were carried out with the R 4.1.2 software (<http://www.r-project.org/>) and the 'car', 'lmerTest' and 'effects' packages for the mixed-effect linear models.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

3. RESULTS

Except for suicide attempt history, all demographic and clinical characteristics were comparable in the two groups (SA and AC). (**Table 1**).

Please insert Table 1

Analysis of the r-SIs in the SA and AC groups did not reveal any significant main effect of group in the lateral PFC (F test = 0.0070; d.f. = 1; p = 0.93), medial PFC (F = 0.2151; d.f. = 1; p = 0.64) nor insula (F = 0.1679; d.f. = 1; p = 0.68). The two-way interactions (group-by-age and group-by-hemisphere) and three-way interactions (group-by-age-by-hemisphere) were not significant (all *ps* >0.37).

We investigated the possible effects of early trauma adding the five CTQ dimensions (emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse) as factors in the previous model. The factor 'emotional abuse' had significant main and interaction effects on the lateral PFC and insula r-SI (Figure 1). Specifically, there was a significant main effect of emotional abuse on the insula r-SI (F = 4.1839; d.f. = 1; p = 0.04), and a significant group-by-'emotional abuse' interaction for the lateral PFC r-SI (F = 5.5437; d.f. = 1; p =

0.02). These findings indicate that the effect of ‘emotional abuse’ on the insula r-SI was the same in patients with and without suicide attempt, while the effect on the lateral PFC r-SI was dependent upon the suicide history (Fig. 1).

Please insert Fig 1

In addition, there was a significant side-by-‘sexual abuse’ for the medial PFC r-SI ($F = 6.3847$; d.f. = 1; $p = 0.014$). The other main and interactive effects were not significant (all $ps > 0.10$).

To control for possible confounding effects of medication load, anger dimensions and impulsivity, all the analyses were reran after addition of these confounding covariates and yielded similar results.

These findings were specific to r-SI features. Indeed, we did not replicate any main nor interactive effects found with r-SI features when the analyses were reran with the mean cortical thickness (all $ps > 0.32$).

4. DISCUSSION

In this first study to investigate the interactions between environmental and neurodevelopmental factors on SB, we found different effects of childhood trauma on the sulcation of brain regions related to emotions (insula) and control (PFC). Specifically, the history of childhood emotional abuse modulates the sulcation of insula and PFC but only in patients with history of suicide attempt for PFC sulcation. Among the maltreatment dimensions, emotional abuse is considered the strongest factor associated with suicide attempts (de Araújo and Lara 2016). However, compared with physical and sexual abuse, little is known so far about the effects of childhood emotional abuse on suicidality and its underlying mechanisms (Lee

2015). By including euthymic patients in the control group (AC), the detected r-SI differences in suicide attempters (SA) can be attributed to differences in suicidal vulnerability traits and not to the depressive state or mood disorder. Using (euthymic) patients as controls therefore allows limiting the influence of the psychopathology (i.e. mood disorder) and medication load, thus isolating specific factors of suicidal vulnerability.

The difference in insula cortex sulcation in patients with history of childhood emotional abuse is in line with a previous study that reported an association between early life event exposure and CT in this region (Baker et al. 2013). Insula is involved in various cognitive, affective, and sensory functions. This region is activated in response to negative emotions, mainly anger and fear, in adults with early-life adversities (Javanbakht et al. 2015, (Neukel et al. 2018). Individuals with history of childhood emotional abuse may be sensitized to conflictual or threatening stimuli through altered emotional processing in insula. Indeed, maltreated children have deficits in emotion discrimination (Fries and Pollak) and display response bias to negative cues (Pollak and Sinha , (Pollak and Tolley-Schell 2003).

The difference in PFC in suicide attempters is in line with structural and functional alterations in the orbital frontal cortex, anterior cingulate cortex and striatum (Zhang et al. 2014). A recent multimodal structural and functional neuroimaging study in adolescent/young adult suicide attempters showed decreased gray matter volumes and structural and functional connectivity abnormalities in the ventral fronto-limbic neural system (Johnston et al. 2017). To our knowledge, only post-mortem studies investigated neurobiological changes in individuals with history of suicide attempt and childhood maltreatment. For instance, BDNF protein level was lower in the anterior cingulate cortex, but not in dorsolateral PFC in people who died by suicide than in individuals who died suddenly, independently of exposure to early life adversity (Youssef et al. 2018). Post-mortem brain analysis of suicide and non-suicide decedents found

reduced CT in PFC, whereas glial density was increased in subjects with early life adversity, independently of their suicide status (Underwood et al. 2019). Moreover, in the medial PFC white matter, the density of pre-myelinating oligodendrocytes was reduced and that of mature oligodendrocytes was increased in suicide decedents with history of childhood abuse compared with decedents without such history and controls (Tanti et al. 2018). These results suggest structural modifications in PFC linked to SB and exposure to childhood adversity and highlight the need of *in vivo* studies.

We showed a hemispheric asymmetry in medial PFC for patients having a history of sexual abuse. Interestingly, altered PFC lateralization has been associated with mood disorders (Yucel et al. 2009, (Zuo et al. 2019) and impairments of executive functions, such as cognitive set shifting (Taylor et al. 1997, (Konishi et al. 2002) and inhibition (Cachia et al. 2014, (Tissier et al. 2018). Sexual abuse, poor cognitive flexibility and inhibition and depression are associated with suicidal risk (Marzuk et al. 2005, (Richard-Devantoy et al. 2014). The lack of significant interaction between sexual abuse and group on PFC sulcation in our data might be due to statistical power issues related to the low frequency of this abuse dimensions in our sample.

Several methodological issues call for caution when interpreting our results. First, we only included women in this study because childhood maltreatment is more frequent in girls (Moody et al. 2018), and to limit bias related to cortex anatomy sexual dimorphism (Duchesnay et al. 2007, (Raznahan et al. 2011). Future studies should be carried out in men to extend the findings. Second, retrospective self-report data on childhood maltreatment may be subject to memory bias, although consistency between such data and documented events has been reported (Martins et al. 2014). Third, the sulcal analyses were performed at the lobe-level and

not at the sulcus-level, which therefore prevents from investigating specific effects within the insular and prefrontal cortices. It was therefore not possible to investigate whether the observed effects were driven by all the sulci, or only by specific sulci (e.g. emerging earliest or latest in gestation), of the studied cortical areas. Four, our euthymic AC sample included many patients with past depressive episodes requiring long-term treatment. We did not take into account the precise duration of all psychotropic treatment because it is supposed to be stable for months in euthymic patients. However, our findings are unlikely not related to medication because 1) analyses controlling for medication yielded similar findings, 2) medication load was comparable between groups (AC and SA), and 3) CTQ emotional sub-scores and medication load were not correlated. Finally, adolescence is a vulnerability developmental window for psychiatric disorders (Paus et al. 2008), including SB (Hawton et al. 2012). As asynchronous maturation of PFC and limbic regions, including insula, is a critical pathophysiological process for mood disorders (Shulman et al. 2016), it could be interesting to replicate the current study in independent sample of adolescent patients.

5. CONCLUSION

Our study is the first to provide evidence that suicidal behavior can be traced back to early stages of brain development in interaction with later environmental factors experienced early in life. As early adversity can interact with genetic factors (e.g. serotonergic system), future multi-level integrative studies should investigate the relative influence of genetic, environmental and neurodevelopmental factors

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7. CONFLICT OF INTEREST: Authors declare no competing financial interests in relation to the work described

8. AUTHORS CONTRIBUTION

EO & AC : Conceptualization ; Investigation ; Formal analysis; Writing - original draft

ELB & JD : Data curation ; Resources; Review & editing.

CO and PC : Supervision ; Writing - review & editing

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10.TABLE

Table 1 : Demographic and clinical characteristics of the 86 participants enrolled in the study:
44 suicide attempters (SA) and 42 affective controls (AC).

	AC (N=42)	SA (N=44)	AC vs SA (p-value)
Age	36.3 ± 7.27	38 ± 9.9	0.31
Level of education (years)	14.64 ± 1.93	14 ± 1.9	0.09
General IQ (NART)	22.02 ± 2.94	22.33 ± 3.63	0.75
Age at first depressive episode	25 ± 8.08	23.47 ± 8.2	0.48
Number of depressive episodes	4.37 ± 8.4	6.21 ± 8.26	0.34
Number of manic episodes	2.1 ± 7.78	2.98 ± 8.66	0.59
Duration of mood disorder	11.30 ± 8.22	15.58 ± 10.96	0.06
Medication load	2.44 ± 2.03	2.88 ± 2.15	0.32
Age at first suicide attempt (years)	-	24.80 ± 8.21	-
Number of suicide attempt	-	3.12 ± 2.57	-
Impulsivity (BIS-10)	46.43 ± 13.3	49.78 ± 14.1	0.25
Anger dimensions (STAXI)			
<i>Trait</i>	19.2 ± 4.1	19.4 ± 5.7	0.81
<i>State</i>	13.33 ± 4.5	13.0 ± 4.2	0.72
<i>Anger in</i>	15.7 ± 4.1	17.4 ± 5.8	0.12
<i>Anger out</i>	13.3 ± 3.8	13.1 ± 4.0	0.80
<i>Anger control</i>	23.7 ± 4.4	23.3 ± 4.2	0.68
<i>Trait temperament</i>	9.1 ± 2.7	9.3 ± 3.1	0.76
<i>Trait reaction</i>	10.1 ± 2.6	10.1 ± 3.2	0.92
Childhood maltreatment (CTQ)			
Moderate/Severe			
<i>Physical abuse</i>	5 (11.9)	3 (6.8)	0,42

<i>Emotional neglect</i>	13 (30.9)	21 (50)	0.12
<i>Sexual abuse</i>	7 (16.6)	9 (20.4)	0.65
<i>Emotional abuse</i>	15 (35.7)	18 (42 .8)	0.62
<i>Physical neglect</i>	7 (16.6)	9 (20.4)	0.65
Bipolar disorder	16 (38.1)	25 (56.8)	0.08
Psychiatric comorbidities			
<i>Current social phobia</i>	2 (4.7)	6 (13.6)	0.16
<i>Current OCD</i>	1 (2.3)	0 (0)	0.30
<i>Current Panic disorder w/o agoraphobia</i>	1 (2.3)	0 (0)	0.30
<i>Current Agoraphobia</i>	3 (7.1)	5 (11.3)	0.50
<i>Current Panic disorder with agoraphobia</i>	1 (2.3)	5 (11.3)	0.10
<i>Current PTSD</i>	0 (0)	1 (2.2)	0.32
<i>Current GAD</i>	8 (19.0)	8 (18.2)	0.91
<i>Current Bulimia nervosa</i>	1 (2.3)	0 (0)	0.30
<i>Past history of alcohol abuse /dependence</i>	5 (11.5)	6 (13.6)	0.55
<i>Past history of illicit drug abuse /dependence</i>	4 (9.2)	6 (13.6)	0.41

Group-comparisons of quantitative [Mean \pm SD] and qualitative [N (%)] data were based on bilateral Student's *t* and Chi2 or Fisher tests, respectively.

BIS-10 : Baratt Impulsivity Scale 10 items ; *CTQ* : Childhood Trauma Questionnaire ; *GAD* : Generalized Anxiety Disorder ; *NART* : National Adult Reading Task ; *OCD* : Obsessive Compulsive Disorder ; *PTSD* : Post Traumatic Stress Disorder ; *STAXI* : State-Trait Anger Expression Inventory

11.FIGURE

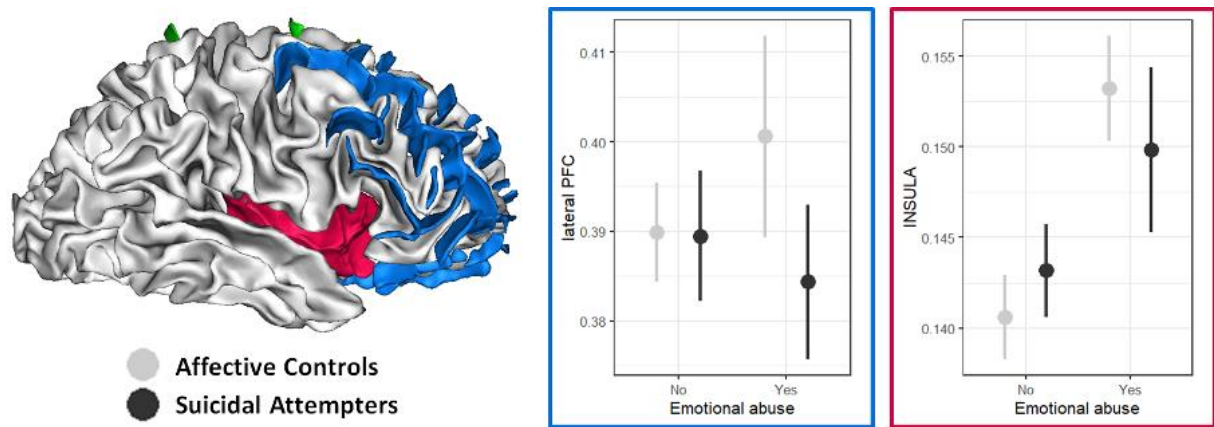


Figure 1: Interaction between emotional abuse and history of suicide attempt on cortical sulcation. Left panel: 3D reconstruction of the inner cortical surface (gray/white interface) with the lateral PFC in blue and insula in red. Middle and right panels: Regional r-SI of the lateral PFC (blue box) and insula (red box) in affective controls (light gray) and suicide attempters (black). Error bars denote the standard error of the mean.