REPATRIATION IS ASSOCIATED WITH ISTHMUS CINGULATE CORTEX REDUCTION IN COMMUNITY-DWELLING ELDERLY

Raffaella Calati, Psy.D., Ph.D.[a, b, c], Jerome J Maller, Ph.D.[d, e], Chantal Meslin, MD[f], Jorge Lopez-Castroman, MD, Ph.D.[a, g], Karen Ritchie, Ph.D.[a], Philippe Courtet, MD, Ph.D.[a, b, c], Sylvaine Artero, Ph.D.[a]

[a] INSERM U1061, La Colombière Hospital, University of Montpellier UM1, Montpellier, France

[b] FondaMental Foundation, France

[c] Department of Psychiatric Emergency & Acute Care, Lapeyronie Hospital, CHU Montpellier, Montpellier, France

[d] Monash Alfred Psychiatry Research Centre, The Alfred & Monash University Central Clinical School, Melbourne Victoria, Australia

[e] General Electric Healthcare, Victoria, Australia

[f] Centre for Mental Health Research, Australian National University, Canberra Australia

[g] Department of Adult Psychiatry, CHRU Nimes, Nimes, France

Running title: stress and imaging in elderly.

To whom correspondence should be addressed:

Raffaella Calati, Psy.D. Ph.D.

INSERM U1061

University of Montpellier UM1, Montpellier, France

E-mail: raffaella.calati@gmail.com

Abstract

Objectives: The impact of stressful life events (SLEs) on brain anatomy is poorly understood, particularly its long-term neural consequences. We tested the hypothesis that a serious SLE (repatriation of French citizens living in Algeria in 1962) is associated with changes in brain regions previously implicated in psychopathology (hippocampus, amygdala, corpus callosum, prefrontal cortex, anterior, posterior and isthmus cingulate cortex (ICC) in a large elderly population.

Methods: Structural magnetic resonance imaging was used to acquire anatomical scans from 82 subjects repatriated from Algeria and 339 subjects without this experience or any other trauma. We derived quantitative regional estimates of subcortical volume using FreeSurfer Software. The General Linear Model was used to test the association between repatriation and changes in brain volume adjusted for confounders (gender, age, education, total brain volume, traumatic brain injury, Mini Mental State Examination score at baseline, current and lifetime major depression, and recent SLEs).

Results: Repatriation to France was associated with reduced volume in a number of areas, however only left and right ICC survived to false discovery rate correction.

Conclusions: In elderly a previous (approximately 40 years before) serious SLE could be associated with long term volume reduction in the ICC, independently of psychopathology.

Key words: stress, brain imaging, biological psychiatry.

INTRODUCTION

Stressful life events (SLEs) are a major risk factor not only for the development of psychopathology, in particular major depression and anxiety disorders (G. W. Brown 1993; Kendler, Karkowski, & Prescott 1999; Kessler 1997; Mandelli, Petrelli, & Serretti 2015), but also for a number of chronic diseases (e.g., cardiovascular disease, type II diabetes, cancer, autoimmune disorders) (Fagundes, Glaser, & Kiecolt-Glaser 2013; Miller, Chen, & Parker 2011) up to premature death (D. W. Brown et al. 2009).

Compared to healthy individuals, subjects with mental disorders (e.g., depression) have been exposed to a higher rate of SLEs, and to more severe ones (Bandelow, Gutermann, Peter, & Wedekind 2013; Horesh, Ratner, Laor, & Toren 2008; Kendler, Kuhn, & Prescott 2004). Some studies have also reported an association between re-victimization (experiencing both childhood and adult sexual abuse) and some mental disorders (mixed anxiety and depression, generalized anxiety disorder, phobia, post-traumatic stress disorder (PTSD), and suicidal ideation) (Chou 2012). Moreover, the type of stressors is relevant: for example, stressors of social origin play a major role in depression (Chaouloff 2013). Additionally, specific biological factors could be linked to the development of psychiatric disorders (e.g., depression (Assareh, Sharpley, McFarlane, & Sachdev 2015; Hughes, Connor, & Harkin 2016)) in response to SLEs and different biological systems are involved, including the immune system and the neuroendocrine one (I. P. Watson, Brune, & Bradley 2016).

Stress has been associated with changes in structure, morphology, and function of some key brain regions. In particular, the experience of stress predicted volume reductions in the hippocampus, amygdala, corpus callosum, prefrontal cortex (PFC), and anterior cingulate cortex (ACC) in non-clinical samples (Cohen et al. 2006; Gianaros et al. 2007; McCrory, De Brito, & Viding 2011; McEwen 2006; Papagni et al. 2011; Zannas et al. 2013). Hence, SLEs *per se* may have detrimental effects on brain integrity, independent of psychopathology. Moreover, the same regions were repeatedly found to be reduced in some psychiatric disorders, such as anxiety disorders (Duval, Javanbakht, & Liberzon 2015), and in particular PTSD (Li et al. 2014; O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos 2015), depression (Arnone, McIntosh, Ebmeier, Munafo, & Anderson 2012), and suicidal behavior in depression (Zhang, Chen, Jia, & Gong 2014), even if contrasting results are present as well (see, as an example, a review reporting inconsistent volumetric findings in pediatric PTSD and obsessive compulsive disorder (Ahmed, Ras, & Seedat 2012)).

In the same line of evidence, functional brain imaging studies evidenced the involvement of the same areas (as an example, see for PTSD (Bremner 2007)). In particular, resting-state functional abnormalities in the cerebral glucose metabolism were found in hippocampus, pre-frontal regions, cingulate gyri, and further areas in PTSD veterans compared to controls, even 20 years after the traumatic events (Molina, Isoardi, Prado, & Bentolila 2010; Shin et al. 2009).

Among others, the areas of the cingulum have been extensively examined but structural changes have been mostly observed in rostral areas. More recently the posterior cingulate cortex (PCC) was reported to be reduced in late-onset depression (Lim et al. 2012). Moreover, a PCC role in the mediation of emotional resilience to stress has been reported (Wood et al. 2015) as well as a higher activation in acute PTSD during functional magnetic resonance imaging (Ke et al. 2015). In addition, the isthmus cingulate cortex (ICC) volume was reported to be bilaterally reduced in highly traumatized male refugees with and without PTSD in comparison with non-traumatized controls (Eckart et al. 2011). However, in this study a high comorbidity between PTSD and major depression was present, so the effect of depression could not be disentangled. In fact, a role of ICC in depression has been reported as well: reduced right ICC volume was found to be associated with lower depressed mood (McLaren et al. 2016). Hence, considering the increasing interest on the relation between SLE exposure and cingulum caudal portions, this area could be a further candidate for the study of stress related changes.

To our knowledge, only a few studies have examined the longitudinal effects of life stress on brain volume in late-life, so we sought to better elucidate them. The considered SLE was the repatriation to France of French citizens living in Algeria after Algeria became independent in 1962 (decolonization conflict). A number of these subjects have been repatriated to Montpellier, in the south of France, where this study took place. They experienced numerous bomb attacks, profound dislocations, they were uprooted from their homes in Algeria, lost almost all their possessions and confronted poor living conditions on arrival. This cohort has some unique features since it has been exposed to a single shared highly stressful event that occurred in a well-defined period. Consequently, the environmental component variable has been rigorously defined in comparison to previous studies.

We examined the association between the repatriation in 1962 and volume of hippocampus, amygdala, corpus callosum, PFC, ACC, PCC, and ICC regions, about 40 years after, in a

cohort of French elderly people from the ESPRIT study (from the name of the project: “Enquête de Santé Psychologique – Risques, Incidence et Traitement”). Based on existing evidence, our a priori hypothesis was that the stressful experience of repatriation (together with concomitant environmental circumstances related to the war) would be associated with reduced volume in the investigated regions.

MATERIALS AND METHODS

Study design and sample

This study was part of a project named "Enquête de Santé Psychologique – Risques, Incidence et Traitement" (ESPRIT), a prospective general population study performed in the Montpellier region of the south of France on lifetime psychiatric disorder in elderly subjects (over 65 years old). The project has been described in detail elsewhere (Ritchie et al. 2004). Briefly, a random sample of 1863 community subjects was collected from the 15 electoral rolls of the Montpellier district between March 1999 and February 2001. In 1962, about 80000 French repatriates arrived in Montpellier from Algeria, constituting at the time a fifth of the population. In our cohort 13% of participants had been repatriated from Algeria.
Participants were examined at the Gui de Chauliac Neurology Hospital of Montpellier. They underwent clinical examination and standardized assessment administered by trained staff. Ethical approval was obtained by the ethics committee and written informed consent was obtained by all the participants.

Measurement of exposure

In the present study we focused on a sub-sample for which the MRI scan data was available. In particular we identified 82 repatriates from Algeria by a questionnaire relating to past SLEs, comprising the repatriation, which has been created for the ESPRIT study and which allows to screen repatriates from other participants (see also (Artero, Touchon, Dupuy, Malafosse, & Ritchie 2011)). Repatriates experienced loss of possessions, unemployment and social disorganization, but also war-related traumatic events such as attacks, witnessing severe injury or death.
A control group was constituted from 339 participants in the ESPRIT study who had not been repatriated and had not experienced any other form of severe trauma (war, sexual abuse, to have seen other people killed, etc.) (measured using the first item of the scale PTSD Interview (PTSD-I) (C. G. Watson, Juba, Manifold, Kucala, & Anderson 1991)). Participants with dementia diagnosis were excluded (n=13, see Figure 1 for the flow-chart).

Other measurements

A standardized interview included questions on demographics characteristics and education level along with a general health questionnaire including medical history, medications, current alcohol consumption, and tobacco use. Lifetime psychiatric disorders were assessed by the Mini International Neuropsychiatric Interview (MINI; French version 5.00), validated in the general population setting, which provides DSM-IV diagnoses (Sheehan et al. 1998). All cases were validated by a panel of psychiatrists masked to repatriation status. Due to the age of the participants (over 65 years), cognitive impairment was included as an adjustment factor in statistical analyses. We used the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh 1975).

A standardized neurological examination based on the International Classification of Diseases (ICD-10) criteria (World Health Organization 1992) was used as well, comprising the diagnosis of dementia and the evaluation of traumatic brain injuries (Folstein et al. 1975). As recent negative life events may confound the relationship with past events, the occurrence of negative events occurring in the past year (notably bereavement, rupture in significant relationships, financial and legal problems, dismissal, severe illness, loss of a highly valued object) was ascertained using the 12-item Gospel Oak questionnaire (Harwood, Prince, Mann, & Ebrahim 1998).

Imaging analyses

Anatomical scans were acquired in the period 1999-2001, almost 40 years after the repatriation from Algeria of 82 participants to this study. A 1.5 T GE Signa Imaging System (General Electric Medical Systems, Milwaukee, WI) was used to acquire a contiguous AC-PC aligned axial IR-prepared SPGR T1-weighted sequence for volumetric estimations (TR=12, TE=2.8, IT=600, matrix size=256×256, pixel spacing=0.9375×0.9375 mm, NEX=1, slice thickness=1.0 mm).

Regional reconstruction and segmentation was performed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). This contains several stages, the first of which comprised the reconstruction of the cortical surface (Dale, Fischl, & Sereno 1999). Normalized intensity images were created, corrected for the variations in intensity due to magnetic field inhomogeneity. Voxels beyond the cerebral cortex, namely the skull, were then removed before segmentation initiated. Segmentation is based on the geometric structure where grey and white matter interface, and subsequently separates the left and right

hemispheres as well as cortical from subcortical structures. The resulting cortical volume is covered in a triangular tessellation and deformed to more accurately represent grey and white matter interface as well as the pial surface. Once the cortex has been reconstructed, this volume is registered to a spherical atlas (Fischl, Sereno, & Dale 1999; Fischl, Sereno, Tootell, & Dale 1999) and parcellated into regions based on the sulcal and gyral structures (Desikan et al. 2006; Fischl et al. 2004). Regions of interest (ROIs) were defined using the Desikan's atlas (Desikan et al. 2006). Each T1-weighted scan is segmented into cortical and subcortical regions in each hemisphere. Data were then exported into SPSS for analysis (the output of FreeSurfer, mm^3 volumes for each region, was in .dat format and then imported into SPSS). Total brain volume (gray plus white matter) was computed for each subject using the 'segment' m-file of the SPM5 software (Wellcome Department of Cognitive Neurology, UK). These data were used as covariates to minimize the effect because of global brain size differences.

Statistical analyses

Statistical analyses were performed using SPSS version 22.0 for Windows (Corp. 2013). Descriptive analyses were carried out using Student t-test or chi square test based on the variable characteristics. Brain measurements were found to be normally distributed based on graphs. The General Linear Model (GLM) was used to compare the brain volume of the 7 selected regions (hippocampus, amygdala, corpus callosum, PFC, ACC, PCC, and ICC) between repatriated subjects (REPAT) and controls subjects. We considered the following variables as potentially associated with brain size structures: gender, age, education level, total brain volume, traumatic brain injury, MMSE score at baseline, current and lifetime major depression, and recent life events.

All p-values were 2-tailed, and the significance threshold was adjusted using the Benjamini-Hochberg false discovery rate (FDR; $q \leq 0.003$) correction for multiple comparisons, in order to reduce false positive results.

RESULTS

Socio-demographic and clinical features of the sample are shown in Table 1. The only slight difference between REPAT subjects and control subjects was the prevalence of current and lifetime PTSD (1.2% versus 0.0%, p=0.04).

GLM was used to test influences of repatriation on brain volume of hippocampus, amygdala, corpus callosum, PFC, ACC, PCC, and ICC. Brain volumes of the investigated regions in the two groups are reported in Table 2. The repatriation to France was associated with reduced volume in a number of areas (left amygdala, anterior and mid-anterior corpus callosum, PFC portions, left caudal ACC, left and right PCC, and left and right ICC), however, after FDR correction, only the left and right ICC were found to be reduced in REPAT subjects (left volume: p=0.001; right volume: p<0.0001). In our model lifetime major depression was not associated with ICC volume (left volume: p=0.98; right volume: p=0.96).

DISCUSSION

In the present study we examined the longitudinal effects of life stress on brain volume in late-life. The hypothesis was that a highly stressful life event - the repatriation of French citizens living in Algeria in 1962 - could be associated with structural changes in brain regions previously reported to show stress- and psychopathology-related changes. In particular, we analyzed differences in hippocampus, amygdala, corpus callosum, prefrontal cortex (PFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and isthmus cingulate cortex (ICC) volumes between 82 elderly subjects repatriated from Algeria (REPAT) and 339 elderly subjects without this experience or any other form of trauma. Structural magnetic resonance imaging was used to acquire anatomical scans about 40 years after the repatriation experience.

REPAT subjects reported reduced volumes in the ICC. This was the only association that survived FDR correction. Volume reductions were found to be bilateral and they were independent of gender, age, education level, total brain volume, traumatic brain injury, Mini Mental State Examination score at baseline, current and lifetime major depression, and recent life events.

The ICC connects the PCC to the parahippocampal gyrus. It is located behind the thalamus, posteroinferior to the splenium of the corpus callosum, and medial to the superior cerebellar cistern (Mark, Daniels, Naidich, & Borne 1993). A larger proportional isthmus has been found in females (both right- and left-handed) in comparison to males (right-handed) (Witelson 1989). Since the isthmus was found to be a language-related area (left hemisphere) (Binder et al. 1997), the reported sexual difference may be linked to differences in hemispheric language organization between males and females. Moreover, the ICC includes the retrosplenial cortex (Brodmann areas 29 and 30) and overlaps with the more broad retrosplenial complex area, that are involved in spatial cognition (Bar & Aminoff 2003) and episodic memory (Valenstein et al. 1987).

Our findings are consistent with previous literature findings, even if the investigated imaging phenotypes were frequently different (volume, thickness). For instance, highly traumatized Kurdish male refugees with and without PTSD (n=20 and n=19) showed reduced bilateral ICC volume in comparison with non-traumatized controls (n=13) (Eckart et al. 2011). Also in this study traumatized participants were exposed to traumatic stress several years before the assessment: 44% reported their first traumatic event 10–20 years before while 41% even more

than 20 years before. Another common point of this study with the present one is the fact that participants were exposed to similar severe traumatic experiences. Authors underlined as a limitation of their study the high comorbidity of PTSD and major depression in their sample. However, in the present study lifetime major depression did not modulate the results. This is in contrast with previous findings: firstly, reduced right ICC volume was found to be associated with lower depressed mood (McLaren et al. 2016); moreover, elderly with high depressive symptom severity were reported to have higher ICC thickness (Szymkowicz et al. 2015); finally, a positive correlation has been found between ICC thickness and memory functions (verbal learning) in late-onset depression (Lim et al. 2012).

In our sample no group difference in terms of depression and anxiety disorder rates affect the group difference in brain volume. In particular, the sample showed a low PTSD rate (1.2%) among REPAT subjects in comparison with previous prevalence studies (Atwoli, Stein, Koenen, & McLaughlin 2015). The REPAT group is a voluntary group from a population study, so we could consider the REPAT group as characterized by high resilience, which could be explained, for example, by the high social support within the community of REPATs. This point is interesting: ICC could be a region related to resilience, however more research is needed to further investigate this issue. Actually, the search of biomarkers allowing the identification of individuals with resilience is warranted (Schmidt et al. 2015). To this aim, a transdiagnostic study inclusive of healthy controls, individuals with SLEs or/and early life stress but without a psychiatric disorder and a psychiatric disorder group composed of PTSD and depressed subjects (the two major psychiatric diagnoses associated with trauma) could be of interest.

The experience of displacements of war-refugees is extremely heterogeneous in its phenomenology. In a recent review, 29 studies on the long-term mental health of 16.010 war-affected refugees have been identified (Bogic, Njoku, & Priebe 2015). Prevalence rates of depression, PTSD and unspecified anxiety disorder were heterogeneous (range: 2.3-88%). However, lower prevalence rates were reported in studies of higher methodological quality. Moreover, pre-displacement traumatic experiences and post-displacement stress were factors associated with the three disorders. In a further recent review of qualitative studies, six sources of resilience have been identified among young refugees: social support, acculturation strategies, education, religion, avoidance, and hope (Sleijpen, Boeije, Kleber, & Mooren 2016). Unfortunately, data on pre-displacement traumatic experiences and post-displacement stress and ways of dealing with adversity were not available for our REPAT sample.

Moreover, the experience of repatriation differs from displacements of war-refugees and this should be taken into account.

Even if findings on the other areas did not survive to correction, they are worthy of consideration and comments. Firstly, we can speculate that the experience of repatriation could have solicited the capacity of adaptation of the involved subjects and that this fact could be associated with a hypothetical restoration of brain integrity. In populations affected by conflict-driven forced migration, resilience was found to be influenced by highlighted family and community cohesion, family and community support, individual personal qualities, collective identity, supportive primary relationships and religion (Siriwardhana, Ali, Roberts, & Stewart 2014). Unfortunately, it was not possible to determine if the other investigated ROIs were affected or not at the time of repatriation.

A secondary consideration could be that the absence of group difference in the rates of psychiatric disorders could be supported by the absence of differences in several further regions of interest (ROIs).

The amygdala and the corpus callosum have been widely studied in relation to trauma. No differences in amygdala volume between PTSD subjects and trauma-exposed controls without PTSD were found in 10 meta-analyzed articles (O'Doherty et al. 2015). However, a medium effect size volume reduction of the combined left and right amygdala was found when PTSD subjects were compared with healthy controls (6 studies). Authors suggested that, rather than amygdala volume itself being a biomarker of PTSD susceptibility, the pre- and post-morbid ratio between the amygdala and the ACC might be relevant. The corpus callosum as well has been widely studied in relation to childhood trauma and it was found to be reduced in its presence (Brietzke et al. 2012; Rinne-Albers, van der Wee, Lamers-Winkelman, & Vermeiren 2013).

The rostral middle frontal area is located near the dorsolateral prefrontal cortex (DLPFC), having a role in emotion regulation, especially pertaining the control of negative emotions (Feder, Nestler, & Charney 2009). It has been found to be reduced in patients with chronic schizophrenia (Kikinis et al. 2010). Consistently with our findings, both PTSD refugees and traumatized refugees without PTSD showed reduced volumes in the left portion of this area (Eckart et al. 2011). In an interesting longitudinal study on disaster survivors, subjects early in the course of PTSD showed greater DLPFC thickness relative to controls (Lyoo et al. 2011). Moreover, this greater DLPFC thickness was associated with earlier improvement in PTSD

symptoms several years later. Hence, a connection between changes in this region and psychological recovery from a severely traumatic event has been underlined. Unfortunately in the present study it was not possible to clarify if present results could be related to the consequences of the distress or to resilience capacities or to both. Future neuroimaging studies focused on resilience could be interesting (van der Werff, Pannekoek, Stein, & van der Wee 2013).

Pertaining to caudal ACC, in a recent study, veterans with and without PTSD showed reduced functional connectivity of this area with the precentral gyrus as compared to healthy controls (Kennis, Rademaker, van Rooij, Kahn, & Geuze 2015). Consequently, trauma exposure, independently of PTSD development, could influence not only the morphology of the caudal ACC but also its network. Moreover, caudal ACC volume was positively correlated with improvement in depressive symptoms after individual cognitive behavioral therapy (Fujino et al. 2015).

Concerning PCC, left PCC thickness showed an opposite association with current severity of PTSD symptoms dependent on history of interpersonal early trauma: patients exposed to trauma showed a positive association between cortical thickness and current PTSD symptoms severity, whereas controls showed a negative association (Corbo et al. 2014). PCC, together with the medial PFC, is a primary node of the default mode network (Leech & Sharp 2014), and it is implicated in memory-related processes, such as internally directed thoughts (e.g., autobiographical memories retrievement). This could be linked to the re-experience of trauma.

This study has some major strengths: the large sample size, the population-based design, and the exposition of REPAT subjects to a single shared highly stressful event that occurred in a well-defined period. However, our findings should be considered with caution because of the following limitations: 1) the small sample size of REPAT subjects (n=82); 2) the fact that we have not obtained brain scans near the repatriation but only brain scans acquired about 40 years after the repatriation experience: thus, it was not possible to establish whether the observed structural changes had become evident within weeks, months, or years; 3) the lack of information about the connectivity between brain regions; 4) the automatic segmentation in Freesurfer does not currently include the hypothalamus alone (but only together with other ROIs); this is a limitation since the hypothalamus is a key stress-related region, so further studies focusing on it are warranted.

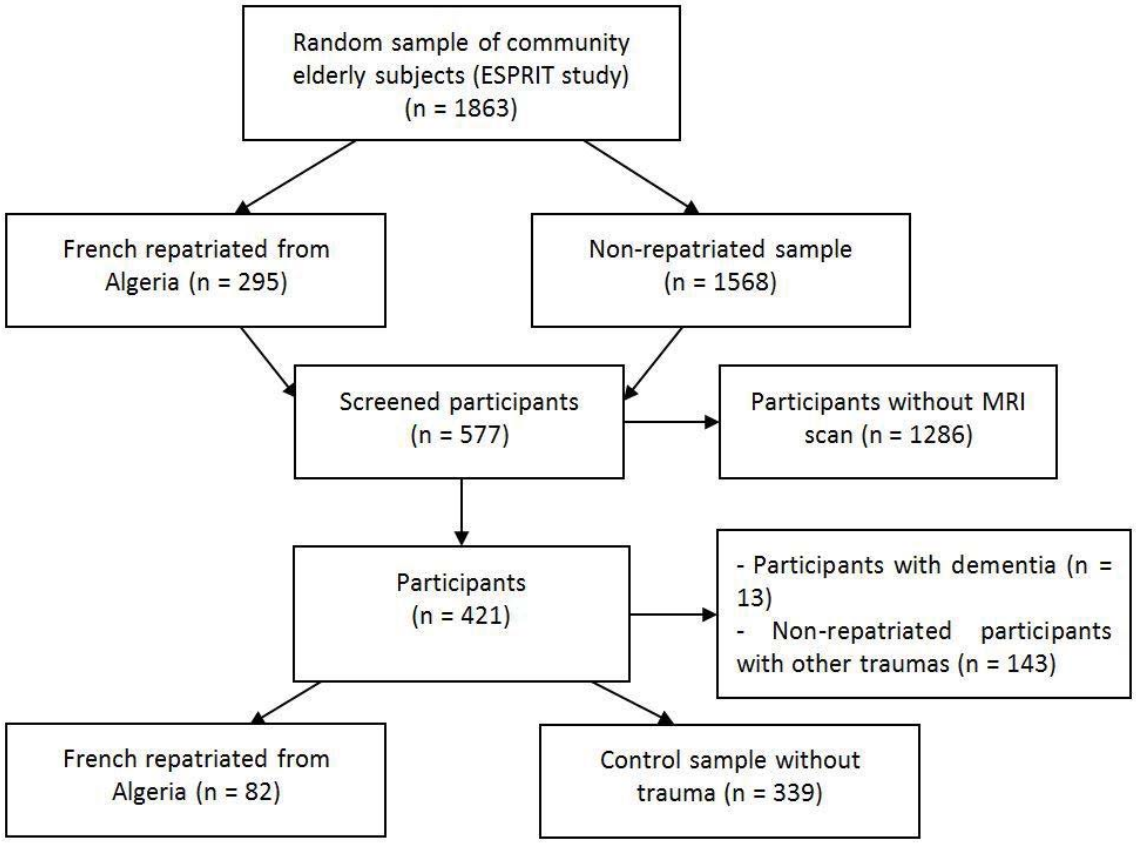
In conclusion, despite these limitations, our observations support previous reports indicating the long-term impact of stressful life events on brain anatomy, independently of co-occurring psychiatric disorders, in an elderly general population.

Acknowledgements

Dr. Raffaella Calati received a grant from FondaMental Foundation, France. Prof. Philippe Courtet received research grants from Servier, and fees for presentations at congresses or participation in scientific boards from AstraZeneca, Bristol-Myers-Squibb, Janssen, Lilly, Lundbeck, Otsuka, Roche, and Servier.

Statement of interest: None to declare

Figure 1. Flow chart of the inclusion/exclusion process of participants.



Socio-demographic and clinical variables	Repatriation from Algeria n, % or mean±SD		t/χ2	d.f.	p
	REPAT group (n=82)	Control group (n=339)			
Gender (males)	37, 45.1%	154, 45.4%	0.01	1	0.96
Age (years)	71.28±3.94	70.88±3.68	-0.87	419	0.39
Education			6.48	3	0.09
None-Low	27, 32.9%	76, 22.4%			
Moderate	25, 30.5%	101, 29.8%			
High	16, 19.5%	64, 18.9%			
Very high	14, 17.1%	98, 28.9%			
Marital status			2.32	4	0.68
Single	2, 2.4%	11, 3.2%			
Married	60, 73.2%	253, 74.6%			
Divorced or separated	8, 9.8%	24, 7.1%			
Widowed	12, 14.6%	45, 13.3%			
Other	0, 0.0%	6, 1.8%			
Living alone (yes) (missing n=1)	18, 22.0%	63, 18.6%	0.46	1	0.49
Total brain volume (cm3)	1017.61±160.64	1021.35±99.82	0.27	419	0.79
Traumatic brain injury	5, 6.1%	26, 7.7%	0.24	1	0.62
MMSE	27.35±1.83	27.57±1.78	0.98	419	0.33
<26	11, 13.4%	42, 12.4%	0.06	1	0.80
≥26	71, 86.6%	297, 87.6%			
Recent life events (yes)	51, 62.2%	196, 57.8%	0.52	1	0.47
Current and lifetime major depressive episode (MINI)	21, 25.6%	75, 22.1%	0.46	1	0.50
Insomnia (missing n=13)	17, 21.8%	62, 18.8%	0.36	1	0.55
PTSD (MINI)	1, 1.2%	0, 0.0%	4.14	1	0.04
Anxiety disorders (MINI)	18, 22.0%	62, 18.3%	0.57	1	0.45
Alcohol (dependence/abuse) (yes) (missing n=62)	1, 1.5%	2, 0.7%	0.45	1	0.50
Tobacco			1.63	2	0.44
No	48, 58.5%	185, 54.6%			
Past smoker	30, 36.6%	123, 36.3%			
Smoker	4, 4.9%	31, 9.1%			
Handedness (missing n=3)			0.06	2	0.97
Left-handedness	2, 2.5%	10, 3.0%			
Ambidexterity	3, 3.7%	12, 3.6%			
Stroke (missing n=2)	2, 2.5%	12, 3.6%	0.24	1	0.63
Hypercholesterolemia (treatment or cholesterol ≥6.2) (yes) (missing n=1)	41, 50.0%	182, 53.8%	0.39	1	0.53
Diabetes at baseline (missing n=2)			2.13	2	0.34

Glycemia <6.1	75, 91.5%	297, 88.1%			
6.1≤ glycemia <7	3, 3.7%	8, 2.4%			
Treatment or glycemia ≥7	4, 4.9%	32, 9.5%			
BMI (missing n=3)	24.98±2.90	24.74±3.28	-0.61	416	0.54

Table 1. Socio-demographic and clinical features in subjects repatriated from Algeria (REPAT, n=82) and controls (n=339) (MMSE: Mini Mental State Examination; PTSD: post-traumatic stress disorder; MINI: Mini International Neuropsychiatric Interview; BMI: Body Mass Index).

Cortical ROIs (volume mm^3)	Hemisphere	Repatriation		F	GLM p
		REPAT group (n=82)	Control group (n=339)		
Hippocampus	L	3527.14±485.66	3604.49±482.95	0.83	0.36
	R	3432.59±432.60	3508.39±439.26	1.21	0.27
Amygdala	L	1254.13±199.17	1319.86±223.18	5.21	0.02
	R	1282.83±206.69	1311.81±240.25	0.57	0.45
Anterior corpus callosum		754.05±169.02	796.73±156.18	3.90	0.05
Mid-anterior corpus callosum		351.53±86.88	378.99±92.45	5.65	0.02
Central corpus callosum		339.97±63.05	354.99±69.43	2.97	0.08
Posterior corpus callosum		826.26±164.81	844.03±148.47	0.55	0.46
Mid-posterior corpus callosum		320.84±66.95	329.59±73.34	0.69	0.41
Frontal pole	L	834.23±192.99	840.83±191.37	0.03	0.87
	R	1082.40±239.67	1051.07±226.90	1.43	0.23
Lateral orbitofrontal cortex	L	5592.10±750.00	5797.29±685.03	5.43	0.02
	R	5716.99±735.25	5929.95±749.40	5.17	0.02
Medial orbitofrontal cortex	L	4678.52±796.92	4832.06±755.31	2.18	0.14
	R	4041.60±623.06	4151.91±566.18	2.44	0.12
Rostral middle frontal cortex	L	11874.99±1847.73	12363.21±1641.70	7.19	0.008
	R	11723.66±1713.80	12205.51±1719.37	5.90	0.02
Caudal middle frontal cortex	L	4473.24±921.02	4639.14±842.81	2.27	0.13
	R	4667.27±837.80	4874.76±884.81	4.33	0.04
Superior frontal cortex	L	17376.73±2232.29	17755.93±2144.17	1.82	0.18
	R	16930.46±2242.10	17325.76±2151.55	1.90	0.17
Rostral anterior cingulate cortex	L	1660.77±373.57	1689.94±398.20	0.09	0.76
	R	1608.38±491.61	1644.92±457.83	0.29	0.59
Caudal anterior cingulate cortex	L	1475.37±313.89	1586.57±390.65	5.43	0.02
	R	1411.96±414.78	1451.18±383.98	0.45	0.50
Posterior cingulate cortex	L	2515.54±433.23	2661.59±435.56	6.72	0.01
	R	2236.52±381.39	2362.35±391.28	6.06	0.01
Isthmus cingulate cortex	L	2071.07±383.73	2217.14±353.55	10.45	0.001*
	R	2075.05±365.02	2247.29±359.53	15.65	<0.0001*

Table 2. Cortical regions of interest in subjects repatriated from Algeria (REPAT, n=82) and controls (n=339) (*: q≤0.003; ROIs: regions of interest; GLM: general linear model; R: right; L: left).

References

Ahmed, F., Ras, J., & Seedat, S. 2012. Volumetric structural magnetic resonance imaging findings in pediatric posttraumatic stress disorder and obsessive compulsive disorder: a systematic review. Front Psychol. 3, 568.

Arnone, D., McIntosh, A. M., Ebmeier, K. P., Munafo, M. R., & Anderson, I. M. 2012. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. Eur Neuropsychopharmacol. 22, 1-16.

Artero, S., Touchon, J., Dupuy, A. M., Malafosse, A., & Ritchie, K. 2011. War exposure, 5-HTTLPR genotype and lifetime risk of depression. Br J Psychiatry. 199, 43-48.

Assareh, A. A., Sharpley, C. F., McFarlane, J. R., & Sachdev, P. S. 2015. Biological determinants of depression following bereavement. Neurosci Biobehav Rev. 49, 171-181.

Atwoli, L., Stein, D. J., Koenen, K. C., & McLaughlin, K. A. 2015. Epidemiology of posttraumatic stress disorder: prevalence, correlates and consequences. Curr Opin Psychiatry. 28, 307-311.

Bandelow, B., Gutermann, J., Peter, H., & Wedekind, D. 2013. Early traumatic life events, parental attitudes, family history, and birth risk factors in patients with depressive disorder and healthy controls. Int J Psychiatry Clin Pract. 17, 56-63.

Bar, M., & Aminoff, E. 2003. Cortical analysis of visual context. Neuron. 38, 347-358.

Binder, J. R., Frost, J. A., Hammeke, T. A., Cox, R. W., Rao, S. M., & Prieto, T. 1997. Human brain language areas identified by functional magnetic resonance imaging. J Neurosci. 17, 353-362.

Bogic, M., Njoku, A., & Priebe, S. 2015. Long-term mental health of war-refugees: a systematic literature review. BMC Int Health Hum Rights. 15, 29.

Bremner, J. D. 2007. Functional neuroimaging in post-traumatic stress disorder. Expert Rev Neurother. 7, 393-405.

Brietzke, E., Kauer Sant'anna, M., Jackowski, A., Grassi-Oliveira, R., Bucker, J., Zugman, A., . . . Bressan, R. A. 2012. Impact of childhood stress on psychopathology. Rev Bras Psiquiatr. 34, 480-488.

Brown, D. W., Anda, R. F., Tiemeier, H., Felitti, V. J., Edwards, V. J., Croft, J. B., & Giles, W. H. 2009. Adverse childhood experiences and the risk of premature mortality. Am J Prev Med. 37, 389-396.

Brown, G. W. 1993. Life events and affective disorder: replications and limitations. Psychosom Med. 55, 248-259.

Chaouloff, F. 2013. Social stress models in depression research: what do they tell us? Cell Tissue Res. 354, 179-190.

Chou, K. L. 2012. Childhood sexual abuse and psychiatric disorders in middle-aged and older adults: evidence from the 2007 Adult Psychiatric Morbidity Survey. J Clin Psychiatry. 73, e1365-1371.

Cohen, R. A., Grieve, S., Hoth, K. F., Paul, R. H., Sweet, L., Tate, D., . . . Williams, L. M. 2006. Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. Biol Psychiatry. 59, 975-982.

Corbo, V., Salat, D. H., Amick, M. M., Leritz, E. C., Milberg, W. P., & McGlinchey, R. E. 2014. Reduced cortical thickness in veterans exposed to early life trauma. Psychiatry Res. 223, 53-60.

Corp., I. (2013). IBM SPSS Statistics for Windows (Version 22.0): Armonk, NY: IBM Corp.

Dale, A. M., Fischl, B., & Sereno, M. I. 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage. 9, 179-194.

Desikan, R. S., Segonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., . . . Killiany, R. J. 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 31, 968-980.

Duval, E. R., Javanbakht, A., & Liberzon, I. 2015. Neural circuits in anxiety and stress disorders: a focused review. Ther Clin Risk Manag. 11, 115-126.

Eckart, C., Stoppel, C., Kaufmann, J., Tempelmann, C., Hinrichs, H., Elbert, T., . . . Kolassa, I. T. 2011. Structural alterations in lateral prefrontal, parietal and posterior midline regions of men with chronic posttraumatic stress disorder. J Psychiatry Neurosci. 36, 176-186.

Fagundes, C. P., Glaser, R., & Kiecolt-Glaser, J. K. 2013. Stressful early life experiences and immune dysregulation across the lifespan. Brain Behav Immun. 27, 8-12.

Feder, A., Nestler, E. J., & Charney, D. S. 2009. Psychobiology and molecular genetics of resilience. Nat Rev Neurosci. 10, 446-457.

Fischl, B., Sereno, M. I., & Dale, A. M. 1999. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage. 9, 195-207.

Fischl, B., Sereno, M. I., Tootell, R. B., & Dale, A. M. 1999. High-resolution intersubject averaging and a coordinate system for the cortical surface. Hum Brain Mapp. 8, 272-284.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D. H., . . . Dale, A. M. 2004. Automatically parcellating the human cerebral cortex. Cereb Cortex. 14, 11-22.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 12, 189-198.

Fujino, J., Yamasaki, N., Miyata, J., Sasaki, H., Matsukawa, N., Takemura, A., . . . Murai, T. 2015. Anterior cingulate volume predicts response to cognitive behavioral therapy in major depressive disorder. J Affect Disord. 174, 397-399.

Gianaros, P. J., Jennings, J. R., Sheu, L. K., Greer, P. J., Kuller, L. H., & Matthews, K. A. 2007. Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus. Neuroimage. 35, 795-803.

Harwood, R. H., Prince, M. J., Mann, A. H., & Ebrahim, S. 1998. The prevalence of diagnoses, impairments, disabilities and handicaps in a population of elderly people living in a defined geographical area: the Gospel Oak project. Age Ageing. 27, 707-714.

Horesh, N., Ratner, S., Laor, N., & Toren, P. 2008. A comparison of life events in adolescents with major depression, borderline personality disorder and matched controls: a pilot study. Psychopathology. 41, 300-306.

Hughes, M. M., Connor, T. J., & Harkin, A. 2016. Stress-Related Immune Markers in Depression: Implications for Treatment. Int J Neuropsychopharmacol.

Ke, J., Zhang, L., Qi, R., Li, W., Hou, C., Zhong, Y., . . . Lu, G. 2015. A longitudinal fMRI investigation in acute post-traumatic stress disorder (PTSD). Acta Radiol.

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. 1999. Causal relationship between stressful life events and the onset of major depression. Am J Psychiatry. 156, 837-841.

Kendler, K. S., Kuhn, J. W., & Prescott, C. A. 2004. Childhood sexual abuse, stressful life events and risk for major depression in women. Psychol Med. 34, 1475-1482.

Kennis, M., Rademaker, A. R., van Rooij, S. J., Kahn, R. S., & Geuze, E. 2015. Resting state functional connectivity of the anterior cingulate cortex in veterans with and without post-traumatic stress disorder. Hum Brain Mapp. 36, 99-109.

Kessler, R. C. 1997. The effects of stressful life events on depression. Annu Rev Psychol. 48, 191-214.

Kikinis, Z., Fallon, J. H., Niznikiewicz, M., Nestor, P., Davidson, C., Bobrow, L., . . . Shenton, M. E. 2010. Gray matter volume reduction in rostral middle frontal gyrus in patients with chronic schizophrenia. Schizophr Res. 123, 153-159.

Leech, R., & Sharp, D. J. 2014. The role of the posterior cingulate cortex in cognition and disease. Brain. 137, 12-32.

Li, L., Wu, M., Liao, Y., Ouyang, L., Du, M., Lei, D., . . . Gong, Q. 2014. Grey matter reduction associated with posttraumatic stress disorder and traumatic stress. Neurosci Biobehav Rev. 43, 163-172.

Lim, H. K., Jung, W. S., Ahn, K. J., Won, W. Y., Hahn, C., Lee, S. Y., . . . Lee, C. U. 2012. Regional cortical thickness and subcortical volume changes are associated with cognitive impairments in the drug-naive patients with late-onset depression. Neuropsychopharmacology. 37, 838-849.

Lyoo, I. K., Kim, J. E., Yoon, S. J., Hwang, J., Bae, S., & Kim, D. J. 2011. The neurobiological role of the dorsolateral prefrontal cortex in recovery from trauma. Longitudinal brain imaging study among survivors of the South Korean subway disaster. Arch Gen Psychiatry. 68, 701-713.

Mandelli, L., Petrelli, C., & Serretti, A. 2015. The role of specific early trauma in adult depression: A meta-analysis of published literature. Childhood trauma and adult depression. Eur Psychiatry.

Mark, L. P., Daniels, D. L., Naidich, T. P., & Borne, J. A. 1993. Limbic system anatomy: an overview. AJNR Am J Neuroradiol. 14, 349-352.

McCrory, E., De Brito, S. A., & Viding, E. 2011. The impact of childhood maltreatment: a review of neurobiological and genetic factors. Front Psychiatry. 2, 48.

McEwen, B. S. 2006. Protective and damaging effects of stress mediators: central role of the brain. Dialogues Clin Neurosci. 8, 367-381.

McLaren, M. E., Szymkowicz, S. M., O'Shea, A., Woods, A. J., Anton, S. D., & Dotson, V. M. 2016. Dimensions of depressive symptoms and cingulate volumes in older adults. Transl Psychiatry. 6, e788.

Miller, G. E., Chen, E., & Parker, K. J. 2011. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol Bull. 137, 959-997.

Molina, M. E., Isoardi, R., Prado, M. N., & Bentolila, S. 2010. Basal cerebral glucose distribution in long-term post-traumatic stress disorder. World J Biol Psychiatry. 11, 493-501.

O'Doherty, D. C., Chitty, K. M., Saddiqui, S., Bennett, M. R., & Lagopoulos, J. 2015. A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. Psychiatry Res. 232, 1-33.

Papagni, S. A., Benetti, S., Arulanantham, S., McCrory, E., McGuire, P., & Mechelli, A. 2011. Effects of stressful life events on human brain structure: a longitudinal voxel-based morphometry study. Stress. 14, 227-232.

Rinne-Albers, M. A., van der Wee, N. J., Lamers-Winkelman, F., & Vermeiren, R. R. 2013. Neuroimaging in children, adolescents and young adults with psychological trauma. Eur Child Adolesc Psychiatry. 22, 745-755.

Ritchie, K., Artero, S., Beluche, I., Ancelin, M. L., Mann, A., Dupuy, A. M., . . . Boulenger, J. P. 2004. Prevalence of DSM-IV psychiatric disorder in the French elderly population. Br J Psychiatry. 184, 147-152.

Schmidt, U., Willmund, G. D., Holsboer, F., Wotjak, C. T., Gallinat, J., Kowalski, J. T., & Zimmermann, P. 2015. Searching for non-genetic molecular and imaging PTSD risk and resilience markers: Systematic review of literature and design of the German Armed Forces PTSD biomarker study. Psychoneuroendocrinology. 51, 444-458.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 59 Suppl 20, 22-33;quiz 34-57.

Shin, L. M., Lasko, N. B., Macklin, M. L., Karpf, R. D., Milad, M. R., Orr, S. P., . . . Pitman, R. K. 2009. Resting metabolic activity in the cingulate cortex and vulnerability to posttraumatic stress disorder. Arch Gen Psychiatry. 66, 1099-1107.

Siriwardhana, C., Ali, S. S., Roberts, B., & Stewart, R. 2014. A systematic review of resilience and mental health outcomes of conflict-driven adult forced migrants. Confl Health. 8, 13.

Sleijpen, M., Boeije, H. R., Kleber, R. J., & Mooren, T. 2016. Between power and powerlessness: a meta-ethnography of sources of resilience in young refugees. Ethn Health. 21, 158-180.

Szymkowicz, S. M., McLaren, M. E., Kirton, J. W., O'Shea, A., Woods, A. J., Manini, T. M., . . . Dotson, V. M. 2015. Depressive symptom severity is associated with increased cortical thickness in older adults. Int J Geriatr Psychiatry.

Valenstein, E., Bowers, D., Verfaellie, M., Heilman, K. M., Day, A., & Watson, R. T. 1987. Retrosplenial amnesia. Brain. 110 (Pt 6), 1631-1646.

van der Werff, S. J., Pannekoek, J. N., Stein, D. J., & van der Wee, N. J. 2013. Neuroimaging of resilience to stress: current state of affairs. Hum Psychopharmacol. 28, 529-532.

Watson, C. G., Juba, M. P., Manifold, V., Kucala, T., & Anderson, P. E. 1991. The PTSD interview: rationale, description, reliability, and concurrent validity of a DSM-III-based technique. J Clin Psychol. 47, 179-188.

Watson, I. P., Brune, M., & Bradley, A. J. 2016. The evolution of the molecular response to stress and its relevance to trauma and stressor-related disorders. Neurosci Biobehav Rev.

Witelson, S. F. 1989. Hand and sex differences in the isthmus and genu of the human corpus callosum. A postmortem morphological study. Brain. 112 (Pt 3), 799-835.

Wood, K. H., Wheelock, M. D., Shumen, J. R., Bowen, K. H., Ver Hoef, L. W., & Knight, D. C. 2015. Controllability modulates the neural response to predictable but not unpredictable threat in humans. Neuroimage.

World Health Organization. 1992. International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10). Geneva: WHO.

Zannas, A. S., McQuoid, D. R., Payne, M. E., Steffens, D. C., MacFall, J. R., Ashley-Koch, A., & Taylor, W. D. 2013. Negative life stress and longitudinal hippocampal volume changes in older adults with and without depression. J Psychiatr Res. 47, 829-834.

Zhang, H., Chen, Z., Jia, Z., & Gong, Q. 2014. Dysfunction of neural circuitry in depressive patients with suicidal behaviors: a review of structural and functional neuroimaging studies. Prog Neuropsychopharmacol Biol Psychiatry. 53, 61-66.