Neural signatures of the interaction between the 5-HTTLPR genotype and stressful life events in healthy women

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Abstract

A change in neural connectivity of brain structures implicated in the memory of negative life events has been hypothesized to explain the enhancement of memory encoding during the processing of negative stimuli in depressed patients. Here, we investigated the effects of the interaction between negative life events and the 5-HTTLPR genotype – a polymorphism of the serotonin transporter gene – on the functional and structural connectivity of the hippocampal area in 34 healthy women. All participants were genotyped for the presence of the 5-HTTLPR short variant and for the A/G single-nucleotide polymorphism; they underwent clinical assessment including structured diagnostic interviews to exclude the presence of psychiatric disorders and to assess the presence of stressful life events. Resting state functional magnetic resonance imaging and diffusion tensor imaging scans were performed. We found significant interactions between stressful events and the 5-HTTLPR genotype in both the functional connectivity of the parahippocampus with the posterior cingulate cortex and the structural connectivity between the hippocampus and both the amygdala and the putamen. In addition, we found several genotype-related differences in the relationship between functional/structural connectivity of the hippocampal area and the ability to update expectations or stress-related phenotypes, such as anxiety symptoms. If confirmed by future studies, these mechanisms may clarify the role of the 5HTTLPR genotype as a risk factor for depression, in interaction with negative events.

1. Introduction

Findings have been reported that suggest a role for the serotonin transporter (5-HTT)-linked polymorphic region (5-HTTLPR) in determining the individual vulnerability to depression after exposure to stressful events (Caspi et al., 2003; Uher and McGuffin, 2008; Caspi et al., 2010). Individuals carrying the short (S), transcriptionally less active allele of the 5-HTTLPR polymorphism in the promoter of the serotonin transporter gene are more likely to develop depression after exposure to stressful life events or childhood abuse than homozygous individuals carrying the long (L) allele (Caspi et al., 2003; Kendler et al., 2005; Aguilara et al., 2009). Although this gene–environment interaction is not a cause of depression in itself, it is closely associated with a broader condition of ‘stress sensitivity’, the existence of which has been demonstrated in animal models (Caspi et al., 2010) and largely replicated in human samples (Uher and McGuffin, 2008; Caspi et al., 2010), with a few exceptions (Risch et al., 2009).

Recent research has provided neural models revealing the biological underpinning of this epigenetic effect. There is evidence that the 5-HTTLPR genotype modulates brain activation during face-matching tasks in regions involved in affective processing, such as the amygdala and medial prefrontal cortex (Hariri et al., 2002; Heinz et al., 2005). Human functional magnetic resonance imaging (fMRI) studies have found consistent associations between the short allele and greater amygdala reactivity to negative compared with neutral stimuli (Hariri and Holmes, 2006; Canli and Lesch, 2007). However, the modulatory effects of 5-HTTLPR appear to go beyond the temporary reactivity to emotional stimuli demonstrated by fMRI studies (Canli et al., 2005; Pezawas et al., 2005). Widespread
structural and functional differences between carriers of the short allele (SS and SL) and homozygous carriers of the long allele (LL) have been reported (Canli et al., 2005, 2006), leading to the hypothesis that 5-HTTLPR may play a broader role in determining long-term modifications of the neural systems controlling cognitive functions (Canli et al., 2006; Alexander et al., 2012; Drabant et al., 2012). Most studies, however, concentrated their interest on amygdala reactivity (Lemogne et al., 2011) and connectivity (Lemogne et al., 2011; Alexander et al., 2012) or, for structural connectivity, on the uncinate fasciculus (Pacheco et al., 2009; Jonassen et al., 2012), a tract connecting limbic areas with the prefrontal cortex and implicated in trait anxiety (Kim and Whalen, 2009). Cognitive theories of depression, on the contrary, also subsume the involvement of other gray matter structures fundamental for memory encoding. According to these theories, negative self- and world-related cognitions play a central role in the pathogenesis of depression (Clark et al., 2009; Disner et al., 2011), leading to biased information processing. In particular, depressed individuals show greater memory sensitivity to negative stimuli and greater activation of the right amygdala during encoding of subsequently remembered negative – but not neutral or positive – stimuli. Biased memory does not seem to be due only to amygdalar reactivity (Disner et al., 2011), since Hamilton and Gotlib (2008) found greater functional connectivity between the amygdala and both the hippocampus and the caudate–putamen during encoding. In rats, several experiments have demonstrated that the amygdala modulates competition between hippocampal-mediated cognitive memory and habit learning mediated by the striatum (Wingard and Packard, 2008). In one such experiment, learning was not reversed by anesthetizing the amygdala before a retention test, indicating that the ‘biased’ memory, once encoded, was independent of amygdalar activation (Packard and Teather, 1998).

Depressed individuals are hypothesized to over-recruit the neural networks which enhance memory encoding while they process negative stimuli, resulting in a sustained attention and memory bias which increases subsequent stress sensitivity and the risk of developing depressive phenotypes (Hamilton and Gotlib, 2008; Disner et al., 2011). This hypothesis implies a long-term change in neural connectivity as a possible consequence of negative experiences. This change may become evident during task-related activation studies with exposure to stressful conditions, but also may result in a functional connectivity change at rest, as well as in a change in white matter fractional anisotropy. In this study, we hypothesized that alterations exist in the neural connectivity of brain areas involved in memory bias, as a consequence of the interaction between the 5-HTTLPR genotype and negative life events. To collect evidence in favor of this hypothesis, we tested the effects of this gene–environment interaction on the resting-state functional and structural connectivity of the hippocampus and parahippocampus, given their importance in memory encoding and processing of contextual associations (Aminoff et al., 2007; Eichenbaum and Lipton, 2008; Rudy, 2009; Maren et al., 2013).

2. Methods

2.1. Participants

Thirty-four healthy Caucasian women with no history of psychiatric disorders participated in the study. Psychiatric disorders were excluded by application of the Mini-International Neuropsychiatric Interview (MINI) for DSM-IV Axis I Disorders. Additional exclusion criteria were as follows: Major medical illness, history of neurological problems, head trauma with loss of consciousness, active use of systemic steroids or psychoactive drugs, pregnancy, history of substance/alcohol abuse or dependence, moderate mental impairment (IQ < 65), or any contra-indication for MRI. The mean age of the sample was 25.6 years (S.D. = 2.4; range 19–40 years), years of education 15.5 (S.D. = 2.4; range 8–18), body mass index 21.7 kg/m² (S.D. = 3.1; range 18–29). To enhance the homogeneity of the sample, only women were accepted for the study (Drabant et al., 2012); in addition, women generally show a more significant 5-HTTLPR genotype-mediated vulnerability (Kendler et al., 2005). All subjects gave written informed consent for the use of data in an anonymous form, and the local Ethics Committee approved the study. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

2.2. Assessment of stressful life events

A structured interview was used to assess the presence of lifetime stressful events, using a life-chart method to improve the ascertainment of life-event histories. Although similar to many life-events scales (Caspì et al., 2003), the interview was a variant constructed for the present study. Participants were asked to remember a particular event, indicating the period of life when the event occurred (age) and giving a local score as follows: 1, no significant damage associated to the event; 5, extreme stress. The interview covered 14 categories of events: death of a close relative, death of a friend; personal health problems; health problems of a close person; separations; interpersonal conflicts; occupational, scholastic–academic, legal or other economic problems, personal violence or maltreatment; miscarriages and/or abortions; and any other traumatic or stressful events (some examples are given, such as car accidents, exposure to natural disaster, and relocation). In the present study, a composite measure of stressful life events was used, corresponding to the total number of negative life events with a severity score of at least 3 (i.e., the number of severe negative life events).

2.3. Other measures

All subjects underwent clinical and psychophysiological assessment, including the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970) to measure state anxiety, and the Depression subscale of the Hopkins Symptom Checklist (H_SCL; Derogatis et al., 1974) to assess depression. As an indirect measure of the individual proneness to bias, the ‘learning rate’ parameter of the Iowa Gambling Task was used (GCT; Yechiam et al., 2005); this assesses an individual’s ability to update expectations without being biased by past outcomes. The IGT (Bechara et al., 1994) is a popular method for investigating basic decision-making deficits. Subjects are asked to make a series of 100 choices from four decks of cards, the aim being to maximize their net payoﬀ across trials. Although each card selection may lead to meaningful gains, it may also lead to losses, and the outcome of each of the decks must be learned from experience. Two of the decks are disadvantageous and risky, because they lead to relatively high gains but also to occasional large losses; the other two decks are advantageous, as they tend to lead to smaller losses. Participants are assumed to form expectancies for each deck, which represent the anticipated consequences of choosing a card from a particular deck. The learning parameter has small values when participants display more persistent inﬂuences across longer lags, and large values when they show rapid adjustments, strong recency effects, and rapid discounting of past outcomes (Yechiam et al., 2005).

Handedness was assessed by the Edinburgh Handedness Inventory (Oldﬁeld, 1971). To exclude subjects with mental impairment, participants also completed the Brief Intelligence Test (Colombo et al., 2002; the Italian version of the National Adult Reading Test, a measure of premorbid intellectual ability) if they were aged 18 or over. Subjects under the age of 18 completed the ‘information’ subscale of the Wechsler Intelligence Scale for Children or, if they were aged between 16 and 18, the Wechsler Adult Intelligence Scale.

2.4. 5-HTTLPR genotyping

Participants were genotyped for the presence of the 5-HTTLPR (Lesch et al., 1996) short variant and for the A/G single-nucleotide polymorphism (SNP rs25531), according to standard protocols (see details in Supplementary information). Samples were dichotomized according to the presence or absence of the short variant, and carriers of the G polymorphism were included in the short variant group.

2.5. Imaging

Structural and functional MR imaging was performed in one scanning session, and high-resolution anatomical, resting-state functional and diffusion-weighted image sequences were acquired. Data were collected on a Philips Achieva 1.5 T scanner equipped for echo-planar imaging. A resting state fMRI scan entailed 250 continuous functional volumes (repetition-time = 2035 ms, echo-time = 50 ms, flip angle = 90°, 21 slices, matrix = 128 × 128, acquisition voxel size = 1.8 × 1.8 × 6 mm, acquisition-time = 8 min, and field of view = 23 cm). Participants were asked to remain with their eyes closed during the scan.

For spatial normalization and localization, high-resolution 3D T1-weighted anatomical images were also acquired in a gradient-echo sequence (repetition-time = 20 ms, echo-time = 3.78 ms, flip angle = 20°, 160 slices, acquisition voxel size = 1 × 0.66 × 0.66 mm, and field of view = 21–22 cm).
Diffusion tensor images were acquired with single-shot echo planar diffusion-weighted imaging according to the following parameters: repetition time = 10389, echo time = 80 ms, echo train length: 59, matrix: 128 x 128, acquisition voxel size = 1.75 x 1.75 x 2 mm, SENSE p reduction = 2, slice thickness = 2 mm without gaps, and number of excitations: 2. The axial sections covered the whole brain including the cerebellum. Diffusion-sensitizing gradients were applied along 32 non-collinear gradient encoding directions with maximum gradient strength of 1.75 mT/m. On average, 800 s/mm² was used.

2.6. fMRI data analysis

Resting state scans were preprocessed with the following tools: Analysis of Functional NeuroImages (version AFNI_2010_10_19_1028; http://afni.nimh.nih.gov/afni/; NIMH, Bethesda, MD) and FM-RIB Software Library (version FSL 4.1.6; http://www.fmrib.ox.ac.uk; FMRIB, Oxford, UK) tools. Preprocessing was performed as described in Biswal et al. (2010) and www.nitrc.org/projects/fcon_1000. Details of preprocessing and processing are described in the Supplementary material.

2.7. Diffusion tensor imaging (DTI) data analysis

Structural connectivity between the same brain regions was investigated with probabilistic tractography with the Brain Diffusion Toolbox (version FSL 4.1.6; http://www.fmrib.ox.ac.uk; FMRIB, Oxford, UK; Behrens et al., 2007) and TBSS (Smith et al., 2006). Details of preprocessing and processing are described in Supplementary material. Four pathways were tracked with the hippocampus as seed and the lingual gyrus, posterior cingulate cortex, amygdala, and putamen as targets (for images of the four tracks, see Supplementary material). Targets were chosen according to previous findings of functional connectivity (posterior cingulate cortex and lingual gyrus) and from the literature on circuits involved in memory bias (amygdala and putamen; Disner et al., 2011). The same probabilistic tracking procedure was used for the left and right parahippocampus, but, as the tracks overlapped those tracked with the hippocampal seed by about 95%, only the results from the hippocampal ROI tracking are provided here. The fractional anisotropy appearing in the skeletonized maps of the tracts of interest was then statistically analyzed with two-sample t-tests (between-group comparisons) and multiple regression (correlations). Non-parametric permutation testing was used to correct for multiple comparisons across space, threshold p < 0.05. Graph data were obtained by extracting the average z-value in the brain area of interest for any individual map, and data were processed by IBM Statistical Product and Service Solutions software (SPSS, Inc, Chicago, IL).

2.8. Statistics

Spearman rho was used to test correlations among variables and the chi-square test to analyze genotype differences. Subjects’ clinical and neuropsychological characteristics were compared by conducting group t-tests or general linear models by IBM SPSS Statistics 19.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Genotype distribution

The genotype distribution in our sample was consistent with prior reports and did not deviate from Hardy–Weinberg equilibrium (12 with LL genotype [LaLa]; 15 with LS genotype [LaS = 12, LaG = 3]; and 7 with SS genotype [LG = 0, SS = 7]; \( \chi^2 = 0.33 \)).

The genotype groups did not differ in age, education, or IQ. There were no significant differences between the three groups as regards life stress, depressive and anxiety symptoms, or IGT learning rate.

3.2. Clinical and neuropsychological correlates of stress and stress x 5-HTTLPR interaction

Among participants, 68% reported at least one severe life event, and 32% reported more than one. A significant correlation emerged between the number of life events and depressive symptoms (\( \rho = 0.51, p = 0.003 \)) and between life events and the ‘learning rate’ parameter of the IGT (\( \rho = 0.44, p = 0.010 \)); no significant correlation emerged between stress and state anxiety (\( \rho = 0.13 \)). The interaction between stress and the 5-HTTLPR genotype was significant for depression scores (F(3, 22) = 4.43, \( p = 0.014 \); and F(3, 21) = 3.27, \( p = 0.042 \) using age as covariate; see Fig. S1 in Supplementary material), but the interactions were not significant for the other variables. Although carriers of the short allele reported a higher number of stressful events and higher levels of psychopathology, the three groups did not differ significantly (all comparisons \( p > 0.1 \)).

3.3. Neural correlates of stress x 5-HTTLPR interaction: functional connectivity

A significant genotype \times environment interaction emerged for the functional connectivity between the right parahippocampus and an area in the posterior cingulate cortex. Coactivation in this brain area showed a positive correlation with life events among carriers of the short 5-HTTLPR allele and a negative correlation in carriers of the LL genotype (Fig. 1). Coactivation in this area also showed a significant positive correlation with depressive symptoms (whole sample: \( \rho = 0.43, p = 0.014 \); in LL carriers: \( \rho = 0.42, n.s. \); in S carriers: \( \rho = 0.57, p = 0.007 \)).

No significant interaction between life events and 5-HTTLPR genotype emerged for the functional connectivity of the seeds placed in the hippocampus.

3.4. Functional connectivity and clinical/neuropsychological characteristics according to genotype

Functional connectivity in the hippocampus and parahippocampus did not significantly correlate with depression scores in any genotype group. Conversely, coactivation of the right parahippocampus and bilateral lingual gyrus showed a significant positive correlation with state anxiety among carriers of the short allele (see Fig. 2). In addition, both right and left parahippocampi showed a significant interaction between genotype and the ‘learning parameter’ of the IGT in the right lingual gyrus. Functional connectivity of the parahippocampus bilaterally displayed a negative correlation with the ‘learning parameter’ in carriers of the short allele and a positive correlation among carriers of the LL genotype (Fig. S2 in Supplementary material).

3.5. Neural correlates of stress x 5-HTTLPR interaction: structural connectivity

When the pathways displaying significant correlations in the functional connectivity analysis (Fig. S3A and B) were explored, a negative correlation was found between life stress and fractional anisotropy in the tracts between the right hippocampus/parahippocampus and the posterior cingulate cortex in LL carriers (Fig. S4). However, in carriers of the short allele, no significant correlation emerged between life stress and fractional anisotropy in these tracts. In the tracts between the hippocampus/parahippocampus and the lingual gyrus, fractional anisotropy did not correlate with state anxiety. In contrast, in the same tracts, a positive correlation...
between fractional anisotropy and the ‘learning parameter’ of the IGT emerged in the right hemisphere for LL carriers (Fig. S5).

Lastly, the stress × 5-HTTLPR interaction was explored in the tracts bilaterally connecting the hippocampus/parahippocampus and the putamen/amygdala (Fig. S3C and D). In the left hemisphere, a significant genotype × stress interaction appeared for the fractional anisotropy of tracts connecting the left hippocampus/parahippocampus with the left amygdala and putamen. The interaction was in opposite directions for the two targets (Fig. 3): for the amygdala, life stress correlated positively with fractional anisotropy in LL genotype

Fig. 1. Seed-based analysis for the right parahippocampus, assessing interaction between life stress and 5-HTTLPR genotype. Figure shows area of significant stress × genotype interaction (peaks: −18, −63, 24) (BA 23). Graphs show correlations between average coactivation (z-score) and life stress according to 5-HTTLPR genotype (correlation was significant for carriers of short allele and non-significant for LL genotype). Analyses by non-parametric permutation test, with age, education and hand lateralization as covariates.

Fig. 2. Seed-based analysis for the right parahippocampus, correlating co-activation with state anxiety (STAI-S) in carriers of S allele and those of LL genotype. Figure shows area of significant positive correlation among carriers of short allele (peaks: 15, −60, 6) (Brodmann area 17, right and left lingual gyrus). Graphs show correlations between average coactivation (z-score) and STAI-S according to 5-HTTLPR genotype. Analyses by non-parametric permutation test, with age, education and hand lateralization as covariates.

Fig. 3. Correlation between life events and fractional anisotropy in tracts connecting left hippocampus and amygdala/putamen. Figure shows areas of significant interaction between genotypes (amygdala: peak: −28, −16, −8; putamen: peak: −24, −2, −10). Graphs show correlations between fractional anisotropy and life stress according to 5-HTTLPR genotype. Analyses by non-parametric permutation test, with age, education and hand lateralization as covariates.
carriers and showed no correlation in carriers of the short allele; in contrast, for the putamen, life stress was negatively correlated with fractional anisotropy in the LL genotype and positively correlated in S carriers.

4. Discussion

The aim of our study was to reveal the neural signatures of the effects of negative life events, as mediated by the 5-HTTLPR genotype, on the functional and structural connectivity of the hippocampal and parahippocampal regions. We hypothesized that, in depression, sustained changes in the neural connectivity of hippocampus and parahippocampus, which are involved in contextual representations (Rudy, 2009), would determine biased memory processing. Although several studies have reported increased amygdalar reactivity during exposure to stressful tasks in carriers of the short allele (Hariri and Holmes, 2006; Canli and Lesch, 2007), no study to date has explored the relationship between negative life events and neural connectivity of structures involved in memory encoding. Sustained changes in the neural connectivity of the hippocampus and the parahippocampus may be among the basic mechanisms that determine biased memory processing in depression. We explored these issues in a sample of healthy women, to avoid the interference of possible secondary effects of depression on functional and structural connectivity. We found significant genotype \( \times \) stress interactions in both functional and structural connections of the brain areas of interest.

A significant genotype \( \times \) stress interaction was found in the functional connectivity between the right parahippocampus and the posterior cingulate cortex. Among carriers of the short allele, life stress was positively associated with increased connectivity, whereas the opposite was true among carriers of the LL genotype. The posterior cingulate cortex is involved in autobiographical memory (Maddock et al., 2001) and in some contextual aspects of episodic memory (Uncapher et al., 2006). This inverse correlation in the two genotypes may imply different mechanisms for memory retrieval after the experience of stressful events, and a different proneness to negative memory bias. Carriers of the short allele who have undergone negative life events may be more likely to perform contextual associations between recent events and negative memories, leading to a negative interpretation of real life. Conversely, the negative correlation between life stress and functional connectivity observed in carriers of the LL genotype – reinforced by concomitant changes in structural connectivity – might imply a ‘protective’ mechanism against sensitization produced by negative experiences.

To refine our interpretations of these findings, we explored the relationship between the functional connectivity of the hippocampus/parahippocampus and relative stress-related phenotypes. Although we observed a significant genotype \( \times \) stress interaction in determining levels of depressive symptoms in our non-pathological sample, we did not find any genotype-mediated relationship between depressive symptoms and hippocampal or parahippocampal resting state functional connectivity. However, among carriers of the short allele, right parahippocampal functional connectivity revealed significant positive correlations with anxiety symptoms, supporting the hypothesis that higher co-activation of the parahippocampus might be associated to increased risk for stress-related phenotypes. In addition, from a neuropsychological point of view, the bilateral functional connectivity of the parahippocampus turned out to be negatively associated with the ability to update expectations (as measured by the learning parameter of the IGT) among carriers of the short allele, whereas the opposite was true for those with the LL genotype. This suggests that stronger resting-state co-activation of the parahippocampus may be associated with greater persistence of negative expectations in carriers of the short allele and, in contrast, to better ability to discount past outcomes and derive expectations from the ‘here and now’ in LL-genotype carriers. This last attitude is generally considered to be a feature potentially protecting against the development of depressive symptoms.

It is noteworthy that the co-activation of the parahippocampus which revealed a relationship with stress-related phenotypes in our study predominantly involved the visual cortex. During acute stress, involvement of visual areas in memory formation leads to negative effects on memory performance (Henckens et al., 2009). In contrast, there are few data on the specific role of the visual cortex in memory retrieval of stressful events (Klucken et al., 2013). Stress hormones enhance the sensory-perceptual component of memory (Henckens et al., 2009) and might affect the involvement of the visual cortex in networks linked to stress-related phenotypes. Abnormally low resting state co-activation of the visual cortex, and the lingual gyrus in particular, was found in a recent study on depressed subjects (Veer et al., 2010), but the interpretation of these findings in the context of depression remains speculative and needs clarification with future studies.

Exploration of fractional anisotropy in the tracts involved in our functional connectivity study did not reveal structural change in white matter tracts connecting the hippocampus/parahippocampus with the lingual gyrus, and confirmed a negative correlation between stress and connectivity of the hippocampal-posterior cingulate areas in carriers of the LL genotype. However, our study also found a significant stress \( \times \) genotype interaction for the fractional anisotropy of tracts connecting the hippocampus/parahippocampus with subcortical structures that are crucial for memory formation and learning (Schwabe et al., 2012). In tracts connecting the hippocampus and the putamen, life stress positively correlated with fractional anisotropy in carriers of the short allele, while the opposite was true in LL carriers. In contrast, opposite correlations emerged in tracts between the hippocampus and the amygdala. These correlations are of particular interest, because the amygdala is involved in arousal responses during stress exposure and in subsequent learning to use avoiding reactions after negative experiences (Roozendaal et al., 2009), whereas the putamen plays a role in the formation and storage of implicit memory and automatisms (Yin and Knowlton, 2006; Wingard and Packard, 2008; Disner et al., 2011). Emotional states and stress may reinforce arousal and avoidance reactions (Lonsdorf et al., 2009), but also the use of automatic responses and habit formation (Packard, 2009; Arnsten, 2009). Structural connectivity between the hippocampus and the putamen is enhanced by life stress in carriers of the short allele, allowing us to hypothesize a reinforcement of implicit retrieval of negative memories. The opposite appears to be true for LL carriers, for whom cumulating stress enhances structural connectivity between the hippocampus and the amygdala, and decreases that between the hippocampus and the putamen. As a whole, our data show that the effects of the 5-HTTLPR polymorphism might be evident not only in processes of fear conditioning and extinction (Lonsdorf et al., 2009; VanElzakker et al., 2013; Klucken et al., 2013) that mainly involve amygdala and prefrontal cortex (Lonsdorf et al., 2009), but also in those brain circuits implicated in contextual representation, memory and learning (Wingard and Packard, 2008; Rudy, 2009; Disner et al., 2011; Klucken et al., 2013).

The present study has several methodological advantages, as well as substantial limitations which should be taken into consideration. The subdivision of the sample according to genotypes led to small sample sizes, so that our findings must be considered with caution, as they need to be replicated before generalization. Nor did we measure attention or memory bias directly in our...
sample, although the ICT did provide an ecological measure of the possible effects of implicit learning after a negative experience. Lastly, in order to enhance homogeneity, we provide data only on women. For these reasons, future studies need to be extended to men. In the present study, for the first time, we show a relationship between the ability to update expectations and both previous stressful experiences and the functional connectivity of a brain area involved in the processing of contextual associations, such as the hippocampus. The use and the consistency of two different techniques to measure hippocampal and parahippocampal connectivity, such as resting state fMRI and diffusion tensor imaging, reinforce the findings of the present study.

This study showed that sustained changes in the neural connectivity of the parahippocampus may be involved in the mechanisms underlying biased memory processing in people who have experienced stressful life events. These changes are mediated by the 5-HTTLPR genotype, providing a further explanation of the potential role of this genotype as a risk factor for depression, in interaction with negative life events. We also found an interesting effect of stress, mediated by genotype, on structural connectivity between the left hippocampus and both the amygdala and the putamen. This effect might reveal a genotype-mediated mechanism of implicit learning after negative experiences, which involves contextual representations in memory and might explain cognitive bias in depressed patients. Larger prospective studies with data on both genders will help in understanding the generalizability of our findings and clarify the role of stress-related changes in functional/structural connectivity as predictors of depressive disorders.

Acknowledgments

The study was partially supported by Veneto Region Grant BIOVEDA (DGR 3984/08).

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jpsychres.2014.05.006.

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