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Research report

Hippocampal multimodal structural changes and subclinical depression in healthy individuals

Gianfranco Spalletta[a,*], Fabrizio Piras[a], Carlo Caltagirone[a,b], Sabrina Fagioli[a]

[a] IRCCS Santa Lucia Foundation, Department of Clinical and Behavioral Neurology, Rome, Italy
[b] Tor Vergata University of Rome, Department of Neuroscience, Italy

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ABSTRACT

Background: Several neuroimaging studies report reduced hippocampal volume in depressed patients. However, it is still unclear if hippocampal changes in healthy individuals can be considered a risk factor for progression to clinical depression. Here, we investigated subclinical depression and its hippocampal correlates in a non-clinical sample of healthy individuals, with particular regard to gender differences.
Methods: One-hundred-two participants underwent a comprehensive clinical assessment, a high-resolution T1-weighted magnetic resonance imaging and diffusion tensor imaging protocol using a 3 T MRI scanner. Data of macro-(volume) and micro-(mean diffusivity, MD) structural changes of the hippocampus were analyzed with reference to the Beck Depression Inventory score.
Results: Results of multivariate regression analyses revealed reduced bilateral volume, along with increased bilateral MD in hippocampal formation predicting subclinical depressive phenomenology only in healthy males. Conversely, subclinical depressive phenomenology in healthy female was accounted for by only lower educational level, in the absence of any hippocampal structure variations.
Limitations: To date, this is the only evidence reporting a relationship between subclinical depressive phenomenology and changes in hippocampal formation in healthy individuals.
Conclusions: Our findings demonstrated that reduced volume, along with increased MD in hippocampal formation, is significantly associated with subclinical depressive phenomenology in healthy males. This encourages to study the hypothesis that early macro- and microstructural changes in hippocampi associated with subclinical depression may constitute a risk factor of developing depressive disorders in males.

1. Introduction

Several neuroimaging studies increasingly described that reduced hippocampal volume is present in subjects suffering from Major Depressive Disorder (MDD) (Sheline et al., 1996; Bremner et al., 2000; Mervaala et al., 2000; Steffens et al., 2000; MacQueen et al., 2003). However, findings can vary significantly across studies and, consequently, it is still unclear if smaller volume of the hippocampal formation can be considered a neurobiological signature of depression.

It has been showed that several factors, such as age, medication status, a history of depression, and even anatomical definition of hippocampal formation, may have influenced results on structural changes of the hippocampus in patients with MDD. Indeed, at the very early stages of research on this issue, loss of hippocampal volume had been found to characterize particularly patients with recurrent episodes of MDD (Sheline et al., 1996; Sheline et al., 1999), suggesting that hippocampal atrophy may result from chronic depression. Later, however, other studies reported hippocampal changes also in patients with a first episode of MMD (Frodl et al., 2002; MacMaster and Kusumakar, 2004), revealing that the hippocampus may play a crucial role in the early mechanisms of depression. Furthermore, age has been found to modulate hippocampal volume in patients with MDD, suggesting that hippocampal atrophy may be a characteristic trait of elderly, but not young, depressed patients (McKinnon et al., 2009).

Here, the core question is whether very early structural changes of the hippocampal formation can be associated with subclinical depressive phenomenology also in healthy individuals with no mental disorders. Up until now only a few studies investigated whether hippocampus structural changes associated with MDD can also be observed in healthy subjects, and most of these studies addressed hippocampal volumetry in persons at risk of MDD, such as twins or people with a family history of the disorder. In particular, Chen et al. (2010) revealed significantly

* Correspondence to: Gianfranco Spalletta, IRCCS Santa Lucia Foundation, Neuropsychiatry Laboratory. Via Ardeatina, 306-00179 Rome, Italy. Tel./fax: +39 6 51501575.
E-mail address: g.spalletta@hsantalucia.it (G. Spalletta).

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decreased gray matter (GM) in the bilateral hippocampus of girls aged between 9 and 15 at high familial risk of developing depression, but who have not yet experienced the disorder (Chen et al., 2010). Similarly, Baaré et al. (2010) found that healthy twins at high risk of depression (i.e., having a co-twin with unipolar depression diagnosis) showed reduced hippocampal volume than low-risk twins (Baaré et al., 2010). These studies strongly suggest that variations in the hippocampus volume might precede the development of depression. On the other hand, some methodological issues potentially limit the generalizability of these findings to all healthy individuals. In fact, these studies demonstrated that changes of hippocampal volume in healthy individuals are tightly associated to those subjects at familial risk of depression, leaving unsolved the question of whether the association also exists in people who are not at risk. Further, the vast majority of the research addressing the relationship between the hippocampal structure and mood disorders focused exclusively on the analysis of macrostructural brain correlates (i.e. volumetry), rather than to assess also microstructural variations (i.e. diffusivity) in the hippocampal formation. In addition, all studies that addressed the same issue in healthy subjects focused on hippocampus brain macrostructure only. This probably explains why many studies failed to detect abnormalities in the earlier stages of the disorder. In fact, recent literature suggests that such brain microstructural measures can be an index of early hippocampal changes even in healthy people and that these changes are related with reduced cognitive performances (Carlesimo et al., 2010; Piras et al., 2011).

Given the well-documented difference between males and females in the development of affective disorders (Kessler et al., 1993) and in the processing of emotional signals (Kret and De Gelder, 2012), it is central to explore the issue individually in the two genders. We previously reported evidence of gender-related cerebral mechanisms also in the phenomenology of the subclinical apathy (Spalletta et al., 2012). In addition, gender differences in brain structures with activation level of network involved in processing emotions have been also consistently found (Kret and De Gelder, 2012), and it has been suggested that enhanced responses to negative emotions are linked to an increased risk of depression and anxiety disorders in women (Nolen-Hoeksema, 2001). Moreover, Maller and colleagues showed that hippocampus atrophy in those with MDD is dependent upon gender (Maller et al., 2007). In particular, the entire hippocampal structure was significantly smaller in men with MDD, while in MDD females the volume reduction was confined to the posterior section of the hippocampus, suggesting that hippocampi in men with MDD are more sensitive to the pathophysiology of the disorder than in females. Altogether these findings suggest that it is conceivable to expect gender differences also in the subclinical expression of depressive phenomenology and in its associated neural correlates.

Given these considerations, here we aim to address whether variations in the macro- and micro-structure of the hippocampi are associated with subclinical depressive phenomenology in healthy subjects without family history of depressive disorders, by adopting a combined volumetry and diffusion tensor imaging (DTI) method. Specifically, if subclinical phenomenology of depression is a risk factor for progression in clinically relevant depression, then we expect that higher level of depressive phenomenology should be associated with decreased volume and increased diffusivity in the hippocampal formation in healthy subjects also. As the higher prevalence of depression among women appears to result from a much higher prevalence of a type of depression associated with somatic symptoms (Silverstein, 2002), we addressed whether brain macro- and micro-variations of the hippocampal formation are specifically related to somatic or psychic symptoms of subclinical depression in the two genders.

2. Methods

2.1. Participants and clinical assessment

One-hundred two healthy adults (48 males, 47%; mean age $\pm$ SD $=$ 42.5 $\pm$ 17.38 years, range $=$ 18–80; 54 females, 53%; mean age $\pm$ SD $=$ 43.54 $\pm$ 20.19 years, range $=$ 18–80) were recruited from universities, community recreational centers and hospital personnel by local advertisement.

Inclusion criteria were age between 18 and 80 years and suitability for magnetic resonance imaging (MRI) scanning. Exclusion criteria included (i) suspicion of cognitive impairment or dementia based on Mini Mental State Examination (MMSE) (Folstein et al., 1975) score ≤24, and dementia diagnosis in accordance with the Diagnostic and Statistical Manual of Mental Disorders-IVth Edition, Text Revision (DSM-IV-TR) criteria (APA, 2000) or mild cognitive impairment (MCI) according to the Petersen criteria (Petersen and Negash, 2008), further confirmed by a thorough clinical neuropsychological evaluation using the Mental Deterioration Battery (MDB) (Carlesimo et al., 1996); (ii) subjective complaint of memory difficulties or any other cognitive deficits interfering with daily living activities; (iii) vision and hearing loss that could interfere with testing procedures; (iv) major medical illnesses, e.g., diabetes (not stabilized), obstructive pulmonary disease, or asthma; hematological and oncological disorders; pernicious anemia; significant gastrointestinal, renal, hepatic, endocrine, or cardiovascular system diseases; newly treated hypothyroidism; (v) current or reported past mental disorders, investigated administering the Structured Clinical Interview for DSM-IV Axis I disorders, non-patient edition (SCID-I/NP) (First et al., 2002) and the Structured Clinical Interview for DSM-IV Axis II personality disorders (SCID-II) (First et al., 1997) or neurological disorders, assessed by a clinical–neurological evaluation; (vi) personal or family history of mood disorders; (vii) known or suspected history of alcoholism or drug dependence or abuse during lifetime; and (viii) MRI evidence of focal parenchymal abnormalities or cerebrovascular diseases. In particular, we assessed the presence of mood disorders using the SCID, and excluded subjects who screened positive for any mood disorder, including the minor depressive disorder. Importantly, although all of the subjects who showed clinically relevant depression at the diagnostic level were dropped out from the experimental sample, all included subjects could still differ with regard to subclinical depressive phenomenology, and a quite large range of continuous values (i.e., a Beck Depression Inventory (BDI) score between 0 and 15) was observed. Thus, none of the 102 subjects in the final sample had any mental or neurological disorders.

Apart from categorical depression, assessed by the DSM-IV-TR SCID-I/NP, we also rated continuous severity of depression by administering an Italian version (translated into Italian and back translated into English) of the BDI, which is a 21-item multiple-choice inventory (Beck and Steer, 1987). Each response is assigned a score ranging from 0 to 3, in which higher scores indicate more severe depression. The total test score (BDI-TOT) is defined as the sum of the individual item scores. We also calculated the psychic (i.e. affective–cognitive) score (BDI-PSY) by combining the first 14 items, and the somatic (BDI-SOM) score which is a sum of the remaining 7 items (Beck et al., 1988).

Global cognitive performance was evaluated with the MMSE, a 11-question measure that tests five areas of cognitive function (i.e., orientation, registration, attention and calculation, recall, and language) with scores ranging from 0 to 30. Furthermore, we selected the following tests from the MDB in order to provide information about the functionality of short- (MDB Rey's 15-word Immediate Recall (RIR)) and long-term verbal memory (MDB Rey's 15-word Delayed Recall (RDR)).