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Research paper

Cognitive impairment and medial temporal lobe structure in young adults with a depressive episode

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ABSTRACT

Background: Cognitive deficits are common in patients with a depressive episode although the predictors for their development and severity remain elusive. We investigated whether subjective and objective cognitive impairment in young depressed adults would be associated with cortical thinning in medial temporal subregions.
Methods: High-resolution magnetic resonance imaging, cortical unfolding data analysis, and comprehensive assessments of subjective and objective cognitive abilities were performed on 27 young patients with a depressive episode (mean age: 29.0 ± 5.8 years) and 23 older participants without a history of a depressive disorder but amnestic mild cognitive impairment (68.5 ± 6.6 years) or normal cognition (65.2 ± 8.7 years).
Results: Thickness reductions in parahippocampal, perirhinal and fusiform cortices were associated with subjective memory deficits only among young patients with a depressive episode and a measurable cognitive impairment.
Limitations: Long-term longitudinal data would be desirable to determine the trajectories of cognitive impairment associated with depression in patients with or without cortical structure changes.
Conclusions: The presence of clinically significant cognitive deficits in young people with a depressive episode may identify a patient population with extrahippocampal cortical thinning.

1. Introduction

Patients suffering from a depressive episode frequently experience cognitive deficits. In a meta-analysis of 24 studies investigating cognitive dysfunction in depressed patients, Rock and colleagues identify these impairments as core features of depression (Rock et al., 2014). The authors show moderate deficits in executive function, memory and attention, which could be detected at varying degrees even during remission of a depressive episode (Rock et al., 2014). This is in line with a previous meta-analysis highlighting the importance of executive function impairments in major depressive disorder, which may underlie subsequent impairment in other cognitive domains, such as memory (Snyder, 2013). Greater depression severity is associated with more pronounced cognitive deficits but some antidepressant side effects possibly contribute to the cognitive impairment (McDermott and Ebmeier, 2009; Porter et al., 2007). However, selective serotonin reuptake inhibitor treatment may delay the progression of mild cognitive impairment to Alzheimer's disease (Bartels et al., 2017). Advanced patient age and repeated depressive episodes have been shown to influence cognitive decline (Nakano et al., 2008; Riddle et al., 2017), thus cognitive deficits in late-life depression could indicate a risk for developing dementia (Mackin et al., 2013; Mourao et al., 2016). In contrast, recent longitudinal data suggest that depressive symptoms may be a prodromal sign of dementia rather than a risk factor (Singh-Manoux et al., 2017). This illustrates the challenge to differentiate between depression- and neurodegeneration-associated cognitive deficits in elderly patients.

Neuroimaging markers could be useful to characterize the unique and/or overlapping biological characteristics of cognitive impairment in depression and neurodegenerative diseases. Lebedeva and colleagues

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show a correlation between cognitive status and hippocampal volume in older patients with major depression, and they discuss how these changes may reflect neurodegeneration among individuals with a late-onset of the disease (Lebedeva et al., 2015). Although hippocampal atrophy indicates imminent conversion to dementia in people with mild cognitive impairment (Risacher et al., 2009), we showed that specifically reduced thickness in entorhinal and subicular cortices predicts future cognitive decline in these patients (Burggren et al., 2011). This is consistent with the regions' vulnerability to early neurodegeneration (Braak and Braak, 1995). In young adults with a depressive episode, reduced parahippocampal and fusiform gyrus thickness are familial trait markers for the disease, and the presence of these characteristics in early adulthood makes a neurodegenerative cause unlikely (Papmeyer et al., 2015). Others also detected cortical thinning within extrahippocampal medial temporal and other brain regions in young and middle-aged people at familial risk for major depression (Peterson et al., 2009) and patients with bipolar disorder (Lyoo et al., 2006).

Risk factors and brain pathologies affecting cognitive performance have a differential influence on subregional medial temporal lobe cortical thickness (Burggren et al., 2011; Donix et al., 2010a; Donix et al., 2013). Therefore, to investigate whether cognitive impairment in a depressive episode is associated with medial temporal lobe structure changes, it is important to primarily focus on young adults. In order to examine the specificity of such characteristics, these individuals should then be compared with older patients without a history of mood disorders but suffering from mild cognitive impairment due to prodromal Alzheimer's disease and with healthy older individuals, who experience subjective cognitive deficits more often than young people. Furthermore, neuroimaging data analysis must allow the separation of hippocampal subregions and adjacent medial temporal lobe areas. To achieve this goal, we applied high-resolution magnetic resonance imaging (MRI) and a cortical unfolding approach (Donix et al., 2010a; Ekstrom et al., 2009; Zeineh et al., 2000) as well as detailed assessments of subjective and objective cognitive performance to the above mentioned subject groups. We hypothesized that cognitive deficits in young adults with a depressive episode may reflect a common clinical variant of the disease, associated with cortical thinning in extrahippocampal brain regions.

2. Methods

2.1. Subjects

Fifty subjects underwent MRI scanning and detailed neuropsychological assessments. Twenty-seven young patients with a depressive episode (mean age: 29.0 ± 5.8 years) and 23 older participants with no history of affective disorder but amnestic mild cognitive impairment (68.5 ± 6.6 years) or normal cognition (65.2 ± 8.7 years) were selected from a pool of 180 subjects recruited through our university hospital's memory clinic and advertisements. All participants were right-handed (subjects' report). Individuals with a history of psychiatric or neurological disease other than a depressive episode (ICD10 criteria) or mild cognitive impairment (Petersen, 2004) were not invited to participate, as well as patients with a systemic disease affecting brain function. We obtained written informed consent and the university's ethics committee approved the study. Patients with a depressive episode suffered from mild to moderate depressive symptoms (mean Beck Depression Inventory [BDI] (Beck et al., 1961) score: 24.0 ± 9.0), and were on stable antidepressant medication with serotonine- or serotonine/noradrenaline reuptake inhibitors. The older participants did not receive medication that could have influenced cognitive performance.

2.2. Neuropsychological testing

We investigated the subjective cognitive abilities with the 35-item "Questionnaire for complaints of cognitive disturbances, FLei" (Beblo et al., 2010). Subjects rate their cognitive performance in everyday situations using 5-item scales (e.g., "It is difficult for me to memorize new names": 0 = never to 4 = very often). The assessment allows the differentiation of subjective impairment through subscales of memory (FLei-G), attention (FLei-A) and executive function (FLei-E). Each subscale consists of 10 items, there are also 5 control questions for validity testing. Cronbach's Alpha and split-half reliability are >0.87, and the questionnaire has been used in mood disorder research (Beblo et al., 2017).

Neuropsychological examination was performed for the following domains of cognitive functioning: processing speed (Trailmaking test part A; Stroop test, word reading; d2 test), executive functioning (Regensburg verbal fluency test; Trailmaking test part B; Stroop test, interference), memory encoding (California Verbal Learning Test, learning sum; Wechsler Memory Scale-Revised, visual reproduction and digit span forward/backward), and delayed memory (California Verbal Learning Test, delayed recall; Wechsler Memory Scale-Revised, visual reproduction delayed). We also investigated general intelligence levels using a German version of the Multiple Choice Vocabulary Test (Lehrl et al., 1995), a widely used IQ test in clinical settings [Mehrfachwortschatztest, MWT]. Furthermore, we utilized the UT3-subscore of the Leistungspruefsystem (LPS), a German version of a multiple choice test to detect similarities or dissimilarities between geometric shapes (Kreuzpoitner et al., 2013).

2.3. MRI scanning

We performed MRI scanning on a 3T whole brain MRI scanner (GE Signa HDxt, General Electric Health Care, Waukesha, Wisconsin). We acquired an oblique coronal T2 weighted fast spin echo sequence at high-resolution [repetition time 5200 ms, echo time 105 ms, slice thickness 3 mm, spacing 0 mm, 19 slices, in-plane voxel size 0.39×0.39 mm, field of view 200 mm]. Cortical unfolding (Fig. 1) was then used to improve the visibility of the small and convoluted medial temporal lobe structures, and to enable subregional cortical thickness measurements (Donix et al., 2010a; Ekstrom et al., 2009; Zeineh et al., 2000; Zeineh et al., 2003). First, gray matter is manually defined by masking white matter and cerebrospinal fluid using the high-resolution T2 data. In order to achieve superior in-plane resolution at a reasonable scanning time, we then compensated for greater slice thickness by interpolating the whole sequence and the masks to finally get an approximately isotropic voxel size. Following segmentation, interpolation and manual correction of interpolation errors, gray matter was grown out in connected layers using a region-expansion algorithm. The resulting gray matter volume contains the cornu ammonis (CA) fields 1–3 and the dentate gyrus (separable regions: CA1 and CA23DG), the subiculum (SUB), entorhinal cortex (ERC), perirhinal cortex (PRC), parahippocampal cortex (PHC) und fusiform gyrus (FUS). Unfolding procedures based on metric multidimensional scaling result in a two-dimensional representation of the entire gray matter volume. The boundaries between the individual regions are defined on the original MRI data using anatomical landmarks provided by histological and MRI atlases (Amaral and Insausti, 1990; Duvernoy, 1998), before they are mathematically projected to their flat-map space coordinates. Cortical thickness analyses first include the computation of each gray matter voxel's distance to the nearest non-gray matter voxel in three-dimensional space. Then, for a voxel's representation in two-dimensional space, the maximum distance value of all layers' corresponding three-dimensional voxels is multiplied by two. The topographical accuracy of the technique has been demonstrated previously (Zeineh et al., 2000; Zeineh et al., 2001), as well as high inter-rater and test-retest reliability (Burggren et al., 2008; Donix et al., 2010b). In line with our previous