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Research report

Corpus callosum size may predict late-life depression in women: A 10-year follow-up study

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ABSTRACT

Background: Recent research on late-life depression (LLD) pathophysiology suggests the implication of abnormalities in cerebral white matter and particularly in interhemispheric transfer. Corpus callosum (CC) is the main brain interhemispheric commissure. Hence, we investigated the association between baseline CC measures and risk of LDD.

Methods: We studied 467 non-demented individuals without LLD at baseline from a cohort of elderly community-dwelling people (the ESPRIT study). LLD was assessed at year 2, 4, 7 and 10 of the study follow-up. At baseline, T1-weighted magnetic resonance images were manually traced to measure the mid-sagittal areas of the anterior, mid and posterior CC. Multivariate Cox proportional hazards models stratified by sex were used to predict LLD incidence over 10 years.

Results: A significant interaction between gender and CC size was found ($p=0.02$). LLD incidence in elderly women, but not in men, was significantly associated with smaller anterior (HR 1.37 [1.05–1.79] $p=0.017$), mid (HR 1.43 [1.09–1.86] $p=0.008$), posterior (HR 1.39 [1.12–1.74] $p=0.002$) and total (HR 1.53 [1.16–2.00] $p=0.002$) CC areas at baseline in Cox models adjusted for age, education, global cognitive impairment, ischemic pathologies, left-handedness, white matter lesion, intracranial volume and past depression.

Limitations: The main limitation was the retrospective assessment of major depression.

Conclusion: Smaller CC size is a predictive factor of incident LLD over 10 years in elderly women independently of cognitive deterioration. Our finding suggests a possible role of CC and reduced interhemispheric connectivity in LLD pathophysiology. Extensive explorations are needed to clarify the mechanisms leading to CC morphometric changes in mood disorders.

1. Introduction

Although the frequency of major depression decreases in later life, high rates of clinically significant depressive symptomatology have been consistently observed in people over the age of 65 (Kessler et al., 2010). The generic term of 'late-life depression' (LLD) is commonly used to describe elevated levels of depressive symptomatology in older people – a term which covers both depressive symptoms continuing from early adulthood and incident cases occurring for the first time in old age (Blazer, 2003; Unutzer, 2007).

LLD generates high rates of disability and it has been hypothesized that depression in elderly people may have a different etiology than in younger individuals (Baldwin, 2000; Krishnan, 1993; Lesser et al., 1991). LLD is a heterogeneous illness with poorly understood etiological factors (Blazer, 2003). While psychosocial and genetic factors have a primary causal role in the occurrence of depression in early life (Ebmeier et al., 2006), over

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time some genetic factors may start to play a lesser role (Baldwin, 2000) and pathophysiological variables become predominant (Krishnan, 1993; Lesser et al., 1991). In line with this, MRI studies have shown both white matter changes (Herrmann et al., 2008) and abnormal interhemispheric information transfer in elderly depressed people (Yuan et al., 2010) in comparison to controls.

Corpus callosum (CC) is the main white matter structure connecting the two cerebral hemispheres. CC is essential for interhemispheric communication, particularly by integrating emotional, linguistic, perceptual and cognitive information (Gazzaniga, 2000). CC maturation begins shortly after birth with the myelination of axonal fibers and continues until the middle of the third decade of life (Giedd et al., 1996). Increases in CC volume reflect the ongoing myelination of higher association areas. However, CC size and shape show large inter-individual variations that are independent of individual differences in total brain size (Peters, 1988) and may be influenced by gender, notably through exposure to sex steroids (Moffat et al., 1997; Witelson, 1989), and normal ageing (Salat et al., 1997). Morphological CC alterations have already been described in relation to some psychiatric disorders. Smaller CC size has been reported in bipolar disorder (Arnone et al., 2008a; Kempton et al., 2008), dysthymia (Lyoo et al., 2002), suicidal behavior (Cyprien et al., 2011), post-traumatic stress disorder (De bellis et al., 2002) and schizophrenia (Arnone et al., 2008b, Mohr et al., 2000). Moreover, significantly reduced CC area has been detected in patients with dementia (Di paola et al., 2010; Zhu et al., 2012) and cognitive decline (Shim et al., 2008; Wang et al., 2009). Only one cross-sectional study conducted in elderly people found an association between LLD and smaller CC size (Ballmaier et al., 2008). Similarly, studies conducted in adults (Sun et al., 2009, Xu et al., 2013) and adolescents (Macmaster et al., 2013) also proposed a relationship between CC thinning and depression. Besides, a study conducted in currently depressed adults showed CC expansions (Walterfang et al., 2009) arguing for state-related changes. Overall, these studies suggest that damage or changes of CC structural integrity could be a marker of depression.

However, no study has evaluated the impact of CC size on LLD incidence and the possibility that CC size variations may help identifying elderly people at risk of depression. Finally, although in most studies analyses were adjusted for sex, they did not examine the possibility that the impact of CC size on depression may be different in men and women. This is a major issue due to the importance of sex steroid exposure during early life in CC organization and the hormonal changes occurring in late life. Moreover, previous structural imaging studies have observed gender differences in brain volumes with notably a higher ratio of white matter to whole brain volume in men (Passe et al., 1997). Age-related brain changes, such as increase in white matter lesions (WML), may also be more frequent in older women than men (De leeuw et al., 2001) and we have recently shown that this may be modulated by genetic vulnerability related to estrogen receptor gene variants in postmenopausal women (Ryan et al., 2014). In addition, a close relationship between sex hormone fluctuations and changes in hemispheric transfer has recently been reported in women (Hausmann et al., 2013).

We thus asked whether CC size could predict LLD incidence over a 10-year period in a prospective population-based study of elderly people and whether this may vary in men and women.

2. Methods

2.1. Study population

The data used for this analysis were derived from a population study on psychiatric disorders in older adults in France (the ESPRIT study) (Ritchie et al., 2004). The participants (aged 65 years and over) were randomly selected from the electoral rolls in Montpellier between 1999 and 2001. Subjects were interviewed initially either at the study center or in their own home, if disabled. Refusers (among whom 3.3% were excluded due to severe disability) were replaced by other subjects drawn at random from the same electoral division, such that each division was equally represented. Refusers were generally slightly older and more likely to live alone than people who accepted to take part in the study. The study protocol was approved by the Ethical Committee of the Bicêtre University-Hospital (France) and written informed consent was obtained from each participant. The main aim of this study was to construct a comprehensive database that incorporated clinical, biological, genetic and environmental risk factors of psychiatric diseases and included neuroimaging data. Standardized interviews, neuropsychological tests and neurological examination were carried out at baseline and at year 2, 4, 7 and 10 of the follow-up.

For the present study, individuals from the ESPRIT cohort ($n=1863$) were randomly pre-selected based on the following criteria: age ≤ 80 years and availability of MRI imaging data with estimations of the CC areas and total brain volume ($n=710$). From this initial group, were excluded individuals who received a diagnosis of dementia ($n=18$), had depression at baseline ($n=205$) or did not have proper follow-up for depressive symptoms (i.e., depression assessment at baseline and at least one follow-up visit; $n=20$). Thus, 467 individuals were finally retained for this study (see flow chart in Fig. 1).

The 20 subjects without follow-up did not significantly differ from the 467 retained participants (Chi-square test for qualitative parameters, Mann–Whitney test for quantitative parameters) in terms of sex distribution ($p=0.25$), MMSE score ($p=0.09$) and intracranial volume ($p=0.70$). Conversely, they were older ($p=0.015$) and had bigger WML volumes ($p=0.003$). They also tended to have smaller total ($p=0.07$), posterior ($p=0.07$) and mid ($p=0.06$) CC areas, but not anterior CC area ($p=0.88$).

2.2. Late-life depression (LLD)

LLD is a term that covers a range of symptoms from mild to severe depression in adults aged 65 and over (Blazer, 2003, Unutzer, 2007). This definition has been adopted because in older

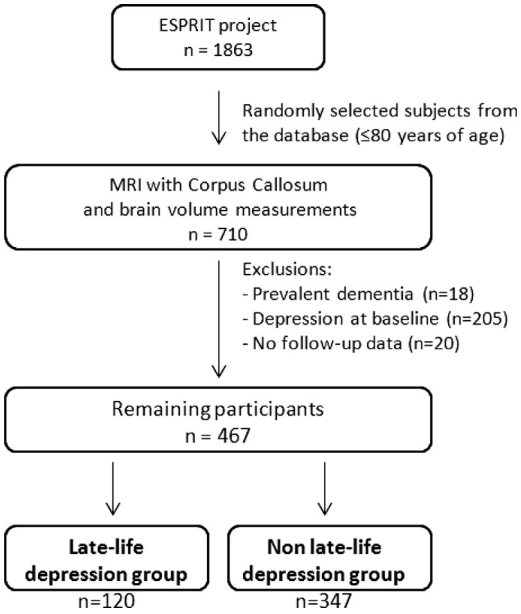

Fig. 1. Flow chart. MRI: magnetic resonance imaging.