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Relationships between years of education and gray matter volume, metabolism and functional connectivity in healthy elders

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ABSTRACT

More educated elders are less susceptible to age-related or pathological cognitive changes. We aimed at providing a comprehensive contribution to the neural mechanism underlying this effect thanks to a multimodal approach. Thirty-six healthy elders were selected based on neuropsychological assessments and cerebral amyloid imaging, i.e. as presenting normal cognition and a negative florbetapir-PET scan. All subjects underwent structural MRI, FDG-PET and resting-state functional MRI scans. We assessed the relationships between years of education and i) gray matter volume, ii) gray matter metabolism and iii) functional connectivity in the brain areas showing associations with both volume and metabolism. Higher years of education were related to greater volume in the superior temporal gyrus, insula and anterior cingulate cortex and to greater metabolism in the anterior cingulate cortex. The latter thus showed both volume and metabolism increases with education. Seed connectivity analyses based on this region showed that education was positively related to the functional connectivity between the anterior cingulate cortex and the hippocampus as well as the inferior frontal lobe, posterior cingulate cortex and angular gyrus. Increased connectivity was in turn related with improved cognitive performances. Reinforcement of the connectivity of the anterior cingulate cortex with distant cortical areas of the frontal, temporal and parietal lobes appears as one of the mechanisms underlying education-related reserve in healthy elders.

Introduction

The protective role of education on age-related or pathological changes in cognition is a long standing well documented concept supported by a large set of complementary data. Epidemiological studies have shown lower prevalence or incidence of dementia in elder population with high level of education (see Meng and D'Arcy, 2012; Valenzuela and Sachdev, 2006 for a review and meta-analysis). Furthermore, neuropsychological studies have reported better cognitive test performance (Plassman et al., 1995; Wilson et al., 2009) and reduced rate of cognitive decline (Albert et al., 1995; Alvarado et al., 2002; Anstey et al., 2003; Christensen et al., 1997; Evans et al., 1993; Farmer et al., 1995; Lyketsos et al., 1999; White et al., 1994) in elders with higher levels of education. These investigations suggest that education affects the risk of late life dementia by its positive association with level of cognition or through its association with decreased rate of cognitive decline in aging. These findings are more generally interpreted under the reserve hypothesis (see Stern, 2002 for a review), with education being considered as one of the main proxy of reserve, although other factors (i.e. Intelligence quotient (IQ), occupation, social and physical activities, complex mental activities) may also be considered (see Satz et al., 2011 for a review). The reserve concept, largely supported by neuroimaging studies, posits that brains with higher reserve could tolerate more aging or pathological effects, thereby minimizing the symptoms. That is, this hypothesis assumes that there are inter-individual differences in the tolerance to brain insult before clinical deficits emerge. At a theoretical level, two different (though not mutually exclusive) conceptualizations to account for reserve mechanisms have been proposed: the brain reserve and the cognitive reserve hypotheses. Under these hypotheses, the inter-individual differences in the tolerance to aging or pathological effects may be explained either by differences in anatomy

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such as greater brain volume, head or intracranial size (cerebral or brain reserve, e.g., Katzman et al., 1988), or by differences in the ability to use brain networks in an effective way (cognitive reserve, Stern, 2002), namely efficiency, capacity or compensation (Stern, 2009). Thus, brain reserve implies quantitative differences of anatomical substrate while cognitive reserve implies variability at the level of brain networks (Stern, 2009). In the field of Alzheimer's disease research, evidence suggests that reserve delays the clinical manifestations of dementia (Stern, 2002). This has important implications including delayed diagnosis and consequently faster progression (Stern, 2002) and shorter duration of diagnosed disease before death (Stern et al., 1995). Thus, the understanding of the mechanisms underlying the protective effect of education is a topic of major interest as it could be a key to delay the onset of dementia. In this line, several studies in Alzheimer's disease patients observed inverse relationships between indicators of reserve and brain measures (see Bartrés-Faz and Arenaza-Urquijo, 2011 for a review). This would be consistent with the idea that reserve allows to compensate or to better tolerate pathological effects, but do not provide evidence regarding the underlying neuroprotective mechanism. Hence, studies in healthy elderly are particularly interesting as they could provide information about education-related neuroprotective mechanisms associated with healthy brain aging, rather than about compensatory mechanisms when the pathology has already impacted the brain. The previous literacy on this topic however focused on pathologic populations while studies in healthy elders remain relatively rare (see Bartrés-Faz and Arenaza-Urquijo, 2011 for a review).

From a structural point of view, although negative relationships (Arenaza-Urquijo et al., 2011; Bastin et al., 2012; Coffey et al., 1999; Querbes et al., 2009) or null findings (Christensen et al., 2009; Seo et al., 2011) have also been reported, several neuroimaging studies in cognitively healthy elders highlighted positive relationships between brain measures and education. Thus, greater gray matter volume and cortical thickness in temporoparietal areas (Foubert-Samier et al., 2013; Liu et al., 2012), larger cortical thickness in orbitofrontal lobe (Liu et al., 2012) as well as greater white matter volume in regions connecting these latter areas (Foubert-Samier et al., 2013) and decreased mean diffusivity in the bilateral hippocampus (Piras et al., 2011) have been found in elderly with greater education.

From a dynamic or functional point of view, several studies have investigated the effect of education by using measures of brain activity while cognitively healthy elderly individuals were performing a cognitive task ($H_2^{15}O$-PET and fMRI studies) or at rest (FDG-PET studies). Studies investigating cerebral metabolism at rest showed a negative association between a proxy of reserve combining education and intelligence and metabolic activity in temporoparietal areas (Bastin et al., 2012) or failed to show any influence of education (Perneczky et al., 2006; Scarmeas et al., 2003a). By contrast, functional studies during memory tasks showed functional reorganization of brain networks (compensation) in healthy elders with higher education compared to young individuals (Scarmeas et al., 2003b; Springer et al., 2005), and more efficient or optimal patterns of brain activation in elders with higher reserve proxies compared to elders with lower reserve proxies (Bosch et al., 2010; Solé-Padullés et al., 2009).

Finally, there has been no study to date assessing both structural and functional brain changes with education. This is important yet to highlight the relative contribution of education to cognitive and brain reserve as well as to provide a further understanding of the role of this factor in healthy brain aging. In a previous study, we failed to evidence positive relationships between a reserve proxy (combining verbal intelligence and education) and FDG-PET or resting state functional connectivity while inverse relationships were found (Bastin et al., 2012). We hypothesize that the selection of a population of healthy elders based on strict criteria including amyloid imaging to exclude preclinical Alzheimer's disease cases would allow highlighting positive relationships. This hypothesis has found support in two recent works using either structural or functional (FDG-PET) imaging and highlighting inverse relationships in cognitively normal elders with normal *versus* pathological amyloid deposition (Arenaza-Urquijo et al., 2013; Ewers et al., 2013). With the aim to further understand the mechanisms underlying the positive effect of education on structural and functional brain measures, we thus selected a population of healthy elders based on both neuropsychological evaluation and cerebral amyloid imaging. We then assessed the relationships between education and gray matter volume, brain metabolism and resting state functional connectivity, expecting to find greater volume and/or metabolism or increased functional connectivity with increased education.

Material and methods

Thirty-nine right-handed healthy elders (mean age (±SD): 67.14 (±5.45), range 60–80; mean MMSE (±SD): 29.33 (±0.96), range 27–30; 24 women) were recruited after detailed clinical and neuropsychological examinations, part of which (25/39) were also included in Bastin et al. (2012). Neuropsychological testing included memory, language, executive functions, visuo-spatial functioning and praxis. All reported scores were in the normal range (i.e. within 1.65 standard deviation of the normal mean for age, gender and education). Subjects were screened for the lack of abnormalities based on stringent inclusion/exclusion criteria: (1) normal somatic examination, (2) body mass index in the normal range (i.e., 18.5–25), (3) no known vascular risk factor and smoking less than 10 cigarettes per day, (4) no alcohol or drug abuse, (5) blood pressure within normal limits (6) no history or clinical evidence of neurological disease, dementia or psychiatric disorder, (7) no current use of medication likely to interfere with cognitive or functional imaging measurements (except birth control pills, estrogen replacement therapy and anti-hypertensive drugs), and (8) normal standard T1 and T2-weighted MRI as assessed by a medical doctor. Moreover, individuals were also screened for the presence of amyloid deposition using florbetapir-PET imaging. They were classified as amyloid-negative or amyloid-positive using a neocortical standardized uptake value ratio cut off value of 1.1 (see La Joie et al., 2012 for the full description of the procedure). Of the initial 39 subjects involved in the study, three subjects with a positive florbetapir-PET scan (i.e., amyloid-positive) were excluded. All the analyses described below were conducted on the 36 remaining amyloid-negative healthy elderly.

The study was approved by the regional ethics committee and all subjects gave their informed consent.

Assessment of years of education

Years of education were assessed as years attending school (mean (±SD), 11.69 (±3.45), range 7–20). Years of education and age were not correlated ($p = .60$).

Imaging protocol

All participants were scanned on the same MRI and PET scans at the CYCERON center (Caen, France). Ten out of the 36 participants only had the T1-weighted MRI scan, while the remaining 26 participants had a structural MRI scan, a FDG-PET scan and a resting-state fMRI scan. All assessments were obtained within 2 months from neuropsychological evaluation.

Structural MRI data

For each participant, a high-resolution T1-weighted anatomical image was acquired on a Philips (Eindhoven, The Netherlands) Achieva 3 T scanner using a 3D fast field echo sequence (3D-T1-FFE sagittal, TR = 20 ms; TE = 4.6 ms; flip angle = 20°; 170 slices; slice thickness = 1 mm; FOV = 256 × 256 mm^2; matrix = 256 × 256).