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REVIEW ARTICLE

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The brain cognitive reserve hypothesis: A review with emphasis on the contribution of nuclear medicine neuroimaging techniques

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Abstract

Neuropathological and clinical evidence indicates that the clinical expression of Alzheimer's disease (AD) occurs as neuropathology exceeds the brain reserve capacity. The brain or cognitive reserve (BCR) hypothesis states that high premorbid intelligence, education, and an active and stimulating lifestyle provide reserve capacity, which acts as a buffer against the cognitive deficits due to accumulating neuropathology. Neuroimaging studies that assessed the BCR hypothesis are critically reviewed with emphasis on study design and statistical analysis. Many studies were performed in the last two decades owing to the increasing availability of positron emission tomography (PET) and PET/computed tomography scanners and to the synthesis of new radiopharmaceuticals, including tracers for amyloid and tau proteins. Studies with different tracers provided complementary consistent results supporting the BCR hypothesis. Many studies were appropriately designed with a measure of reserve, a measure of brain anatomy/function/neuropathology, and a measure of cognitive functions that are necessary. Most of the early studies were performed with PET and [^{18}F]fluorodeoxyglucose, and occasionally with [^{15}O]water, reporting a significant association between higher occupation/education and lower glucose metabolism (blood flow) in associative temporo-parietal cortex in patients with AD and also in patients with MCI, after correcting for the degree in the cognitive impairment. On the contrary, performances on several neuropsychological tests increased with increasing education for participants with elevated [^{11}C]PiB uptake. Studies with the tracers specific for tau protein showed that patients with AD with elevated tau deposits had higher cognitive performances compared with patients with similar levels of tau deposits. BCR in AD is also associated with a preserved cholinergic function. The BCR hypothesis has been validated with methodologically sound study designs and sophisticated neuroimaging techniques using different radiotracers and providing an explanation for neuropathological and clinical observations on patients with AD.

KEYWORDS

[18F]FDG, amyloid imaging, brain cognitive reserve hypothesis, PET/CT

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1 | INTRODUCTION

The brain or cognitive reserve (BCR) hypothesis is a theory that received much attention in the last decades in the neuropsychological, neurological, and neuroimaging fields. There are many similar formulations of this theory. A common formulation states that high premorbid intelligence, education, and an active stimulating lifestyle provides "reserve capacity" that act as a buffer against the cognitive deficits due to accumulating neuropathology of Alzheimer disease (AD; Coffey, Saxton, Ratcliff, Bryan, & Lucke, 1999; Satz, Cole, Hardy, & Rassovsky, 2011). As a consequence, an empirical prediction of the BCR hypothesis is that a highly educated person (with corresponding higher reserve capacity) will compensate for the damage arising from age- or disease-related neurodegeneration as demonstrated by higher cognitive than expected and, therefore, he will be able to cope better with the onset of dementia, maintaining a normal functional level for a longer time than less educated people (Bennett et al., 2006; Christensen et al., 2007; Stern, 2002). Therefore, individuals with more neurons required more brain damage to reach a threshold of clinically evident dementia. Cognitive reserve has been most often estimated using education and intelligence quotient (IQ) although other variables have also been used including literacy, occupational complexity, participation in leisure activities as well as the cohesion of social networks (Scarmeas, Albert, Manly, & Stern, 2006).

There are differences among authors concerning the nature of the buffer and the mechanism through which intelligence or education induce this phenomenon. Moreover, even though the BCR hypothesis was typically formulated for AD, it has also been used to account for cognitive deficits of normal aging and cerebrovascular dementia (Christensen et al., 2007). Stern formulated two main models to fully implement this theory: a brain reserve or passive model, according to which anatomical features (larger brain or head circumference, higher synaptic, or neuronal count) allow the buffer and a reserve, and an active model, according to which existing brain networks activate (i.e., recruitment of a broader brain or an increase in neural activity) areas to undertake a task to compensate for tissue loss or brain damage (Stern, 2002).

It was hypothesized that the BCR is obtained through two forms of neural activity (Stern et al., 2005). In "neural reserve," pre-existing brain networks that are more efficient or have greater capacity are less susceptible to disruption by age-related other pathology; this is equivalent to the formulation of the passive hypothesis. In "neural compensation," alternate networks compensate for disruption of pre-existing networks induced by neurodegeneration; this is equivalent to the formulation of the active model. Both of these activities imply that the differential expression of brain networks as a function of BCR may provide reserve but in different ways. Because the concept of BCR suggests that BCR-related brain networks exist before the advent of age-related or disease-related pathology, such networks must be expressed in young and in older subjects (Stern et al., 2005).

There is no single date or author to which the formulation of the BCR theory can be ascribed to. Most initial studies were done between the 30s' and 70s' (Roth, Tomlinson, & Blessed, 1966; Rothschild, 1937; Tomlinson, Blessed, & Roth, 1970). Autopsy data indicated a discrepancy between the burden of AD lesions (amyloid plaques and neurofibrillary tangles) in the brain and the expression of dementia symptoms during life, such that some individuals with high levels of plaques and tangles at autopsy did not have dementia proximate to death (Katzman et al., 1988). Many studies found that 25–67% of subjects characterized as cognitively normal throughout longitudinal assessments meet pathological criteria for dementia at autopsy (Steffener & Stern, 2012).

The BCR hypothesis should be viewed in the more general frame of the interaction between gene expression (i.e., accumulation of neuropathology) and phenotypic expression (cognitive decline). Indeed several factors have been identified that may influence the relationship between the expression of AD pathology and cognitive deficits, such as the age of onset and the expression of Apolipoprotein E genotype, which can be associated with a faster cognitive decline (Kim et al., 2005; Mosconi et al., 2004; Serrano-Pozo, Qian, Monsell, Betensky, & Hyman, 2015). Similarly, increased evidence has highlighted the role of oxidative stress in AD because of the increased production of reactive oxygen species and the influence of oxidative stress on brain energy metabolism (Picco et al., 2014). Other factors are intuitively associated with buffer capacities including measurements of head circumference, brain size (Mortimer, Snowdon, & Markesbery, 2003), and synaptic or neuronal count (Bartres-Faz & Arenaza-Urquijo, 2011).

1.1 | Methodological/statistical considerations

Which experimental design is needed to prove the BCR theory? An appropriate study design requires at least three variables, that is, (1) a measure of reserve, typically a proxy of a cognitive reserve, which is a variable indirectly related to the BCR; (2) a measure of brain damage/impairment (often a biological measure of brain burden); and (3) a measure of disease severity and cognitive function. Years of education and occupational attainment are the most common proxies. The index of brain pathology represents typically the dependent variable, the BCR proxy represents the independent variable, and the cognitive performance together, eventually with other demographic or neuropsychological variables are entered as covariates to correct for the degree of the cognitive performance (Garibotto et al., 2012). Many studies performed so far lack at least one of these variables and, therefore, provide results that may be consistent with but are not confirmatory of the BCR hypothesis.

Strategies that were previously used to measure the BCR hypothesis were earlier reviewed (Christensen et al., 2007), and they will be only briefly summarized in this paper. One strategy consists in correlating measurements of education with either indices of brain size (e.g., intracranial or brain volume) or with cognitive performance. This is typically applied to cross-sectional data and it has been used in many early neuropsychological/neurological studies. An association between education and an index of brain size is usually claimed to support the BCR hypothesis, even though this is inappropriate because of the lack of a buffer variable. In other words, an association may provide support to

use intelligence as a proxy measurement of brain size, or support that individuals with higher education have greater functional reserve because of the larger brain, but the design does not allow testing the hypothesis that higher education or larger brain volume would act as a buffer to maintain the cognitive skills. Such a demonstration would require evidence that those with more brain tissue have better cognitive outcomes in the face of brain damage/injury (Christensen et al., 2007).

In the last decade, the dramatic increase in the use of neuroimaging techniques provided numerous measurements of brain damage, such as atrophy as imaged by computed tomography (CT) or magnetic resonance imaging (MRI), cerebral blood flow (CBF) as imaged by positron emission tomography (PET) or functional MRI, and cerebral glucose metabolism, brain amyloid and tau protein deposits, as imaged by PET. There has also been an increasing number of studies where neurologists, radiologists, and nuclear medicine physicians worked in strict collaboration with neuropsychologists designing appropriate studies to address this issue. Many studies were done in the last two decades owing, especially, to the increased availability of PET and PET/CT scanners.

In this paper, we will briefly review the main studies relevant to the BCR hypothesis performed with neuroimaging techniques.

1.2 | Studies based on morphological brain measurements

Staff, Murray, Deary, & Whalley (2004) used test measurements of cognitive performance taken 70 years earlier to estimate the cognitive decline, two measures of brain aging (a white matter hyperintensities score and an index of brain atrophy), and measures of occupational and educational status as indicators of brain reserve. The sample included 90 healthy volunteers. Measures of reserve included education, intelligence, brain size, and intracranial volume. Using analysis of covariance, these authors assessed the effect of intracranial volume on verbal and fluid intelligence taking into account IQ scores from early life and measures of brain damage, as reflected by white matter hyperintensities and brain atrophy. They found that intracranial volume did not predict cognitive performance. White matter hyperintensities did not correlate with performance scores as well. However, occupation and education significantly predicted cognitive performance when brain atrophy was used as a measure of brain burden. They concluded that education and occupation functions as a reserve (Staff et al., 2004).

Dufouil, Alperovitch, & Tzourio (2003) examined the relationship between white matter hyperintensities and cognitive skills over a 4-year period in elderly subjects. They found a significant interaction between cognitive performance and Mini–Mental Score Examination (MMSE), that is, individuals with the greatest education and with severe white matter hyperintensities had no cognitive deficits on the MMSE, while subjects with severe white matter hyperintensities and lowest education performed worse than subjects with moderate or mild white matter hyperintensities. They concluded that education modulates the effects of white matter hyperintensities (Dufouil et al., 2003).

Bennett et al. (2003); Bennett, Schneider, Wilson, Bienias, & Arnold (2005) investigated the relationship between education, cognitive functions, and autoptic measurements of the neuritic and diffuse plaques and neurofibrillary tangles. They tested the BCR hypothesis by examining the interaction between education and pathology in predicting the cognitive decline. Results showed that education protected against the negative cognitive effects of neuritic plaques and diffuse plaques but not against the negative effect of neurofibrillary tangles (Bennett et al., 2003). In a follow-up study, the same sample was reinvestigated using a stainless biased towards detecting plaques and confirming that education did not modify the effect of neurofibrillary tangles (Bennett et al., 2005).

Christensen et al. (2007) in a well-designed cross-sectional study including 446 individuals aged 60–64 years investigated (1) the relationship between measures of brain burden (atrophy, white matter hyperintensities) and measures of reserve (creativity, education, and intelligence); (2) the relationship between cognitive deficits and brain reserve; (3) whether measures of reserve mediate the effect of atrophy on cognitive functions; and (4) the association between cerebral risk factors, education, and atrophy. Results showed no association between estimated cognitive decline and brain burden (atrophy, white matter hyperintensities). Risk factors of brain damage were not associated with greater brain atrophy in the less well-educated subjects. Measurements of education, intelligence, and creativity did not provide a buffer for cognitive decline in subjects with high levels of cerebral atrophy (Christensen et al., 2007).

Active participation in different forms of leisure activities can also affect the risk of developing AD. The effects of participation in 13 groups of activities were assessed: knitting, listening to music, or other hobby; walking for pleasure or excursion; visiting friends or relatives; being visited by relatives or friends; physical conditioning; going to movies, restaurants, or sporting events; reading magazines, newspapers, or books; watching television or listening to the radio; doing unpaid community volunteer work; playing cards, games, or bingo; going to a club or center; going to classes; and going to church, synagogue, or temple. Participants were allocated according to low (six or fewer activities) or high (more than six activities) participation in leisure activities. Those who engaged in more than six leisure activities had a 38% lower risk of developing dementia than participants who partook in fewer activities (Scarmeas, Levy, Tang, Manly, & Stern, 2001).

Most studies on the BCR were cross-sectional and these studies might be subject to different biases. Stern et al. (1994) designed a longitudinal study to determine whether the limited educational level and occupational attainment are risk factors for incident dementia. The study included 593 nondemented individuals aged 60 years or older who underwent extensive neuropsychological testing during the follow-up. They used Cox proportional hazards models, adjusting for age and gender, to estimate the relative risk of incident dementia associated with low educational and occupational attainment. Of the 593 subjects, 106 became demented; all but five of these met the research criteria for AD. The risk of dementia was increased in

subjects with either low education (relative risk, 2.02; 95% confidence interval [CI], 1.33–3.06) or low lifetime occupational attainment (relative risk, 2.25; 95% CI, 1.32–3.84). The risk was greatest for subjects with both low education and low lifetime occupational attainment (relative risk, 2.87; 95% CI, 1.32–3.84). The authors concluded that higher educational and occupational attainment may reduce the risk of incident AD, either by hampering the clinical detection of AD or by proving a reserve that delays the onset of clinical symptoms (Stern et al., 1994).

1.3 | CBF and glucose metabolism studies

CBF and glucose cerebral metabolic rate for glucose (CMRglu) are coupled in normal brain and are related to the synaptic activity. The coupling is preserved in normal aging as well as in AD. Therefore, their value provides a direct measurement of brain function and an indirect measurement of brain pathology. PET (occasionally single photon emission tomography for CBF), allowed to use these neurobiological measurements, such as CBF, CMRglu, and lately amyloid load to test the BCR hypothesis (Baskin et al., 2013).

Stern, Alexander, Prohovnik, & Mayeux (1992) tested the hypothesis whether the individuals with more years of education have a more advanced AD before it is clinically evident. As a measure of pathophysiological severity, they quantified CBF with the ^{133}Xenon inhalation technique. A specific pattern of CBF reduction in the parieto-temporal cortex was detected likely corresponding to the effect of AD pathology on the brain function. Parieto-temporal perfusion deficit was significantly greater in the group with the highest level of education, indicating that AD was more advanced in this group. They concluded that education may provide a reserve that compensates for the neuropathological changes of AD and delays the onset of its clinical manifestations (Stern et al., 1992).

Scarmeas et al (2003) evaluated the intellectual, social, and physical activities in nine patients with early AD and 16 healthy elderly controls underwent brain PET with [^{15}O]water. In voxelwise multiple regression analysis that controlled for age and clinical severity, they investigated the association between education, estimated premorbid IQ, activities, and CBF. An inverse association between education and CBF and IQ was detected in patients with AD. In addition, they found a negative correlation between activity score and CBF in parieto-temporal and occipital cortex in patients with AD. When both IQ and education were added as covariates to the model, a higher activity score was still associated with greater CBF deficits. No significant associations were detected in the control subjects. The authors concluded that at any given level of clinical disease severity, a greater degree of brain pathology can be found in patients with AD who are more engaged in lifetime activities, even when IQ and education are taken into account. These results might suggest that inter-subject differences in lifestyle could affect brain reserve by mediating the relation between neuropathology and clinical manifestation of AD (Scarmeas et al., 2003).

Garibotto et al (2008) tested the presence of the reserve mechanism in patients with amnestic mild cognitive impairment (aMCI). In their study, they assessed the impact of occupation and education on CMRglu measured with PET and [^{18}F]FDG in aMCI and in a very large sample of subjects with probable AD (pAD). Their sample population included 242 patients with pAD, 72 with aMCI, and 144 healthy controls. A voxel-based (SPM2) regression analysis was conducted, with CMRglu as dependent variable and occupation and education as independent variables, adjusting for global cognitive status, demographic data, and neuropsychological scores. Results showed a significant association between higher occupation/education and lower CMRglu in posterior temporo-parietal cortex and precuneus in pAD and in aMCI converters, and no correlation was found in aMCI nonconverters and in healthy controls. Therefore, pAD and aMCI converters with higher education/occupation have for comparable cognitive impairment, a more severe CMRglu reduction than those with lower occupation/education. The authors concluded that education and occupation might be proxies for brain/cognitive reserve, reducing the severity and delaying the clinical expression of the AD pathology. They also speculated that because the mechanism of BCR was demonstrated in aMCI converters, the functional reserve must be already ongoing in the predementia phase of AD (Garibotto et al., 2008).

Morbelli et al (2013) investigated the metabolic basis for resilience to neurodegeneration in highly educated patients with prodromal AD. Sixty-four patients with aMCI who later converted to AD dementia during follow-up and 90 controls underwent brain [^{18}F]FDG PET. Both groups were divided into a poorly educated subgroup and a highly educated subgroup. Results showed that highly educated prodromal patients with AD had more severe hypometabolism than poorly educated prodromal patients with AD in the left inferior and middle temporal gyri and the left middle occipital gyrus (metabolic depression). Conversely, they showed relative hypermetabolism in the right inferior, middle, and superior frontal gyri (metabolic compensation). The sites of compensation, mainly corresponding to the right dorsolateral prefrontal cortex showed wide metabolic correlations with several cortical areas in both hemispheres (frontotemporal cortex, parahippocampal gyrus, and precuneus) in highly educated prodromal patients with AD but not in poorly educated prodromal patients with AD. To provide evidence on whether these metabolic correlations represent the preservation of the physiologic networks of highly educated control subjects (neural reserve) or rather the recruitment of alternative networks (neural compensation), or a combination of the two, a connectivity analysis of the dorsolateral prefrontal cortex was performed in highly educated controls as well. The correlation sites of right dorsolateral prefrontal cortex partly overlapped those of highly educated prodromal patients with AD but were less extended. The authors concluded that highly educated prodromal patients with AD can cope better with the disease, thanks not only to the neural reserve but also to the recruitment of compensatory neural networks in which the right dorsolateral prefrontal cortex plays a key role (Morbelli et al., 2013).

Ewers, Insel, Stern, & Weiner (2013) designed a study to examine the effect of education on CMRglu in elderly cognitively healthy subjects with preclinical AD. The study included 52 healthy subjects

who underwent [^{18}F]FDG PET and cerebrospinal fluid (CSF) measurement of Aß$_{1-42}$. Healthy controls were classified as preclinical AD if CSF Aß$_{1-42}$ was <192 pg/ml (Aß$_{1-42}$ [+]) versus healthy controls with normal Aß (Aß$_{1-42}$ [−]). In regression analysis, they tested the interaction effect between education and CSF Aß$_{1-42}$ status (Aß$_{1-42}$ [+] vs. Aß$_{1-42}$ [−]) on [^{18}F]FDG PET metabolism in some cerebral regions of interest (posterior cingulate, angular gyrus, inferior/middle temporal gyrus) and in the whole brain (voxel-based). They found an interaction between education and CSF Aß$_{1-42}$ status for [^{18}F]FDG PET in the posterior cingulate and angular gyrus, after controlling for age, sex, and global cognitive ability. The interaction effect was such that higher education was associated with lower glucose metabolism in the Aß$_{1-42}$ (+) group, with higher glucose metabolism in the Aß$_{1-42}$ (−) group. Voxel-based analysis showed that this interaction effect was primarily restricted to temporo-parietal and ventral prefrontal brain areas. The authors concluded that higher education was associated with lower cerebral glucose metabolism in preclinical AD (Aß$_{1-42}$ [+]), suggesting that BCR had a compensatory function to sustain cognitive ability in the presence of early AD pathology that alters the brain metabolism (Ewers et al., 2013).

Perneczky et al. (2006) provided evidence for the BCR hypothesis using [18F]FDG PET and a comprehensive measure of global cognitive impairment to control for disease severity (total score of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery) and an approach unbiased by predefined regions of interest for the statistical analysis as implemented in SPM. They enrolled 93 patients with mild AD and 16 healthy controls. Statistical analysis included linear regression with education as independent and glucose utilization as dependent variables, adjusted for global cognitive status and demographic variables. Results showed a marked inverse association between years of schooling and CMRglu in the precuneus, in the left hemisphere and in the posterior temporo-occipital association cortex. These results suggested that education is associated with CBR and that subjects with higher education can cope better with brain damage for a longer time. (Perneczky et al., 2006).

One year later, the same group designed a study to assess gender differences in metabolic deficits due to AD pathology at the same level of clinical disease severity (Perneczky, Drzezga, Diehl-Schmid, Li, & Kurz, 2007). Ninety-three patients with mild AD neuropsychological examination and PET with [^{18}F]FDG. An analysis of covariance (with age, neuropsychological tests scores, and years of school education as covariates) was performed. Controlling for covariates, lower glucose metabolism in men than in women was found in the right inferior frontal, superior temporal and insular cortex, and in the hippocampus. The authors concluded that the same clinical severity of dementia is associated with greater reductions in brain glucose metabolism in men than in women indicating a greater brain reserve in men (Perneczky et al., 2007).

1.4 | Amyloid imaging

Amyloid imaging has the potential for being the optimal proxy of brain neurodegeneration for two main reasons. (1) First, tracers bind with desirable sensitivity and specificity to β-amyloid (Aβ); (2) β-amyloid deposition is thought to occur before neural dysfunction, as expressed by CBF and CMRglu, or neuropsychological deficits (Jack et al., 2010). The first tracer that was developed for imaging β-amyloid was the [^{11}C]-labeled Pittsburgh Compound ([^{11}C]PiB). Subsequently, several [^{18}F]-fluorinated compounds were synthesized and are now commercially available, namely [^{18}F]florbetaben, [^{18}F]florbetapir, and [^{18}F]flumetamol (Curtis et al., 2015).

Seed connectivity analyses were performed with PET and [^{18}F]florbetapir, and it was demonstrated that the education was positively related to the functional connectivity between the anterior cingulate cortex on one side and hippocampus, inferior frontal lobe, posterior cingulate cortex, and angular gyrus on the other side (Arenaza-Urquijo, Landeau et al., 2013; Arenaza-Urquijo, Molinuevo et al., 2013).

Kemppainen et al. (2008) reported increased [^{11}C]PiB uptake in high-educated patients in the lateral frontal cortex compared with low-educated patients. Moreover, high-educated patients had significantly lower glucose metabolic rate in the temporo-parietal cortical regions compared with low-educated patients. This study has some limits. As commented by the authors the small sample size (n = 25) limited the statistical power. Moreover, there was an anatomical discrepancy between the areas with increased [^{11}C]PiB uptake (laterofrontal cortex) and those with reduced CMRglu (temporo-parietal regions), which could be attributed to the different spatial distribution of neurofibrillary tangles. Moreover, there was no control group to assess the significance of changes in CMRglu or [^{11}C]PiB uptake (Kemppainen et al., 2008).

Roe et al. (2008) designed a study to evaluate the BCR hypothesis by examining whether individuals of greater educational attainment have better cognitive function than individuals with less education in the presence of elevated fibrillar brain amyloid, as quantified by [^{11}C]PiB PET. Results showed that [^{11}C]PiB uptake interacted with years of education in predicting scores on the Clinical Dementia Rating scale, the Mini–Mental State Examination, and the Short Blessed Test, such that the performance on these measures increased with increasing education for participants with elevated [^{11}C]PiB uptake. Education was unrelated to global cognitive functioning scores among those with lower PiB uptake. They concluded that cognitive reserve influences the association between AD pathology and cognition (Roe et al., 2008).

Two years later, the same group published a study in which they tested whether factors thought to influence the association of AD pathology and dementia might help to accurately identify patients with AD when considered together with amyloid imaging (Roe et al., 2010). The population included subjects with normal cognition (n = 180) and patients with AD (n = 25), who underwent clinical, neurologic, and psychometric assessments as well as [^{11}C]PiB PET. Logistic regression was used to generate receiver operating characteristic curves and the areas under those curves (AUC) to compare the predictive accuracy of mean cortical [^{11}C]PiB binding alone versus mean cortical [^{11}C]PiB binding together with other variables selected using a stepwise selection procedure to identify

participants with AD versus normal cognition. Results showed that the AUC resulting from [^{11}C]PiB PET alone was 0.84 (95% CI, 0.73–0.94). The AUC for the predictive equation was generated by a stepwise model including education, normalized whole brain volume, physical health rating, gender, and use of medications that may interfere with cognition, which was 0.94 (95% CI, 0.90–0.98) with a significant improvement over that yielded using mean cortical [^{11}C]PiB binding alone. They concluded that factors reported to influence associations between AD pathology and dementia can improve the predictive accuracy of amyloid imaging for the identification of symptomatic AD (Roe et al., 2010).

Amyloid imaging could be used also for the identification of patients with MCI that have a greater likelihood to progress to AD. For example, Ciarmiello et al (2018) showed that the extent of cerebral amyloid burden, measured with regional semiquantitative indices by means of PET/CT and [^{18}F]florbetaben, is associated with cognitive impairment in patients with MCI. In their study, 66 patients with aMCI underwent clinical, neuropsychological, and PET amyloid imaging tests. Amyloid status was defined on the basis of the optimal cutoff for discrimination determined by unsupervised k-means clustering method. Results showed that patients with MCI with uptake value >1.3 (i.e., Aß+) had poorer global cognitive and episodic memory performance than patients with low amyloid deposition. The Aß positivity identified individuals with episodic memory impairment with a sensitivity and specificity of 80% and 79%. Overall, these results indicated that a semiquantitative value of amyloid burden allows early identification of patients with MCI who might progress to AD (Ciarmiello et al., 2018).

1.5 | Tau imaging

Studies also addressed their attention towards the tau protein. For example, Almeida et al. (2015) investigated whether BCR modifies the adverse influence of age on key CSF biomarkers of AD. They enrolled 268 individuals (211 in a cognitively normal group and 57 in a cognitively impaired group) that underwent lumbar puncture for collection of CSF samples, from which Abeta42, total tau (t-tau), and phosphorylated tau (p-tau) were immunoassayed. Cognitive reserve was defined as high for 16 or more years. There were significant age x BCR interactions for CSF t-tau, p-tau, and p-tau/Abeta42. With increasing age, subjects with high BCR exhibited milder adverse alterations in these CSF biomarkers compared with individuals with low BCR. This attenuation of age effects by BCR tended to be more pronounced in the group of patients with cognitive deficits compared with the cognitively normal group. There was evidence of a dose-response relationship such that the effect of age on the CSF biomarkers was progressively attenuated given the additional years of schooling. The authors concluded that higher BCR was associated with a diminution of age-related alterations in CSF biomarkers of AD (Almeida et al., 2015).

More recently, radiopharmaceutical developments have made it possible to quantify the accumulation of tau in the brain through PET imaging. Different classes of tau tracers, such as flortaucipir, THK5317, and PBB3 have been developed and utilized in clinical studies (Okamura et al., 2018). In AD, the topographical distribution of tracer binding follows the known distribution of neurofibrillary tangles and is closely associated with neurodegeneration. Retention of tracers has also been observed in the frequent site of the 4-repeat tau isoform deposits in non-AD tauopathies, such as in progressive supranuclear palsy. However, in vitro binding studies indicate that most tau tracers are less sensitive to straight tau filaments, which is a contrast to their high binding affinity to paired helical filaments of tau (PHF-tau). The first-generation of tau tracers shows off-target binding in the basal ganglia, midbrain, thalamus, choroid plexus, and venous sinus. Off-target binding of THK5351 to monoamine oxidase B has been observed in cerebral regions linked to neurodegeneration and is associated with astrogliosis in areas of misfolded protein accumulation. The second generation of tau tracers was produced, such as [^{18}F]MK-6240, which was highly selective to PHF-tau with little off-target binding and enabled a reliable assessment of PHF-tau burden in aging and AD (Okamura et al., 2018).

Rentz et al. (2017) explored the cross-sectional relationships between Aβ and inferior temporal tau deposition on cognitive performance and whether BCR modifies these associations. They studied 156 participants classified into groups of clinically normal (n = 133), MCI (n = 17), and AD (n = 6). IQ served as a proxy of BCR and cognitive functions were assessed using the MMSE. In the whole sample, the interaction between BCR and tau deposition in the inferior temporal gyrus was significant, such that higher BCR participants with elevated tau deposits had higher MMSE scores compared with low BCR participants with similar levels of tau deposits. The interaction between BCR and Aβ status was not significant. In healthy controls only, no cross-sectional interactions among BCR, Aβ, and tau depositions were observed on MMSE. They concluded that BCR may be protective against early AD and enabled some patients to remain cognitively stable despite increased tau and Aβ burden (Rentz et al., 2017).

Whether the cholinergic system is effective in mediating the BCR hypothesis was investigated by Garibotto et al. (2013). A possible association between the cholinergic system and reserve was suggested by preclinical observations that the cholinergic system allows cortical plasticity and by clinical observations of variable responses to cholinergic treatments depending on the patient's educational level. Acetylcholinesterase activity was measured voxel-wise by PET with [^{11}C]MP4A in nine healthy controls, seven patients with early pAD, and nine subjects with MCI at the time of PET imaging, who progressed to AD at follow-up (prodromal AD) and it was related to reserve proxies, that is, education and occupation. The analysis of prodromal and early AD showed positive correlations between education and acetylcholinesterase activity in the hippocampus, bilaterally, and between occupation and acetylcholinesterase activity in the right posterior cingulate gyrus. The significant correlation between acetylcholinesterase activity in structures belonging to the memory network and reserve proxies suggests that the brain reserve in AD is associated with a preserved/stimulated cholinergic neurotransmission (Garibotto et al., 2013).

2 | CONCLUSIONS

In summary, the BCR hypothesis represents since many decades a the focus of research attracting the attention of the psychological, neurological, radiological, and nuclear medicine areas. Appropriate study designs including a measure of reserve, a measure of brain anatomy/function/neuropathology, and a measure of cognitive functions are necessary. The increasing availability of PET and PET/CT scanners over the last two decades allowed carrying out numerous studies with in vivo indices of neural activity (CBF, CMRglu) or neuropathology (amyloid, tau). Recently, PET/MR tomographs were developed that allowed the simultaneous acquisition of PET and MR data without the need of repositioning of the patient (Giovacchini, Giovannini, Riondato, & Ciarmiello, 2017). PET/MR tomographs are particularly suited for brain studies, where MR morphological information can be used for quantification of brain volume or other indices of damage (atrophy, white matter hyperintensities) or for registration of PET data. The main limit of PET/MR tomographs lies in the difficulty of performing accurate quantification, even though substantial achievements have been made in the last years. From a logistical point of view, other disadvantages include high prices and the need for highly qualified interdisciplinary personnel for maintenance. No study with PET/MR on BCR has been performed to the best of our knowledge with such tomographs to date. It is likely to expect that the next future studies will be carried out combining morphological and functional information in the assessment of the BCR hypothesis. With respect to the measure (or proxy) of the reserve, most studies focused on years of education, as easily quantifiable, but it would be interesting to see in more detail whether intellectual activities exerted in subsequent years also has some protective effect on the onset of cognitive deficits.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

G. G. and A. C. were involved in concept designing, drafting of the article, and final approval; E. G., E. B., P. L., R. L., and V. D. were involved in final approval.

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