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ORIGINAL ARTICLE

Cognitive Correlates of Basal Forebrain Atrophy and Associated Cortical Hypometabolism in Mild Cognitive Impairment

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Abstract

Degeneration of basal forebrain (BF) cholinergic nuclei is associated with cognitive decline, and this effect is believed to be mediated by neuronal dysfunction in the denervated cortical areas. MRI-based measurements of BF atrophy are increasingly being used as in vivo surrogate markers for cholinergic degeneration, but the functional implications of reductions in BF volume are not well understood. We used high-resolution MRI, fluorodeoxyglucose-positron emission tomography (PET), and neuropsychological test data of 132 subjects with mild cognitive impairment (MCI) and 177 cognitively normal controls to determine associations between BF atrophy, cortical hypometabolism, and cognitive deficits. BF atrophy in MCI correlated with both impaired memory function and attentional control deficits, whereas hippocampus volume was more specifically associated with memory deficits. BF atrophy was also associated with widespread cortical hypometabolism, and path analytic models indicated that hypometabolism in domain-specific cortical networks mediated the association between BF volume and cognitive dysfunction. The presence of cortical amyloid pathology, as assessed using AV45-PET, did not significantly interact with the observed associations. These data underline the potential of multimodal imaging markers to study structure–function–cognition relationships in the living human brain and provide important in vivo evidence for an involvement of the human BF in cortical activity and cognitive function.

Key words: Alzheimer's disease, AV45-PET, cholinergic degeneration, FDG-PET, MRI, nucleus basalis Meynert, substantia innominata

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Introduction

Cholinergic neurons in the basal forebrain (BF) send their axons to wide parts of the cortical mantle and the hippocampus, where they act upon their cortical target neurons by the release of the neurotransmitter acetylcholine (Mesulam et al. 1983; Mesulam MM 2004; Hasselmo and Sarter 2011). This cortical cholinergic innervation is particularly dense in limbic and heteromodal association areas, which are also the primary sources for cortical back projections to the cholinergic BF (Mesulam et al. 1992; Ghashghaei and Barbas 2001). Several lines of evidence indicate that the modulation of cortical activity through the BF cholinergic system subserves cognitive functions, particularly in the domains of memory and attentional processing (Hasselmo and Sarter 2011). Selective lesions to the cholinergic BF in animal models disrupt cortical cholinergic neurotransmission and induce hypometabolism in the denervated cortical projection sites, which is paralleled behaviorally by impaired performance on spatial learning and target detection tasks (Yamaguchi et al. 1990; Everitt and Robbins 1997; Browne et al. 2001; Gelfo et al. 2013).

The role of the cholinergic BF in human brain function and cognition is less well explored. An important line of evidence emerges from the study of age- and disease-related degeneration of the cholinergic BF and ensuing decline in cholinergic function. Thus, structure and function of the cholinergic BF significantly decrease in the aging brain (Perry et al. 1992; Schliebs and Arendt 2011) and even cognitively intact elderly subjects exhibit an increased susceptibility for cognitive side effects of prescription drugs with anticholinergic properties (Mulsant et al. 2003; Campbell et al. 2009). On the other hand, several clinicopathologic correlation studies in neurologic dementing disorders, most notably Alzheimer's disease (AD) and Lewy body disorders, including Parkinson's disease and dementia with Lewy bodies, indicate that the marked degeneration of cholinergic BF neurons and associated loss of cortical cholinergic activity that occurs in these neurodegenerative conditions contributes to the development of severe cognitive disturbances (Gaspar and Gray 1984; Iraizoz et al. 1999; Pappas et al. 2000; Tiraboschi et al. 2002; Schliebs and Arendt 2006). Consistent with this "cholinergic hypothesis," enhancing cholinergic neurotransmission by medical treatment with acetylcholinesterase inhibitors may reduce cognitive decline in these diseases (Birks 2006; Mori et al. 2012; Rolinski et al. 2012).

However, postmortem clinicopathologic correlation studies are usually limited by relatively small sample sizes, the number of sampled brain regions, and significant offsets between last cognitive evaluation and neuropathologic examination. In vivo neuroimaging markers may overcome some of these limitations and allow assessment of brain–behavior correlations in living subjects (Salmon et al. 2008; Grothe et al. 2010). Using MRI to study volumetric changes in the BF as an in vivo surrogate marker of cholinergic degeneration, it could be demonstrated that this region shows an increased vulnerability to age-related structural decline and is severely atrophied in demented patients with AD or Lewy body disease (Hanyu et al. 2002; Whitwell et al. 2007; Hall et al. 2008; George et al. 2011; Choi et al. 2012; Grothe et al. 2012; Gao et al. 2013; Grothe, Schuster, et al. 2014). Mild cognitive impairment (MCI) is considered a transitional state between normal cognitive aging and dementia (Gauthier et al. 2006), and has been associated with increased cholinergic BF degeneration compared with healthy controls, both in terms of neuropathologic changes (Mesulam M 2004; Mufson et al. 2007) as well as reduced volume on MRI (Grothe et al. 2010; Muth et al. 2010; Grothe et al. 2013). While previous in vivo studies have helped delineating the course of declining BF volume during normal and pathological aging, much less is known on how the decrease in BF volume that accompanies the transition from cognitively normal (CN) aging to dementia relates to cortical dysfunction and the expression of cognitive deficits. In previous studies, we found that reduced BF volumes in MCI correlated with deficits in global cognition and episodic memory function (Grothe et al. 2010; Grothe et al. 2013), whereas correlations with cognition were less pronounced in normally aging subjects (Wolf et al. 2014). Here, we expand upon these previous findings by studying the cognitive correlates of reduced BF volumes in a large and independent sample of neuropsychologically well-characterized elderly subjects with age-appropriate cognition and MCI, respectively, from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Moreover, for the first time we examined whether reduced BF volume on MRI is associated with cortical synaptic dysfunction as measured by [18F]-fluorodeoxyglucose (FDG)-positron emission tomography (PET), and whether this association mediates the effect of BF atrophy on cognitive deficits, as would be predicted by functional models of the corticopetal BF cholinergic system derived from preclinical research (Everitt and Robbins 1997; Browne et al. 2001). We hypothesized that normal age-related decline in BF volume may be functionally silent, whereas increased BF atrophy in MCI would be associated with specific cognitive deficits in the domains of memory and attentional processing, as well as with hypometabolism in cortical target areas that mediate the effect of BF atrophy on cognition. Given that approximately 60% of the MCI subjects in our sample harbor cortical amyloid pathology indicative of prodromal AD, and BF atrophy is exacerbated in these subjects compared with amyloid-negative MCI subjects (Teipel et al. 2014), we further assessed the impact of amyloid status on associations between BF volume, cognitive deficits, and cortical hypometabolism in MCI. Finally, functional and cognitive correlates of BF atrophy were compared with the effects of hippocampus atrophy, given the wealth of neuroimaging literature on age- and dementia-related changes in the hippocampus–memory network.

Methods

Data Source

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu, Last accessed 23/3/15). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and non-profit organizations, with the primary goal of testing whether neuroimaging, neuropsychologic, and other biologic measurements can be used as reliable in vivo markers of AD pathogenesis. A complete description of ADNI and up-to-date information is available at www.adni-info.org, Last accessed 23/3/15.

Subjects

One hundred and thirty-two MCI subjects and 177 CN controls were selected from the ADNI-2 extension of the ADNI project, based on the availability of concurrent structural MRI, FDG-PET, amyloid-sensitive AV45-PET, and neuropsychological assessments. Only MCI subjects from the ADNI diagnostic category "late MCI (LMCI)" were selected for this study. The LMCI category has been introduced in ADNI-2 as a distinction to the new category "early MCI (EMCI)," which is based on a more lenient cutoff for objective memory impairment and aims to detect subjects in their

earliest stages of cognitive impairment. Apart from cognitive differences, previous studies have shown that EMCI is characterized by a lower degree of BF atrophy (Grothe, Ewers, et al. 2014) and cortical hypometabolism (Wu et al. 2012; Kljajevic et al. 2014) compared with LMCI, which renders it a less appropriate clinical population for studying cognitive and hypometabolic correlates of BF atrophy in pathological when compared with normal aging.

Detailed inclusion criteria for the diagnostic categories can be found at the ADNI website (http://adni.loni.usc.edu/methods/, Last accessed 23/3/15). Briefly, LMCI subjects have Mini-Mental State Examination (MMSE) scores between 24 and 30 (inclusive), a subjective memory concern reported by subject, informant, or clinician, objective memory loss measured by education adjusted scores on delayed recall (DR; one paragraph from Wechsler Memory Scale Logical Memory II; education adjusted scores: ≥16 years: ≤8; 8–15 years: ≤4; 0–7 years: ≤2), a clinical dementia rating (CDR) = 0.5, the absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and the absence of dementia. CN subjects have MMSE scores between 24 and 30 (inclusive) and a CDR = 0, are non-depressed, non-MCI, and non-demented.

Demographics, neuropsychological profiles, and proportions of APOE4 allele carriers of the MCI and CN groups used in the present study are summarized in Table 1. While being based on the ADNI diagnostic category "LMCI," the overall neuropsychological deficit of the MCI group in this study (MMSE = 27.5 ± 1.9) does not appear to be more advanced compared with MCI samples from other cohorts.

All subjects from the CN and MCI groups had also been included in one of our previous studies assessing the effect of PET-measured amyloid pathology on BF and hippocampus volumes across diagnostic categories (Teipel et al. 2014).

Neuropsychological Assessment

Cognitive performance was assessed using a cognitive test battery covering several cognitive domains, including memory, attention/executive function, and semantic memory/verbal fluency. Specifically, total learning (LRN), 5-min and 30-min DR (DR-5 and DR-30), and total recognition (RCG) of the 15-item wordlist of the Rey Auditory Verbal Learning Test were used to assess aspects of episodic memory function. Simple visuospatial perception/processing speed and attentional control/executive functions were quantified by the Trail Making Test (TMT) part A and B, respectively. The Boston Naming Test (BNT) and the Categorical Fluency Test (CFT) were used to assess semantic memory/verbal fluency.

Imaging Data Acquisition

ADNI-GO/-2 MRI data were acquired on multiple 3T MRI scanners using scanner-specific T_1-weighted sagittal 3D MPRAGE sequences. To increase signal uniformity across the multicenter scanner platforms, original MPRAGE acquisitions in ADNI undergo standardized image preprocessing correction steps. FDG- and AV45-PET data were acquired on multiple instruments of varying resolution and following different platform-specific acquisition protocols. Similar to the MRI data, PET data in ADNI undergo standardized image preprocessing correction steps aimed at increasing data uniformity across the multicenter acquisitions. More detailed information on the different imaging protocols employed across ADNI sites and standardized image preprocessing steps for MRI and PET acquisitions can be found in the ADNI website (http://adni.loni.usc.edu/methods/, Last accessed 23/3/15).

Table 1 Sample characteristics

	CN	MCI	Cohen's *d*
N	177	132	N/A
Age (years)	73.8 ± 6.5	72.4 ± 8.0	0.20
Gender (M/F)	88/89	72/60	N/A
Education (years)	16.6 ± 2.5	16.5 ± 2.7	0.03
APOE4 (–/+)	128/49	53/79*	N/A
MMSE	29.1 ± 1.2	27.5 ± 1.9*	1.03
LRN	45.4 ± 10.8	33.0 ± 11.0*	1.14
DR-5	8.8 ± 3.6	4.6 ± 3.8*	1.13
DR-30	7.5 ± 4.0	3.3 ± 3.9*	1.06
RCG	12.7 ± 2.3	10.1 ± 3.3*	0.94
TMT-A	33.7 ± 12.0	42.5 ± 19.5*	−0.56
TMT-B	80.3 ± 39.5	120.7 ± 67.9*	−0.75
BNT	28.3 ± 2.1	26.0 ± 3.7*	0.80
CFT	21.4 ± 5.3	17.2 ± 4.9*	0.82

Note: Sample size (*N*), demographics, proportion of APOE4 allele carriers (+) and non-carriers (–), and neuropsychological test performance for CN and MCI groups. Numbers indicate group mean and standard deviation or number of subjects in each category for bivariate variables. Asterisk indicates significant difference between MCI and CN groups ($P < 0.001$) based on two-sample *t*-test for continuous variables or Fisher's exact test for bivariate categorical variables (APOE4). Effect size of the group difference is indicated by Cohen's *d*. Age, gender distribution, and years of education did not differ significantly between CN and MCI groups (all $P > 0.05$).

LRN, DR-5, DR-30, RCG: total learning, 5-min and 30-min delayed recall, and total recognition, respectively, of the 15-item wordlist of the Rey Auditory Verbal Learning Test; TMT-A and -B: Trail Making Test part A and B; BNT: Boston Naming Test; CFT: Categorical Fluency Test.

Imaging Data Processing

Figure 1 shows a flowchart of the main preprocessing steps and computational analyses used in the present study. Imaging data were processed using the Statistical Parametric Mapping software (SPM8, Wellcome Trust Center for Neuroimaging) and the Voxel-Based Morphometry toolbox (VBM8, http://dbm.neuro.uni-jena.de/vbm/, Last accessed 23/3/15) implemented in MATLAB R2007a (MathWorks, Natick, MA, USA).

MRI Data Processing

MRI data were processed as described previously (Grothe, Ewers, et al. 2014; Teipel et al. 2014). First, MRI scans were automatically segmented into gray matter (GM), white matter, and cerebrospinal fluid partitions of 1.5 mm isotropic voxel size, using the segmentation routine of the VBM8 toolbox. The resulting GM and white matter partitions of each subject in native space were then high-dimensionally registered to an aging/AD-specific reference template from a previous study (Grothe et al. 2013) using the DARTEL algorithm (Ashburner 2007). Individual flow fields obtained from the DARTEL registration to the reference template were used to warp the GM segments, and voxel values were modulated for volumetric changes introduced by the high-dimensional normalization, such that the total amount of GM volume present before warping was preserved. All preprocessed GM maps passed a visual inspection for overall segmentation and registration accuracy.

Automated Volumetry of BF and Hippocampus Regions of Interest

Individual GM volumes of BF and hippocampus regions of interest (ROIs) were extracted automatically from the warped

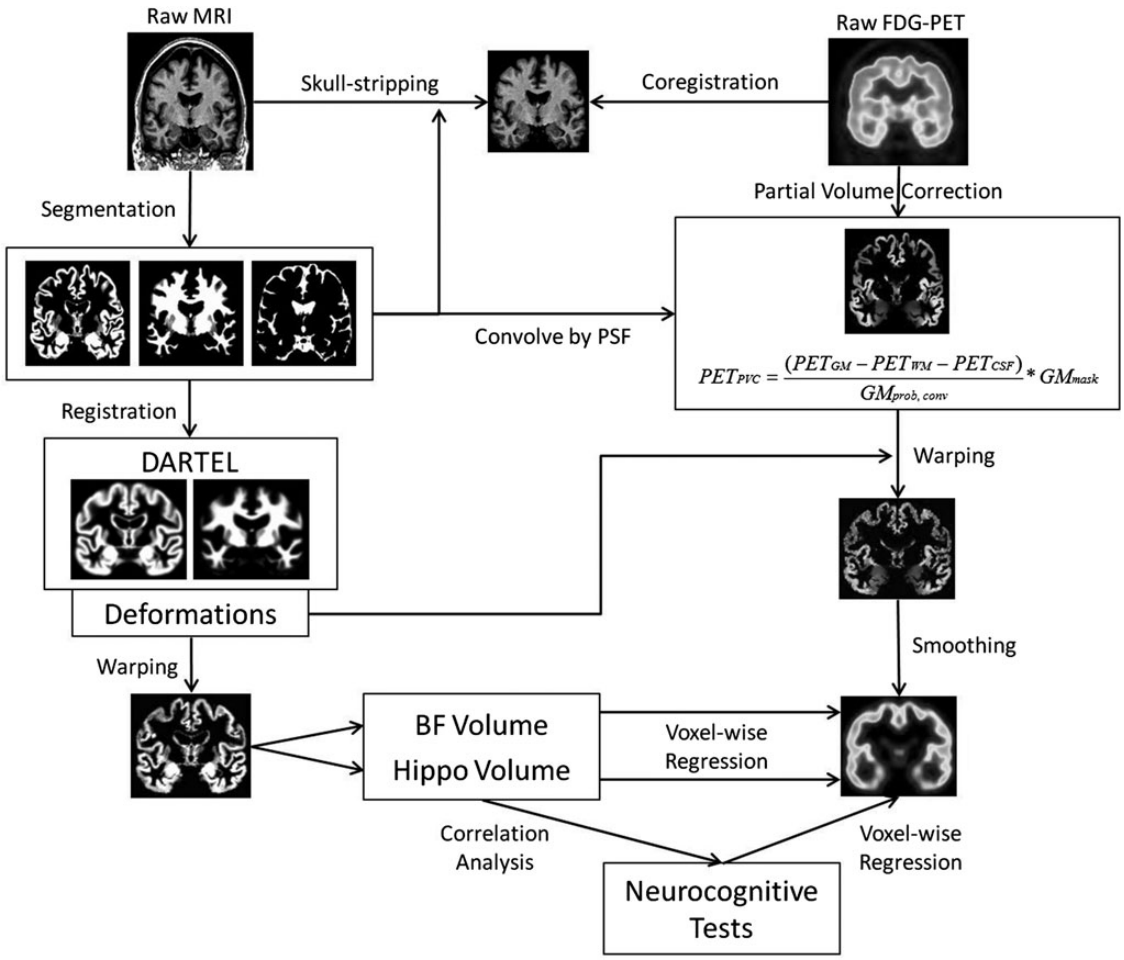

Figure 1. Overview of main image processing and analysis steps. Structural MRIs of each subject were segmented and high-dimensionally registered to a population-specific reference template. BF and hippocampus volumes were extracted from warped and modulated GM maps using ROI masks in the template space. FDG-PET scans were coregistered to skull-stripped versions of the corresponding MRIs, corrected for PVEs, and high-dimensionally warped to the reference template using the deformation fields derived from registration of the MRI scans. BF and hippocampus volumes were tested for correlations with neuropsychological test performance, and regressed on preprocessed FDG-PET scans to reveal patterns of cerebral hypometabolism associated with BF and hippocampus atrophy, respectively. Finally, associations between BF-related hypometabolism and neuropsychological test performance were assessed using additional voxel-wise regression models. See text for details. BF: basal forebrain; DARTEL: Diffeomorphic Anatomical Registration using Exponentiated Lie algebra; GM_{mask}: gray matter mask; $GM_{prob,\,conv}$: gray matter probability map convolved by point spread function; Hippo: hippocampus; PET_{PVC}: partial volume-corrected PET image; PET_{WM}: estimated (virtual) PET image reflecting white matter activity; PET_{CSF}: estimated (virtual) PET image reflecting cerebrospinal fluid activity; PSF: point spread function.

GM segments by summing up the modulated GM voxel values within the respective ROI masks in the reference space.

Given that the cholinergic BF nuclei lack clear anatomical borders that could serve manual delineation on MRI scans, definition of the BF mask was based on a recently published cytoarchitectonic map of BF cholinergic nuclei in the MNI space, derived from combined histology and in cranio MRI of a postmortem brain (Kilimann et al. 2014). This cytoarchitectonic map matches the standard MNI space and was projected into the aging/AD-specific template space using non-linear warping parameters obtained from a DARTEL registration of the MNI152 template. Although the cytoarchitectonic BF map comprises detailed outlines of different cholinergic subdivisions within the BF, including cell clusters corresponding to the medial septum, diagonal band, nucleus subputaminalis, and nucleus basalis Meynert, in the current study we only considered the entire volume of the cholinergic BF map, including all cholinergic subdivisions, as a proxy for overall BF cholinergic system integrity. The ROI mask for the hippocampus was obtained by manual delineation of the hippocampus in the reference template of aging/AD-specific anatomy (Grothe et al. 2013) using the interactive software package Display (McConnell Brain Imaging Centre at the Montreal Neurological Institute) and a previously described protocol for segmentation of the medial temporal lobe (Pruessner et al. 2000). Supplementary Figure 1 provides an illustration of the BF and hippocampus ROIs in the reference space.

For further analyses, the extracted regional GM volumes were scaled by the total intracranial volume and calculated as the sum of total volumes of the GM, white matter, and cerebrospinal fluid partitions.

FDG-PET Data Processing

Each subject's FDG-PET scan was rigidly coregistered to a skull-stripped version of the corresponding structural MRI scan and corrected for partial volume effects (PVEs). PVE correction followed the algorithm proposed by Muller-Gartner et al. (1992) and was implemented using in-house written MATLAB scripts

based on SPM8's image processing routines. PVE correction involved correction for spill-in effects of white matter and cerebrospinal fluid signal into the GM compartment as well as correction for spill-out effects of GM signal into adjacent tissue compartments.

PVE-corrected FDG-PET scans were warped to the aging/AD-specific reference space (without modulation of voxel values) using the DARTEL flow fields derived from the registration of the corresponding MRI scans (Kljajevic et al. 2014). Finally, warped FDG-PET scans were proportionately scaled to pons uptake values and smoothed with a Gaussian smoothing kernel of 8 mm.

Statistical Analysis

Statistical analyses were carried out using SPM8 and the software package IBM SPSS Statistics version 21.

Association Between BF Volume and Cognitive Deficits

Associations between BF volume and neuropsychometric test performance were assessed separately for MCI and CN groups using Pearson's correlation coefficients, and statistical significance was set at $P < 0.05$ (two-tailed), Bonferroni-corrected for the number of tested psychometric measures. For those neuropsychometric tests that showed a significant bivariate correlation with BF volume, additional partial correlation analyses, controlling for age, gender, and education, were conducted to assess the specificity of the associations. For comparison, identical analyses were conducted using bilateral hippocampus volume in place of BF volume.

Association Between BF Volume and Cortical Hypometabolism

The association between reduced BF volume and regional hypometabolism was assessed separately for MCI and CN groups using voxel-wise regression analyses of BF volume on preprocessed FDG-PET maps, controlling for age, gender, education, and MMSE. Analysis was restricted to a GM mask of the reference template, thresholded at 50% GM probability, and voxel-wise results were assessed at an FDR-corrected statistical threshold of $P < 0.05$. For comparison, a corresponding voxel-wise regression analysis was conducted for bilateral hippocampus volume in the MCI group.

Mediation Analysis of Cortical Hypometabolism and Cognitive Impairments Related to Reduced BF Volume in MCI

In additional analyses, we wished to test whether the association between BF volume and domain-specific cognitive deficits in MCI is mediated by regional cortical hypometabolism. In a first step, we determined how BF-associated cortical hypometabolism relates to memory (DR-30) and attentional control deficits (TMT-B), which were found to be sensitive to reductions in BF volume (see Results). Although several psychometric indices of memory function correlated with BF volume, in this additional analysis only DR performance (DR-30) was examined as a representative and widely used index of episodic memory deficits in MCI (Grundman et al. 2003, 2004; Fjell et al. 2008). Thus, DR-30 and TMT-B scores were used as predictor variables in a voxel-wise regression model on FDG-PET maps, where the search region was limited to the areas associated with reduced BF volumes. To detect hypometabolic subnetworks specific for memory and attentional control deficits, the regression analyses were controlled for age, gender, education, MMSE, and TMT-B or DR-30, respectively. Voxel-wise results were assessed at a statistical threshold of $P < 0.05$, FDR-corrected.

In a second step, we used path analyses to test whether the effect of BF volume on cognitive deficits is mediated by hypometabolism in domain-specific cortical networks. Thus, 2 independent mediation models were constructed using BF volume as the *causal variable*, cognitive test performance as the *outcome variable*, and mean FDG-PET signal extracted from the respective domain-specific cortical network (normalized to pons uptake) as the *mediator variable*. Path coefficients were estimated using multiple regressions and the statistical significance of the mediation was assessed using Sobel's test implemented in SPSS (Preacher and Hayes 2004).

Impact of Amyloid Pathology on the Associations Between BF Volume, Cognitive Deficits, and Cortical Hypometabolism

To assess whether associations between BF volume, cognitive deficits, and cortical hypometabolism in MCI were mainly driven by subjects that harbor cortical amyloid pathology indicative of prodromal AD (Albert et al. 2011), we tested the associations for a significant interaction with amyloid status as determined from amyloid-sensitive AV45-PET scans (Fleisher et al. 2011).

Amyloid status was derived from cortex-to-whole cerebellum standardized uptake value ratios (SUVRs) that have been calculated and made available on the ADNI server by one of the ADNI PET core laboratories (Jagust Lab, UC Berkley; Landau et al. 2012). This cortex-to-whole cerebellum SUVR was derived for each subject by averaging AV45 uptake within frontal, cingular, lateral parietal, and lateral temporal cortical regions, known to be particularly affected by amyloid pathology even in prodromal stages of AD (Kemppainen et al. 2007), and dividing this value by averaged uptake within the cerebellar reference region. Cortical and cerebellar ROIs were segmented in each individual's MRI scan using the Freesurfer software (version 4.5.0). More detailed information on AV45-PET processing is provided in Supplementary Material. Based on this global cortical SUVR, amyloid positivity was established using a recommended threshold of ≥1.17, which has been found to be indicative of pathological levels of amyloid associated with AD dementia in clinicopathologic correlation studies (Fleisher et al. 2011).

Interaction effects of amyloid status on the associations between BF volume, cognitive deficits, and cortical hypometabolism were assessed using separate linear regression models with BF volume, amyloid status, and their interaction term as predictor variables, and psychometric test performance or mean FDG-PET signal extracted from the domain-specific cortical networks (normalized to pons uptake), respectively, as dependent variables. Complementary analyses used a more lenient SUVR threshold for defining amyloid positivity, as well as APOE4 genotype instead of PET-evidenced amyloid status as an indicator of AD dementia risk in MCI (Fei and Jianhua 2013).

Results

Cognitive Correlates of Reduced BF and Hippocampus Volumes in MCI and Normal Cognitive Aging

Results of the correlation analyses between BF and hippocampus volumes and psychometric measures of cognitive impairment in the CN and MCI groups are summarized in Table 2. In the MCI group, smaller BF volumes correlated significantly with worse

Table 2 Correlation coefficients for associations of BF and hippocampus volumes with cognitive test performance

	BF		Hippocampus	
	CN	MCI	CN	MCI
LRN	**0.228** (**$P = 0.002$**)	**0.378*** (**$P < 0.001$**)	0.066 ($P > 0.1$)	**0.353*** (**$P < 0.001$**)
DR-5	**0.235** (**$P = 0.002$**)	**0.370*** (**$P < 0.001$**)	0.170 ($P = 0.024$)	**0.456*** (**$P < 0.001$**)
DR-30	0.155 ($P = 0.04$)	**0.346*** (**$P < 0.001$**)	0.130 ($P = 0.085$)	**0.449*** (**$P < 0.001$**)
RCG	0.096 ($P > 0.1$)	0.219 ($P = 0.012$)	0.014 ($P > 0.1$)	**0.326*** (**$P < 0.001$**)
TMT-A	−0.105 ($P > 0.1$)	−0.194 ($P = 0.026$)	0.007 ($P > 0.1$)	−0.137 ($P > 0.1$)
TMT-B	−0.159 ($P = 0.034$)	**−0.268*** (**$P = 0.002$**)	−0.114 ($P > 0.1$)	−0.099 ($P > 0.1$)
BNT	0.068 ($P > 0.1$)	0.098 ($P > 0.1$)	−0.054 ($P > 0.1$)	0.136 ($P > 0.1$)
CFT	0.102 ($P > 0.1$)	0.130 ($P > 0.1$)	−0.078 ($P > 0.1$)	0.208 ($P = 0.017$)

Note: Pearson's correlation coefficients for associations between BF and hippocampus volumes with cognitive test performance in the CN and MCI groups. Cognitive tests are grouped according to overall cognitive domain. *P*-values are given in parentheses and correlations meeting the Bonferroni-corrected significance threshold ($\alpha_{critical} = 0.00625$) are printed in bold letters. Asterisks mark volume–cognition associations that remain significant after controlling for age, gender, and education.
LRN, DR-5, DR-30, RCG: total learning, 5-min and 30-min delayed recall, and total recognition, respectively, of the 15-item wordlist of the Rey Auditory Verbal Learning Test; TMT-A and -B: Trail Making Test part A and B; BNT: Boston Naming Test; CFT: Categorical Fluency Test.

performance on several psychometric tests of episodic memory function, including LRN, DR-5, and DR-30, as well as with attentional control deficits indexed by the TMT-B. Performance measures of RCG, TMT-A, BNT, and CFT were not significantly associated with BF volume after correction for multiple comparisons. Smaller hippocampus volumes were significantly associated with worse performance on all measures of episodic memory function (LRN, DR-5, DR-30, and RCG), but not with performance measures of other cognitive domains. The differential associations of BF and hippocampus volume with episodic memory (DR-30) and attentional control (TMT-B) deficits in the MCI group are illustrated in Figure 2. All of the associations between BF or hippocampus volume and psychometric test performance also remained significant (at $P < 0.05$) after controlling for age, gender, and education, albeit at reduced partial correlation coefficients.

In the CN group, smaller BF volumes correlated weakly, but significantly, with worse performance on LRN and DR-5. However, these associations did not remain significant when controlling for age, gender, and education. Hippocampus volume did not show significant correlation with any psychometric measure in the CN group.

Cortical Hypometabolism Associated with Reduced BF and Hippocampus Volumes in MCI and Normal Cognitive Aging

Results from the voxel-based regression of BF volume on preprocessed FDG-PET maps in the MCI group are illustrated in Figure 3. At an FDR-corrected voxel-wise threshold of $P < 0.05$, smaller BF volume was significantly associated with reduced glucose metabolism in widespread bilateral limbic, paralimbic, and heteromodal association areas of the cortex, independently of age, gender, education, and global cognitive impairment. Pronounced effects were seen in medial, orbital, and lateral prefrontal cortex, anterior insula, anterior and posterior cingulate, retrosplenial cortex, ventral precuneus, lateral temporo-parietal areas, and the medial temporal lobe, including entorhinal cortex, amygdala, and hippocampus. BF atrophy was also significantly associated with bilateral subcortical hypometabolism in the basal ganglia, the thalamus, and the BF proper. Smaller bilateral hippocampus volume was associated with hypometabolism in a more closely circumscribed network, encompassing the bilateral medial temporal lobes, including amygdala, entorhinal cortex, and hippocampus proper, as well as the bilateral posterior cingulate and retrosplenial cortices (Fig. 3).

Lower BF volumes among CN subjects were only associated with bilaterally reduced metabolism in the BF itself as well as in parts of the basal ganglia and the thalamus, but not with cortical hypometabolism (see Supplementary Fig. 2).

Hypometabolism in Domain-Specific Cortical Networks Mediates the Association Between BF Volume and Cognitive Dysfunction in MCI

When searching the hypometabolic areas related to reduced BF volume for associations with cognitive impairments in MCI, worse performance on DR-30 was found to correlate with hypometabolism in a circumscribed bilateral network encompassing the hippocampus, medial septum, posterior cingulate, retrosplenial cortex, ventral precuneus, and the inferior parietal cortex (Fig. 4). A further cluster was located in the left dorsolateral prefrontal cortex. Worse performance on the TMT-B was associated with hypometabolism in a widespread and largely non-overlapping bilateral fronto-temporo-parietal network, mainly involving the lateral, orbital, and medial prefrontal cortex, anterior insula, subgenual cingulate cortex, ventral precuneus, and lateral temporo-parietal areas. Smaller subcortical clusters were also seen in thalamus, medial septum, and right posterior hippocampus extending into the retrosplenial cortex. Overlap of the hypometabolic networks associated with DR-30 and TMT-B performance was limited to the ventral precuneus, inferior parietal cortex, medial septum, and right posterior hippocampus/retrosplenial cortex.

Complementary path analyses showed significant indirect effects of BF volume on cognitive test performance through hypometabolism in the respective cortical networks (illustrated in Supplementary Fig. 3). The effect of BF volume on DR-30 performance (total effect: $\beta(c) = 0.35$, $P < 0.001$) was markedly reduced when controlling for hypometabolism in the hippocampus–posterior cingulate network [direct effect: $\beta(c') = 0.17$, $P = 0.04$], and Sobel's test revealed a significant mediation [indirect effect: $\beta(ab) = 0.18$, $Z_{Sobel} = 3.64$, $P < 0.001$]. Similarly, the effect of BF volume on TMT-B performance [total effect: $\beta(c) = -0.27$, $P = 0.002$] was markedly reduced when controlling for hypometabolism in the fronto-temporo-parietal network [direct effect: $\beta(c') = -0.08$, $P > 0.1$], and Sobel's test revealed a significant mediation [indirect effect: $\beta(ab) = -0.19$, $Z_{Sobel} = -3.68$, $P < 0.001$].

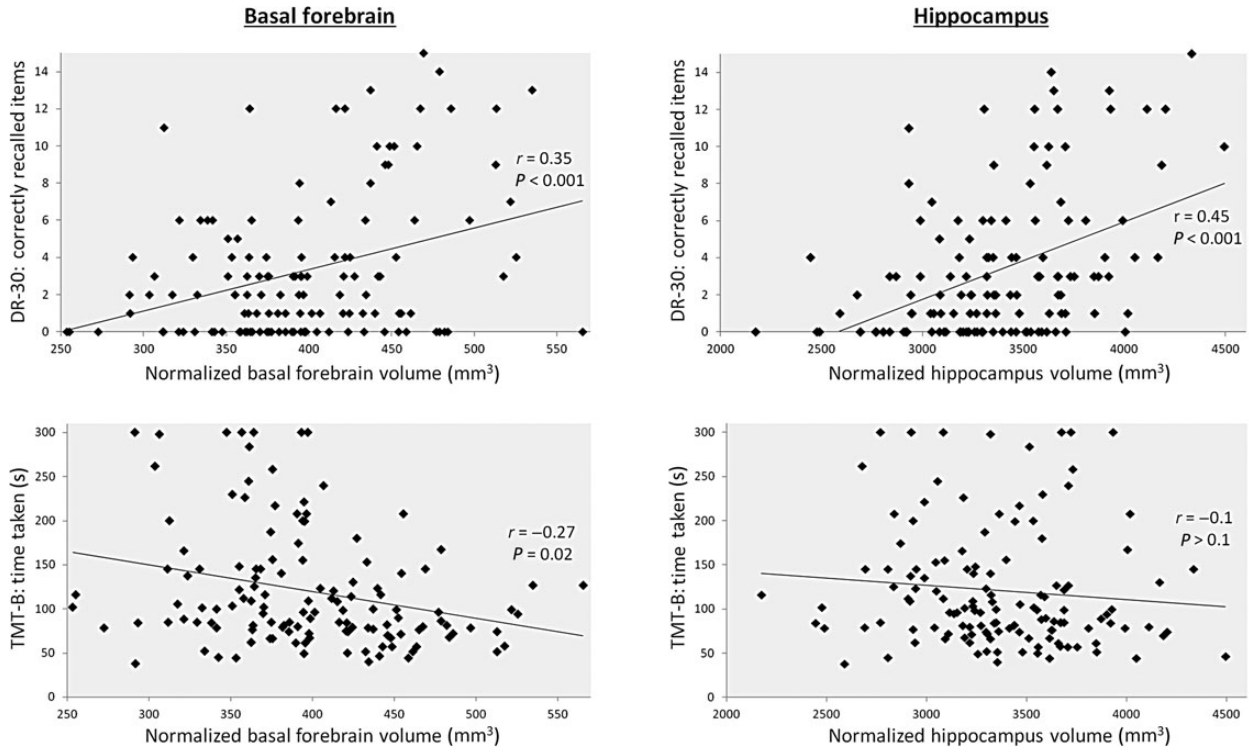

Figure 2. Associations of BF and hippocampus volume with episodic memory and attentional control deficits in MCI. Normalized BF (left) and hippocampus (right) volumes of MCI subjects are plotted on the x-axis against the number of correctly recalled wordlist items at 30-min DR (DR-30, top panel) and the time taken to complete the TMT part B (TMT-B, bottom panel) on the y-axis. BF volumes correlate with both performance on the DR-30 episodic memory test and the TMT-B indexing attentional control. Hippocampus volumes show significant correlation with DR-30 performance, but not with TMT-B performance.

Impact of Amyloid Pathology on the Observed Associations

Based on suprathreshold AV45-PET SUVRs, 85 MCI subjects (64%) showed cortical amyloid pathology indicative of prodromal AD (Albert et al. 2011). Interaction analyses testing the impact of amyloid status on the associations between BF volume, cognitive deficits, and cortical hypometabolism did not reveal any significant effects ($P > 0.1$ for the interaction term in all models; see Supplementary Fig. 4). All interaction effects of amyloid status remained non-significant ($P > 0.1$) when amyloid positivity was established using a lower threshold of SUVR ≥1.11, indicative of any detectable amyloid pathology as opposed to levels typical for AD dementia (Fleisher et al. 2011). Similarly, APOE4 genotype did not significantly interact with the associations between BF volume and cognitive deficits or cortical hypometabolism, respectively (see Supplementary Fig. 4).

Discussion

High-resolution MRI-based volumetry of carefully defined BF ROIs is emerging as a promising in vivo surrogate marker of cholinergic degeneration in normal and pathological aging. Recent findings from this line of research indicate that the BF is particularly vulnerable to normal age-related loss of GM volume, and that MCI and AD are associated with an exacerbation of BF atrophy over and above the effects of normal aging (Hanyu et al. 2002; Whitwell et al. 2007; Hall et al. 2008; Muth et al. 2010; George et al. 2011; Grothe et al. 2012, 2013; Gao et al. 2013; Teipel et al. 2014). In the present study, we aimed to expand on these findings by characterizing the functional and cognitive correlates of BF atrophy in a large sample of MCI subjects and normally aging elderly, who had been examined with FDG-PET imaging and a detailed neurocognitive test battery in addition to the high-resolution structural MRI scan. We found that among MCI subjects, but not among subjects with age-appropriate cognition, lower BF volumes were associated with specific impairments in tests of episodic memory and attentional control, as well as with hypometabolism in a widespread neuronal network covering most parts of the limbic and heteromodal association cortex. Further path analytic analyses supported a directed model, where the effects of BF atrophy on cognitive deficits are mediated by hypometabolism in domain-specific cortical networks.

Cognitive Correlates of BF Atrophy

The role of the BF cholinergic system in cognition has been extensively studied in animal models, where selective lesions to the cholinergic BF were found to alter performance in specific behavioral tests of memory function and attentional processing (Everitt and Robbins 1997). Although this system is less amenable to direct experimental manipulation in humans, there are several lines of evidence that implicate the cholinergic BF in human memory and higher cognitive processes.

For example, functional neuroimaging studies in healthy subjects found activation of the BF in response to salient visual stimuli (Morris et al. 1997), but also in the context of conditional learning (Morris et al. 1998), episodic memory retrieval (Fujii et al. 2002), and proactive interference resolution (De Rosa et al. 2004). On the other hand, case reports of patients with selective damage to the BF caused by surgical resection of brain tumors (Morris et al. 1992; Chatterjee et al. 1993; Kobayashi et al. 2004)

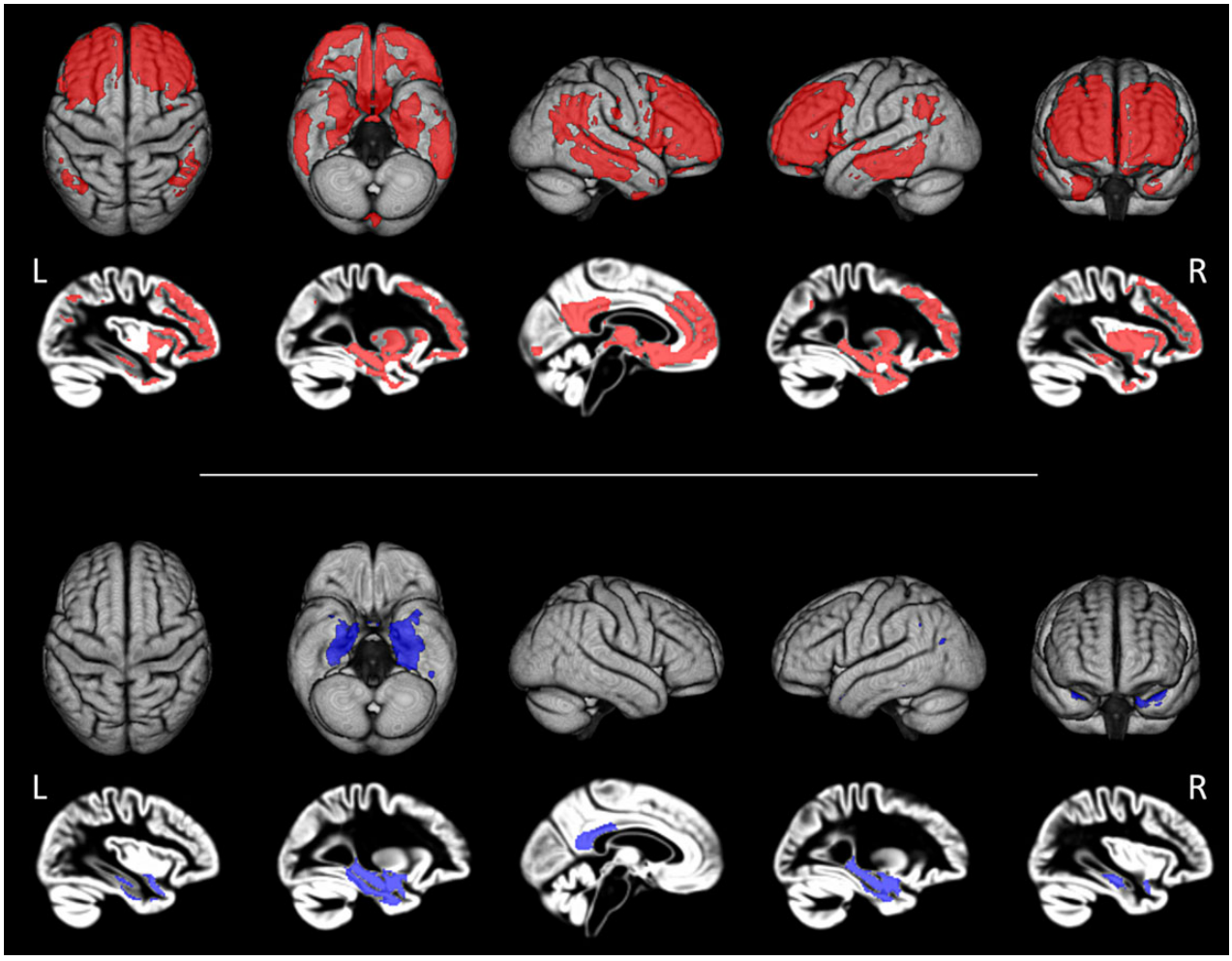

Figure 3. Hypometabolism associated with BF and hippocampus atrophy in MCI. The figure depicts regional effects of voxel-wise regressions of normalized BF (top, effects in red) and hippocampus volumes (bottom, effects in blue) on preprocessed FDG-PET scans, scaled to pons uptake values, in the MCI group. Analyses were corrected for age, gender, education, and MMSE scores, and results were thresholded at a corrected statistical threshold of $P(FDR) < 0.05$. Effects are depicted on cortical surface renderings as well as sagittal sections running from left (L) to right (R) through the brain. Lower BF volumes are associated with reduced metabolism in widespread cortical networks spanning limbic, paralimbic, and heteromodal association areas of the frontal, temporal, and parietal lobes. Lower hippocampus volumes are associated with reduced metabolism in the medial temporal lobe and the posterior cingulate/retrosplenial cortex.

or rupture of anterior communicating artery aneurysm (Benke et al. 2005) indicate that discrete BF lesions may be sufficient to cause severe amnestic syndromes or delirium. Although the degree to which cholinergic nuclei within the BF are affected by these lesions may be variable and is typically not known, improvement of symptoms after pharmacological stimulation of cholinergic neurotransmission has been reported in some cases (Chatterjee et al. 1993; Kobayashi et al. 2004; Benke et al. 2005). Another line of evidence for the importance of an intact BF cholinergic system for the maintenance of higher cognitive functions in humans is derived from the study of age- and disease-related neurodegeneration of the cholinergic BF and ensuing decline in cholinergic function. Thus, moderate neurodegenerative changes in the cholinergic BF are observed in normal physiologic brain aging and are believed to underlie aspects of cognitive aging and an increased susceptibility for cognitive side effects of anticholinergic drugs (Campbell et al. 2009; Schliebs and Arendt 2011). Moreover, several postmortem autopsy studies have shown that neuropathologic measures of cholinergic BF atrophy (Gaspar and Gray 1984; Lehericy et al. 1993; Samuel et al. 1994; Iraizoz et al. 1999; Schliebs and Arendt 2006) and cortical cholinergic depletion (Perry et al. 1985; Bierer et al. 1995; Pappas et al. 2000; Tiraboschi et al. 2002) correlate with antemortem dementia severity across a wide range of neurologic dementing diseases, most notably AD and Lewy body-associated dementias. More recently, studies using MRI-based volumetry of BF ROIs as surrogate markers of cholinergic BF degeneration could provide in vivo evidence for correlations between reduced BF volume and dementia severity in AD and Lewy body-associated dementias (Hanyu et al. 2002; George et al. 2011; Choi et al. 2012; Gao et al. 2013; Kim et al. 2013; Grothe, Schuster, et al. 2014). However, evidence for the functional role of BF volume reductions that occur in the normal aging process and in MCI is still limited. In 2 previous studies on independent MCI samples ($N = 50$ and 33, respectively), we found that BF volumes correlated with global cognitive function (Grothe et al. 2013) as well as with more specific measures of delayed verbal recall performance (Grothe et al. 2010). In contrast, in a sample of 43 elderly subjects with age-appropriate cognition, BF volumes were not significantly correlated with specific cognitive domain scores when accounting for the effect of age as the indirect driver of the associations (Wolf et al. 2014). Here, we expand upon these previous findings by

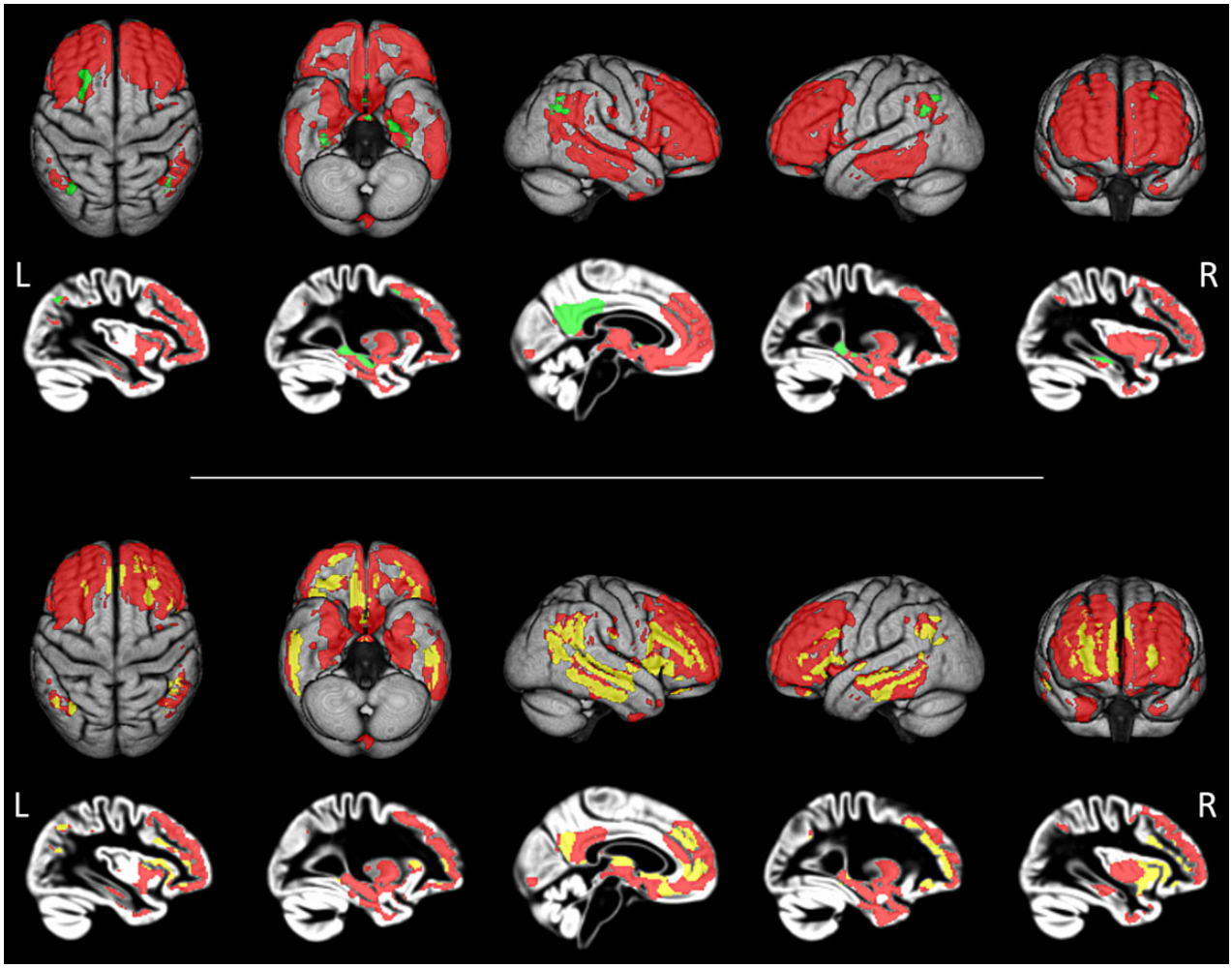

Figure 4. Hypometabolism associated with BF atrophy and domain-specific cognitive deficits in MCI. Hypometabolic areas related to BF atrophy in MCI (red) were tested for their association with DR-30 (top, effects in green) and TMT-B performance (bottom, effects in yellow) using voxel-wise regressions of the respective test scores on preprocessed FDG-PET scans, scaled to pons uptake values. Analyses were corrected for age, gender, education, MMSE scores, and TMT-B or DR-30 performance, respectively. Search space was limited to hypometabolic areas related to BF atrophy (red) and results were thresholded at a corrected statistical threshold of P (FDR) < 0.05. Effects are depicted on cortical surface renderings as well as sagittal sections running from left (L) to right (R) through the brain. DR-30 performance (numbers of correctly recalled wordlist items at 30-min DR) was positively associated with metabolism mainly in the hippocampus and the posterior cingulate/retrosplenial cortex. The time taken to complete the TMT-B was negatively associated with metabolism in a distinct network covering wide parts of the frontal, temporal, and parietal association areas while sparing the medial temporal lobe. DR-30: 30-min delayed recall; TMT-B: Trail Making Test part B.

studying the cognitive correlates of reduced BF volumes in a large sample of CN and MCI subjects using a more detailed neurocognitive test battery, including various tests of learning and episodic memory, attention/executive function, and semantic memory/verbal fluency. In accordance with our hypothesis, reduced BF volumes in MCI correlated specifically with worse performance on tests of episodic memory and attentional control. In contrast, and consistent with previous studies in MCI (Grundman et al. 2003), hippocampal volume was only significantly correlated with performance on tests of learning and episodic memory, but not with tests of other cognitive domains. It has to be noted that the significant correlations between these regional brain volumes and cognition are only of mild-to-moderate effect size, suggesting that cognition in MCI is also influenced by other factors. In addition to the characteristic volumetric changes in the BF and hippocampus, atrophic changes in MCI also affect other brain regions, likely contributing to cognitive deficits in at least partially independent ways (Grothe et al. 2010; Nho et al. 2012). Moreover, associations between volumetric brain changes and cognition are generally expected to be indirect, being mediated by the functional consequences of the neurodegenerative process that is indexed by reduced volume. This possibility has been addressed in the present study by examining the mediational effect of cortical hypometabolism on BF–cognition relationships, which is discussed below.

Weak correlations between BF volume and select memory scores in the CN group did not remain significant when controlling for age, gender, and education as possible mediator variables. This is largely consistent with our previous finding in an independent cohort (Wolf et al. 2014) and indicates that reductions in BF volume that occur in the normal aging process are of minor functional significance, probably because the normal age-related degenerative changes do not result in sufficiently severe functional changes in the cholinergic system to markedly impact upon cognition (Schliebs and Arendt 2006). However, declining BF volume in normal aging may still be associated with subtle changes in cognition not captured by the psychometric tests in our study (Butler et al. 2012).

BF Atrophy and Cortical Hypometabolism

The cholinergic BF innervates wide parts of the cortical mantle and influences the activity of cortical target circuits through the release of acetylcholine (Metherate et al. 1992; Hasselmo and Sarter 2011). In accordance with its proposed role in memory and higher cognitive functions, the primary cortical projection sites of the BF cholinergic system correspond to core limbic, paralimbic, and heteromodal association areas of the prefrontal, temporal, and parietal lobes (Mesulam et al. 1992; Ghashghaei and Barbas 2001). In animal models, cortical cholinergic denervation, induced by selective lesions to the cholinergic BF, leads to a reduction in high-frequency cortical EEG activity (Berntson et al. 2002) and a decrease of metabolic activity in primary cortical projection sites [Yamaguchi et al. 1990; Browne et al. 2001; Gelfo et al. 2013; however, see also Le Mestric et al. (1998) for contradicting findings]. In human neuropathologic examinations, degeneration of cholinergic BF nuclei in AD and dementia with Lewy bodies correlates with depletion of cholinergic activity in cortical projection sites (Koshimura et al. 1987; Mesulam and Geula 1988; Lippa et al. 1999), and lower neuropathologic estimates of frontal cortex cholinergic activity in AD were found to be associated with antemortem slowing of EEG activity (Soininen et al. 1992). More recently, similar associations between a compromised cholinergic system and alterations in cortical EEG activity could be demonstrated in MCI subjects in vivo, using an MRI-based marker of white matter lesions along cholinergic tracts as a surrogate marker for cholinergic denervation (Babiloni et al. 2009). Here, we provide the first in vivo evidence that BF atrophy on MRI is associated with reductions in cortical metabolic activity as measured with FDG-PET in subjects with MCI. Interestingly, the regional pattern of this association corresponds to the differential cholinergic innervation pattern of functional subdivisions of the cortex (Mesulam et al. 1992; Ghashghaei and Barbas 2001). Thus, BF atrophy correlated with reduced metabolic activity mainly in areas characterized by high cholinergic innervation, such as core limbic structures of the medial temporal lobe, the prefrontal cortex, anterior insula, anterior and posterior cingulate cortex, ventral precuneus, and lateral temporo-parietal association areas. Glucose metabolism in the less innervated primary sensory–motor areas and the cerebellum, on the other hand, did not show significant associations with BF atrophy. The association between BF atrophy and cortical hypometabolism may, in principle, also be driven by a shared underlying factor such as overall severity of age- or disease-related neurodegeneration. However, the observed regional associations were controlled for age and MMSE score, as a measure of disease severity, arguing for a rather specific effect where the regional pattern of the association might be driven by the differential cortical innervation preference of the cholinergic BF. In contrast to the MCI group, variation in BF volume among CN individuals was not associated with cortical hypometabolism. This coincides with the lack of association with cognitive function in this group and reinforces the interpretation that normal age-related decline in BF volume may not result in marked functional changes of the cholinergic system (Schliebs and Arendt 2006).

In vivo associations between local measures of atrophy and neuronal dysfunction in remote but anatomically connected regions have previously been studied within other functional systems of the brain and using a wide range of neuroimaging techniques (Guedj et al. 2009; Villain et al. 2010; Yakushev et al. 2011; Cross et al. 2013). A particularly well-investigated phenomenon is the association between atrophy of the hippocampal formation and dysfunction of the posterior cingulate cortex in MCI and AD. For example, Yakushev et al. (2011) studied brain-wide metabolic correlates of hippocampal degeneration in a group of very mildly demented AD patients by regressing a diffusion imaging-based index of hippocampal tissue disruption on FDG-PET scans. Interestingly, the results of our control analysis of the effects of hippocampal atrophy on regional metabolism closely resemble the effects reported by Yakushev et al., including associations with hypometabolism in the bilateral medial temporal lobes and the posterior cingulate cortex. The spatial extension of the hypometabolic effects of BF atrophy across several cortical systems is in striking contrast with the spatially more restricted effects of hippocampus atrophy and may likely reflect the particular connectional anatomy of the corticopetal BF cholinergic system. Of course, BF atrophy may not be the only factor influencing cortical function in MCI, and the strength of the correlation between BF volume and cortical hypometabolism, averaged over all significant voxels, was $r = 0.43$ (see also Supplementary Fig. 3). Other factors may include white matter lesions along cholinergic fiber tracts (Behl et al. 2007; Babiloni et al. 2009), but also pathologic processes independent of cholinergic denervation. Thus, cortical metabolism can be influenced by both local pathologic processes, such as amyloid or tau-mediated toxicity (Spires-Jones and Hyman 2014), as well as by disconnection from other functionally interacting systems, such as has been demonstrated here and in previous studies for the effect of hippocampus atrophy on posterior cingulate cortex hypometabolism (Chetelat et al. 2009; Villain et al. 2010; Yakushev et al. 2011).

Unlike studies on animal models using direct experimental manipulation (Yamaguchi et al. 1990; Browne et al. 2001; Gelfo et al. 2013), the present correlational in vivo findings in humans do not allow inferences to be made about the direction of the effects. Hence, the detected associations could also be interpreted to reflect retrograde BF degeneration due to primary cortical lesions, and indeed such mechanisms have also been reported from animal studies (Sofroniew and Pearson 1985). However, given the use of partial volume correction of the FDG-PET scans in the present study, the measured hypometabolism is unlikely to be confounded by cortical atrophy. Future longitudinal studies may reveal further insights into the sequence of events that couple BF atrophy and cortical hypometabolism in age and disease (Villain et al. 2010).

Cortical Hypometabolism as the Neuronal Substrate of Cognitive Deficits Associated with BF Atrophy

Effects of cholinergic degeneration on cognitive functions are believed to be mediated by the resulting disruption of cortical cholinergic neurotransmission and ensuing cortical dysfunction. Given that in the present study BF atrophy was indeed associated with cortical hypometabolism in widespread limbic and heteromodal association areas known to subserve higher cognitive functions (Mesulam 1998; Meehan and Bressler 2012), we further aimed to investigate whether this cortical hypometabolism may account for the observed correlation between BF atrophy and cognitive dysfunction.

Searching the cortical hypometabolic areas related to BF atrophy for associations with cognitive test performance, we found that hypometabolism in a circumscribed hippocampus–posterior cingulate subnetwork was associated with episodic memory deficits, whereas attentional control deficits were associated with hypometabolism in a more widespread network including frontal, temporal, and parietal areas. These findings are in good

agreement with existing models of the distributed representation of episodic memory and executive control functions across intrinsically connected neurocognitive networks in the human brain (Mesulam 1998; Meehan and Bressler 2012; Ranganath and Ritchey 2012), and complement findings from several previous imaging studies examining neural correlates of memory and executive function deficits in MCI and other neurodegenerative conditions (Salmon et al. 2008; Habeck et al. 2012; Schroeter et al. 2012; Terada et al. 2013).

In addition, statistical path analyses examining the differential relationships between BF atrophy, cortical hypometabolism, and cognitive dysfunction were consistent with a model where the effect of BF atrophy on memory and attentional functions is mediated by its effect on hypometabolism in domain-specific cortical networks. Such a model of functional and cognitive consequences of BF atrophy is also supported by studies on animal models where experimental lesions to the cholinergic BF led to reduced cortical cholinergic synapse density and decreased metabolic activity in primary cortical projection sites, which in turn predicted behavioral deficits (Yamaguchi et al. 1990; Browne et al. 2001; Gelfo et al. 2013). In AD patients, it has been shown that pharmacologic treatments aimed at enhancing cholinergic function may stabilize or even increase cortical metabolic activity (Tuszynski et al. 2005; Teipel et al. 2006). More importantly, beneficial cognitive outcomes of such treatments were found to depend on the treatment-induced modulations of cortical metabolism (Potkin et al. 2001; Stefanova et al. 2006; Kadir et al. 2008). In the present study, hypometabolism in distinct cortical networks mediated the association between reduced BF volume as a surrogate marker of cholinergic degeneration and domain-specific cognitive deficits in MCI. The regional specificity of these associations is also in good accordance with previous findings from a neuropathologic study, where cholinergic depletion in medial frontal areas selectively predicted antemortem attentional function, whereas decreased cholinergic activity in the hippocampus correlated with performance on memory tests (Pappas et al. 2000). However, the mediation between BF volume and cognitive performance through hypometabolism in the domain-specific cortical networks was only complete for the TMT-B model, whereas there was only partial mediation in the DR-30 model. While this may suggest that there is a direct link between BF volume and DR-30 performance, a more plausible possibility is that the association is additionally mediated by other factors that have not been considered in the mediation model, such as hypometabolism outside of the closely circumscribed hippocampus–posterior cingulate "memory network," or functional consequences of BF atrophy not captured by FDG-PET imaging.

Impact of Amyloid Pathology

The employed correlational analyses rely on age- and disease-induced variance in BF volume, cognitive function, and cortical metabolism. In this respect, MCI provides a valuable clinical study model given that it is considered a transitional phase between normal cognitive aging and dementia, and has been shown to be associated with marked changes in the studied parameters (Mesulam et al. 2004; Mosconi 2005; Gauthier et al. 2006; Grothe et al. 2013). However, MCI as a clinical entity is heterogeneous with respect to the underlying pathology. Thus, while most of the MCI subjects harbor significant cerebral amyloid pathology, indicating prodromal AD (Albert et al. 2011), other etiologies are also common, and a significant proportion of MCI subjects develops other forms of dementia or remains clinically stable (Gauthier et al. 2006; Grimmer et al. 2013). In a recent study on the same cohort, we have shown that BF atrophy is more severe in amyloid-positive MCI subjects compared with amyloid-negative MCI subjects (Teipel et al. 2014), and this finding has already been replicated in an independent cohort (Kerbler et al. 2015). This raises the question whether the observed associations between reduced BF volume, cortical hypometabolism, and cognitive dysfunction may be primarily driven by MCI subjects with prodromal AD. However, interaction analyses assessing the impact of PET-measured amyloid status and APOE4 genotype on the observed associations did not reveal any significant effects, indicating that reductions in BF volume are similarly associated with cognitive deficits and cortical hypometabolism in MCI subjects with and without underlying amyloid pathology. This finding agrees with the notion that lesions of the cholinergic BF have been associated with cognitive impairments not only in AD, but across a wide range of clinical conditions, including Lewy body-associated dementias, Korsakow Syndrome, Creutzfeld–Jacob disease, hemorrhagic lesions, traumatic brain injury, and dementia pugilistica (Bartus et al. 1982; Rogers et al. 1985; Arciniegas 2003; Bosboom et al. 2004; Kobayashi et al. 2004; Benke et al. 2005; Schliebs and Arendt 2011). Here, we can only speculate about the pathologic mechanisms underlying BF volume reductions in the studied MCI sample. The main pathologic correlate of cholinergic degeneration in AD is considered to be tau pathology (Mesulam et al. 2004; Mesulam 2012), and tau pathologic changes are also frequently found in aged individuals in the absence of amyloid pathology, where they are typically associated with mild cognitive deficits (Crary et al. 2014). Furthermore, cholinergic BF neurons in the aging brain have been reported to show impaired retrograde transport of cortical nerve growth factor as well as downregulation of its cellular receptors, and this disruption of trophic factor support is more pronounced in subjects with MCI (Strada et al. 1992; Mufson et al. 2007; Schindowski et al. 2008). Finally, BF volume may also be influenced by other non-AD factors, such as lesions secondary to cerebrovascular disease (Gao et al. 2013) or Lewy body pathology (Lippa et al. 1999; Jellinger 2004).

Limitations

Compared with previous postmortem studies examining correlations between antemortem cognitive deficits and detailed neuropathologic markers of BF cholinergic degeneration or cortical cholinergic depletion, the present in vivo neuroimaging approach is limited by the indirect nature of BF volumetry on MRI as a surrogate marker for cholinergic degeneration. Although great care was taken in defining the BF ROI in correspondence with histologic delineations of cholinergic forebrain nuclei (Kilimann et al. 2014), volumetric GM changes in this region may also reflect tissue changes other than cholinergic cell degeneration. However, given that cholinergic neurons are particularly vulnerable to neurodegenerative processes in normal and pathological aging (Mesulam et al. 2004; Geula et al. 2008; Schliebs and Arendt 2011), it is reasonable to assume that a large portion of the variance in BF volumes across MCI subjects may be accounted for by differences in structural integrity of cholinergic nuclei. By demonstrating significant associations with regionally selective cortical hypometabolism as well as with specific cognitive deficits in the domains of memory and attentional function, the present study further underlines the functional and clinical significance of reduced BF volumes in MCI. To ensure that these findings did not critically depend on the particular BF ROI employed, we repeated all analyses using a previously published cytoarchitectonic

mask of the cholinergic BF based on a different postmortem brain (Teipel et al. 2005), and results were virtually identical (data not shown). However, cortical cholinergic signaling has not been assessed directly, and thus its role in the observed associations remains unclear. Although there is ample evidence that MCI is associated with neurodegenerative changes and disrupted neurotrophic regulation of the cholinergic BF (Mesulam et al. 2004; Mufson et al. 2007; Geula et al. 2008), these processes may not scale linearly with cortical cholinergic depletion, as maintained or even regionally increased choline-acetyltransferase (ChAT) activity levels have been reported in a neuropathological study on MCI (DeKosky et al. 2002). However, it has also been commented that ChAT activity levels may not be a good indicator of intact cholinergic transmission, and that cholinergic BF neurons in MCI are most likely rendered dysfunctional by the documented neurodegenerative processes and disruptions in trophic factor regulation (Sarter and Bruno 2002). Future studies may employ PET-based imaging tracers of cholinergic neurotransmission (Klein et al. 2010; Kendziorra et al. 2011) to study in more detail the role of cortical cholinergic synapse function on the observed associations between BF volume, cortical hypometabolism, and cognitive deficits.

Conclusion

Using a multimodal in vivo neuroimaging approach in a large group of MCI subjects and normally aging controls, we found that reduced BF volume in MCI correlated with specific cognitive deficits in the domains of memory and attentional function, and was also significantly associated with hypometabolism in a widespread cortical network, mainly involving the prefrontal cortex, the medial temporal lobes, and temporo-parietal association areas. Further regression analyses demonstrated that hypometabolism in a hippocampus–posterior cingulate subnetwork mediated the association with decreased memory function, whereas hypometabolism in a largely non-overlapping fronto-temporo-parietal network accounted for the association with attentional control deficits. These data based on MCI as a clinical lesion model underline the potential of multimodal imaging markers to study structure–function–cognition relationships in the living human brain and provide important in vivo evidence for an involvement of the human BF in cortical activity and cognitive function.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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Notes

Conflict of Interest: None declared.

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