EEG in Silent Small Vessel Disease: sLORETA Mapping Reveals Cortical Sources of Vascular Cognitive Impairment No Dementia in the Default Mode Network

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Introduction: Vascular cognitive impairment, no dementia (vCIND) is a prevalent and potentially preventable disorder. Clinical presof the small vessel subcortical subtype may be insidious and difficult to diagnose in the initial stage. We investigated electroencephalographic sources of subcortical vCIND in comparison to amnesic multidomain mild cognitive impairment (amdMCI) to determine the additional diagnostic value of quantitative electroencephalograhy (EEG) in this setting.

Methods: Fifty-seven community residing patients with an uneventful central neurological history and first presentation of cognitive decline without dementia were included, 35 patients were diagnosed with vCIND and 22 with amdMCI. A cognitive control group, deliberately recruited from a cerebrovascular impaired cohort, consisted of cognitively healthy participants who experienced a fully recovered first ever transient ischemic attack (TIA) without clinical or magnetic resonance imaging evidence of stroke. From standard EEGs, the differences in standardized low-resolution brain electromagnetic tomography (sLORETA) sources were determined for the discrete frequency ranges 1–4 (delta), 4–8 (theta), 8–10.5 (alpha1), 10.5–13 (alpha2), 13–22 (beta1), and 22–30 (beta2) Hz.

Results: In vCIND, a statistically significant decrease in parietooccipital alpha1 relative power current density compared with TIA and mild cognitive impairment patients was found. There was a significant decrease in frontal and parietooccipital beta1 relative power current density in vCIND compared with TIA patients. A significant increase in (pre) frontal delta relative power current density in vCIND compared with amdMCI was found as well. In amdMCI, delta relative power current density was significantly increased in the core limbic system.

Discussion: Cortical sources of abnormal EEG activity in regions implicated in the default mode network are revealed by sLORETA at an early stage in vascular cognitive impairment. Mapping of parietooccipital alpha1, frontoparietooccipital beta1 and (pre) frontal delta loci in vCIND may reflect early executive and visuospatial dysfunction in this cohort. Standard EEG with sLORETA mapping might be an additional, noninvasive, and cost-effective tool in the diagnostic workup of patients presenting with a cognitive decline.

Key Words: Vascular cognitive impairment, Silent stroke, EEG, sLORETA, Mild cognitive impairment.

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Vascular cognitive impairment, no dementia (vCIND) is a heterogeneous disorder in which the pattern of neurocognitive deficits is determined by the size and location of the vascular lesions. Subcortical vCIND caused by small vessel disease is relatively common in elderly. Frequently, its presentation is insidious with an unclear temporal relation between cognitive decline and brain imaging findings (O'Brien et al., 2003; Selnes and Vinters, 2006). Mild cognitive impairment (MCI), especially amnesic multidomain mild cognitive impairment (amdMCI), may represent an early symptomatic stage of dementia of the Alzheimer type (DAT) (Palmer et al., 2008; Petersen et al., 1995). Vascular risk factors and previous stroke increase the risk of dementia (Di Carlo et al., 2007; Solfrizzi et al., 2004; Viswanathan et al., 2009). In the Canadian Study of Health and Aging, including over 10,000 participants, vCIND was the most prevalent form of vascular cognitive impairment among those aged 65 to 84 years (Rockwood et al., 2000). Importantly, the rate of institutionalization in patients with vCIND is similar to that in vascular dementia, and the mortality rate in vCIND is similar to that in vascular dementia or mixed DAT (Rockwood et al., 2000). Patients with subcortical ischemic vascular disease were found to have a threefold risk of developing dementia independently of age, gender, education, and medial temporal lobe atrophy after 3 years of follow-up (Jokinen et al., 2009).

Although the cognitive profile in vascular cognitive impairment may be variable, especially in the early stage, the pattern is characterized by executive and visuospatial dysfunction (Galluzzi et al., 2005; Jokinen et al., 2006; Jokinen et al., 2009; Sachdev et al., 2004), whereas in amdMCI episodic memory, impairment is a hallmark feature (Kramer et al., 2006; Lopez et al., 2006; Petersen et al. 1999). Structural magnetic resonance or computed tomography brain imaging is crucial for diagnosing vascular cognitive impairment by demonstrating white matter lesions and/or lacunar infarcts (Erkinjuntti et al., 2000; Roman, 2000). In patients with MCI, deep white matter and periventricular lesions predicted progression to non-Alzheimer dementia, while only medial temporal lobe atrophy but not vascular disease was associated with progression to Alzheimer disease (Staekenborg et al., 2009; van de Pol et al., 2007).

Subcortical lacunar infarcts and white matter lesions regardless of their location impair frontal lobe function (Reed et al., 2004;

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Tullberg et al., 2004) with a negative impact on cognitive status (Kuczynski et al., 2008; Kwan et al., 1999; Reed et al., 2001), consistent with the hypothesis of disruption of frontosubcortical circuits in subcortical vascular cognitive impairment (Cummings, 1994). Cognitive impairment secondary to subcortical infarcts is often accompanied by generalized cortical blood flow and metabolic changes (De Reuck et al., 1998; Sultzer et al., 1995). Electroencephalograhy (EEG) allows a noninvasive, inexpensive, and sensitive evaluation of cerebral function. EEG abnormalities correlated with cognitive function in and discriminated between various types of dementia (Bonanni et al., 2008; Gawel et al., 2007; Gawel et al., 2009; Jeong, 2004; Lindau et al., 2003; Martin-Loeches et al., 1991; Yener et al., 1996). Some studies investigated the value of EEG in MCI (Jelic et al., 1998; Jelic et al., 2000; Moretti et al., 2007b; Liedorp et al., 2009) and the influence of vascular lesions in MCI on the EEG (Babiloni et al., 2008a; Babiloni et al., 2008b; Moretti et al., 2007a; Moretti et al., 2008a; Moretti et al., 2008b). Subcortical lesions in mixed dementia induce an increase of slow frequency EEG power (Schreiter Gasser et al., 2008). White matter lesions in vascular cognitive impairment induce a widespread increase of delta and theta power (d'Onofrio et al., 1996; Moretti et al., 2007a; Szelies et al., 1999), while cholinergic deafferentiation and corticocortical disconnection in MCI and DAT induce a significant reduction in alpha and beta power (Baker et al., 2008; Kwak, 2006; Moretti et al., 2004; Wada et al., 1997).

Disruptions in resting state brain activity, the default mode network (DMN), were found in DAT (Greicius et al., 2004; Supekar et al., 2008; Zhang et al., 2009) and in amnesic MCI (Rombouts et al., 2005; Sorg et al., 2007). Furthermore, in cognitively normal subjects with brain amyloid deposition, before any manifestations of cognitive or behavioral changes, differences were found in resting state functional magnetic resonance imaging connectivity of the precuneus to hippocampus, parahippocampus, anterior cingulate, dorsal cingulate, gyrus rectus, superior precuneus, and visual cortex similar to the observed changes in the DMN in DAT (Sheline et al., 2010). Several studies suggest that the DMN consists of brain regions, including ventral parietal, posterior cingulate, medial frontal, and hippocampal regions with spontaneous activity during the conscious resting state with a deactivation during cognitive tasks (Damoiseaux et al., 2006; Greicius et al., 2003; Mazoyer et al., 2001; Raichle et al., 2001; Vincent et al., 2006).

Using low-resolution brain electromagnetic tomography, the resting state power of occipital, parietal, and temporal alpha 1 sources was correlated with normalized hippocampal volume in patients suffering from MCI and DAT (Babiloni et al., 2009a; Babiloni et al., 2009b). Frontal delta sources and parietal and occipital alpha 1 sources were found to be altered in amnesic MCI and in DAT, while in nonamnesic MCI, differences were found in parietal and occipital alpha 2 sources compared with healthy elderly subjects (Babiloni et al., 2006; Babiloni et al., 2010). In MCI, severity of vascular damage was associated with increased delta power and decreased alpha2 EEG spectral power (Moretti et al., 2007a). In low-resolution brain electromagnetic tomography–estimated source analysis, resting state posterior delta source amplitude was negatively correlated and alpha1 source amplitude was positively correlated with white matter vascular lesion load in patients with amnesic MCI and DAT (Babiloni et al., 2011).

In this study, we aimed to investigate the cortical sources of subcortical vCIND in comparison to amdMCI and cerebrovascular impairment without cognitive decline by standardized low-resolution brain electromagnetic tomography (sLORETA) from eye-closed resting state EEG with special reference to the DMN.

PATIENTS AND METHODS

Study Population

The EEG was recorded in 57 patients from our memory clinic with a clinical diagnosis of amdMCI (n = 22) or vCIND (n = 35). These patients presented with cognitive complaints confirmed by an informant. Inclusion criteria were as follows: (1) first presentation of cognitive decline, (2) age ≥55 years, (3) intact activities of daily living, and (4) able and willing to undergo full cognitive assessment. Exclusion criteria were as follows: (1) reversible cause for cognitive dysfunction, (2) dementia as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (McKhann et al., 1984; Roman et al., 1993), (3) mass (effect) lesion on neuroimaging, (4) history of cerebrovascular event, (5) large vessel disease and imaging findings showing cortical infarction, and (6) axis 1 DSM-IV [Diagnostic and Statistical Manual of Mental Disorders, fourth edition] disorder (American Psychiatric Association, 1994).

A control group consisting of 21 patients who presented with a transient ischemic attack (TIA) and complete recovery of symptoms with a normal neurological and neuropsychological examination, negative diffusion weighted MR imaging, and absence of epileptiform graphoelements on EEG was included as reference to cerebrovascular impairment without cognitive decline.

All patients underwent physical, neurological, radiological (brain computed tomography or magnetic resonance imaging), and biochemical (including thyroid function, vitamin B12, folic acid, and syphilis serology) evaluation as part of the diagnostic routine. The study was conducted according to the revised Declaration of Helsinki (1998) and was approved by the central Institutional Review Board of Ziekenhuis Netwerk Antwerpen.

Neuropsychological Assessment

The neuropsychological test battery for all study participants consisted of the Mini Mental State Examination (Folstein et al., 1975), the Wechsler Memory Scale III (Wechsler, 1997a), matrix reasoning from the Wechsler Adult Intelligence Scale III (Wechsler, 1997b), the Trail Making Test (Reitan and Wolfson, 2002), the Rey-Osterrieth Figure (Osterrieth, 1944), the Boston Naming Test (Kaplan et al., 1983; Mariën et al., 1998) a semantic and phonological verbal fluency task (one minute generation of names of animals, means of transport, vegetables, clothes, and words starting with phoneme F, A, and S) (unpublished norms), Raven Progressive Matrices (Raven et al., 2003), and Hierarchic Dementia Scale (Rönnberg and Ericsson, 1994). To account for individual age and education effects and to allow comparisons, neuropsychological test results were transformed to Z scores. The Z scores of the Wechsler Memory Scale III subtests were averaged to create the mean Wechsler Memory Scale III score as a composite measure of global memory function. Hachinski Ischemic Score (Hachinski et al., 1975) was determined as well.

Mild cognitive impairment was defined clinically as an impairment in one or more cognitive domains larger than expected for age or education, typically below −1.5 SD, but insufficient to interfere with social and occupational functioning (Petersen, 2004). Patients with clinically significant memory impairment that did not meet the criteria for dementia, and at least one other nonmemory-related dysfunction were diagnosed with amdMCI. Patients were diagnosed with vCIND if (1) the cognitive impairment did not meet the NINDS-AIREN (Roman and Goldstein 1993) criteria for

vascular dementia, (2) the cognitive impairment was presumed to have a vascular cause (e.g., by evidence of sudden onset, stepwise progression, patchy deficits on cognitive testing, other evidence of atherosclerosis, focal neurological findings), and (3) evidence of subcortical lacunes and/or white matter lesions, excluding patients with cortical or nonvascular lesions, on neuroimaging, according to previously suggested criteria (Erkinjuntti et al., 2000; Ingles et al., 2002).

Electroencephalograhy Analysis

The EEG was recorded during at least 10 minutes in an eyes closed state with the patient awake and alert using a Brainlab Measure Station (OSG bvba, Rumst, Belgium) as previously described (Sheorajpanday et al., 2009). Nineteen silver/silver chloride electrodes were positioned in accordance to the international 10 to 20 systems, with impedances <5 k Ohm. Analog to digital conversion rate was 250 Hz for all channels using a 16-bit analog to digital convertor. Visual artifact rejection and data analysis were performed in EEGLAB (Delorme and Makeig, 2004) with supplementary scripts operating in the MATLAB environment. After data filtering (high pass 0.3 Hz, low pass 30 Hz) and visual artifact rejection, 128 seconds of EEG were analyzed. We have shown that 128 seconds of artifact-free EEG serves as a reliable sample of a particular EEG recording for classic spectral parameters with excellent intrarecord and intrarater and interrater reproducibility (Sheorajpanday et al., 2009).

Standardized Low-Resolution Brain Electromagnetic Tomography Analysis

Standardized low-resolution brain electromagnetic tomography is a functional imaging method based on electrophysiological and neuroanatomical constraints (Pascual-Marqui et al., 1994; Pascual-Marqui et al., 2002) to find the maximum likelihood solution of the inverse electromagnetic problem by computing the cortical localization of EEG activity from the scalp distribution of the electric field (Pascual-Marqui et al., 1994). The 3-shell sphere head model (Ary et al., 1981) using the electric potential lead field computed with the boundary element method (Fuchs et al., 2002) and registered to the Talairach human brain atlas (Talairach and Toumoux, 1988) and registration between spherical and realistic head geometry based on the EEG electrode coordinates (Jurcak et al., 2007; Towle et al., 1993) are integrated in the sLORETA software package (http://www.uzh.ch/keyinst/loreta.htm). The sLORETA solution space consists of 6239 voxels at 5-mm spatial resolution in the 3-dimensional plane (Pascual-Marqui et al., 2002). Power current density at each voxel was normalized with the power current density averaged across all voxels and all frequencies from 0.3 to 35 Hz.

Statistical Analysis

Clinical and neuropsychological data were analyzed using the Statistical Product and Service Solution 16.0 software package for Windows (SPSS Inc., Chicago, IL). Results of neuropsychological tests were transformed to Z scores. Comparisons between Z scores of neuropsychological tests were made by the paired t-test. Between-group comparisons were made by independent sample t-test and Mann–Whitney test according to distribution. Significance level was set at $P < 0.05$ with adjustment for multiple comparisons as indicated.

For the sLORETA analysis, the localization of the differences in relative current density power between the independent groups in the six frequency bands was assessed with voxel-by-voxel paired t-tests of the ratio of group averaged relative current density power. The nonparametric randomization method (Nichols and Holmes, 2002) was used to calculate multiple comparison–corrected critical probability threshold values based on empirical probability distributions (Pascual-Marqui et al., 2002).

RESULTS

Patient characteristics are listed in Table 1. There was a significant difference in Hachinski Ischemic Score between patients with vCIND and amdMCI (mean ± standard error of the mean: 5.1 ± 0.14 vs. 4.5 ± 0.14, Mann–Whitney test $P = 0.006$), but not between patients with vCIND and TIA (5.1 ± 0.14 vs. 4.9 ± 0.17, $P = 0.253$).

The patients with vCIND had significantly ($P < 0.0033$) lower Z scores compared with patients with amdMCI on working memory (−1.53 ± 0.11 vs. −0.95 ± 0.15), verbal fluency (−2.43 ± 0.27 vs. −0.61 ± 0.17), and matrix reasoning (−1.55 ± 0.19 vs. −0.69 ± 0.19).

Differences in Standardized Low-Resolution Brain Electromagnetic Tomography Activity According to Frequency Band

Alpha1 (8 to 10.5 Hz) Band

We found a statistically significant ($P = 0.00020$) decrease in alpha1 relative power current density in vCIND compared with cerebrovascular impairment without cognitive impairment in cuneus (occipital lobe), precuneus (parietal lobe), lingual gyrus, middle occipital gyrus, posterior cingulate gyrus, insula, middle temporal, superior temporal, subgyral, and parahippocampal gyrus bilaterally, left more than right (Fig. 1).

There was a statistically significant ($P = 0.0074$) decrease in alpha1 relative power current density in vCIND compared with mild (nonvascular) cognitive impairment in cuneus, precuneus, middle occipital gyrus, posterior cingulate gyrus, and inferior occipital gyrus on the left (Fig. 2).

We did not find a statistically significant ($P > 0.05$) decrease in alpha1 relative power current density in amdMCI (nonvascular) compared with cerebrovascular impaired cognitive normal controls.

Alpha2 (10.5 to 13 Hz) Band

There was no statistically significant decrease ($P > 0.05$) in alpha2 relative power current density in vCIND compared with cerebrovascular impaired control group.

We did not find a statistically significant difference ($P > 0.05$) in alpha2 relative power current density in vCIND compared with MCI (nonvascular).

Beta1 (13 to 22 Hz) Band

There was a statistically significant ($P < 0.000005$) decrease in beta1 relative power current density in vCIND compared with cerebrovascular impairment without cognitive impairment in the left cuneus, precuneus, middle occipital gyrus, anterior cingulate gyrus, and medial frontal gyrus (Fig. 3).

We did not find a statistically significant difference ($P > 0.05$) in beta1 relative power current density in vCIND compared with MCI (nonvascular).

Beta2 (22 to 30 Hz) Band

There was no statistically significant difference in beta2 relative power current density in vCIND compared with cerebrovascular impairment without cognitive impairment. We did not find

TABLE 1. Characteristics of Patients Group With Special Reference to Cerebrovascular Risk Factors

		Patient Group Characteristics		
		vCIND, n = 35	**TIA, n = 21**	**amdMCI, n = 22**
Demographics	Mean age ± SD, yrs (range)	75 ± 6.3 (55–85)	69 ± 13.1 (55–86)	73 ± 7.7 (57–87)
	Male gender	24	11	9
Risk factors	Arterial hypertension	29	13	11
	Carotid stenosis ≥50%	2	4	0
	Cardiac arrhythmia	8	3	2
	Congestive heart failure	13	4	1
	Coronary disease	17	4	2
	Diabetes mellitus	6	2	0
	Dyslipidemia	16	8	5
	Regular alcohol consumption	3	1	0
	Current smoking	2	1	2
Prior treatment	Antiplatelets	25	7	7
	Anticoagulants	7	2	2

amdMCI, amnesic multidomain mild cognitive impairment; TIA, transient ischemic attack; vCIND, vascular cognitive impairment, no dementia.

a statistically significant difference in beta2 relative power current density in vCIND compared with MCI (nonvascular).

Theta (4 to 8 Hz) Band

We did not find a statistically significant difference in theta relative power current density in vCIND compared with cerebrovascular impairment without cognitive impairment. There was no statistically significant difference in theta relative power current density in vCIND compared with MCI (nonvascular).

Delta (1 to 4 Hz) Band

We did not find a statistically significant difference in delta relative power current density in vCIND compared with cerebrovascular impairment without cognitive impairment. There was a statistically significant ($P = 0.0142$) increase in delta relative power current density in vCIND compared with MCI (nonvascular) in the right precentral gyrus, middle frontal gyrus, and inferior frontal gyrus (Fig. 4).

There was a statistically significant ($P = 0.0184$) increase in delta relative power current density in MCI (nonvascular) compared with cerebrovascular impairment without cognitive impairment in the right anterior cingulate gyrus, parahippocampal gyrus, uncus, and insula (Fig. 5).

DISCUSSION

In many memory clinics, EEG is part of the diagnostic protocol as memory disturbances, confusion, and even dementia symptoms may be the sole clinical manifestation of a complex focal status or a protracted postictal state in elderly patients (Sheorajpanday and De Deyn, 2007). In this exploratory analysis, we wanted to evaluate a group effect of diagnosis (vCIND, amdMCI, or

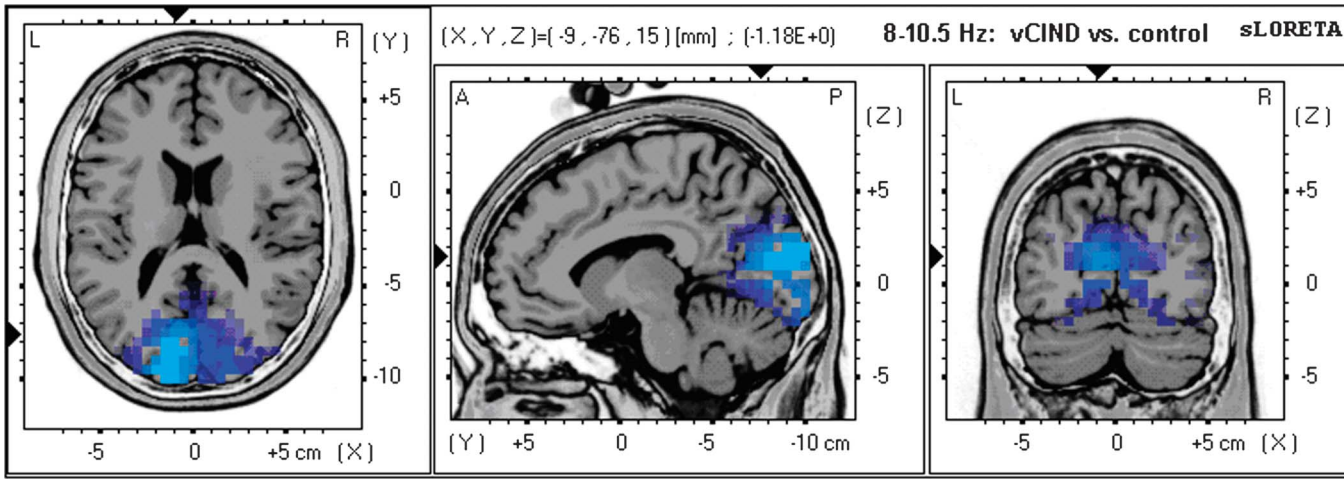

FIG. 1. Statistically significant decrease in alpha 1 source activity in vascular cognitive impairment, no dementia compared with cerebrovascular impairment without cognitive impairment as evidenced by statistical nonparametric mapping–based standardized low-resolution brain electromagnetic tomography in cuneus, precuneus, lingual gyrus, middle occipital gyrus, posterior cingulate gyrus, insula, middle temporal, superior temporal, subgyral, and parahippocampal gyrus bilaterally, left more than right.

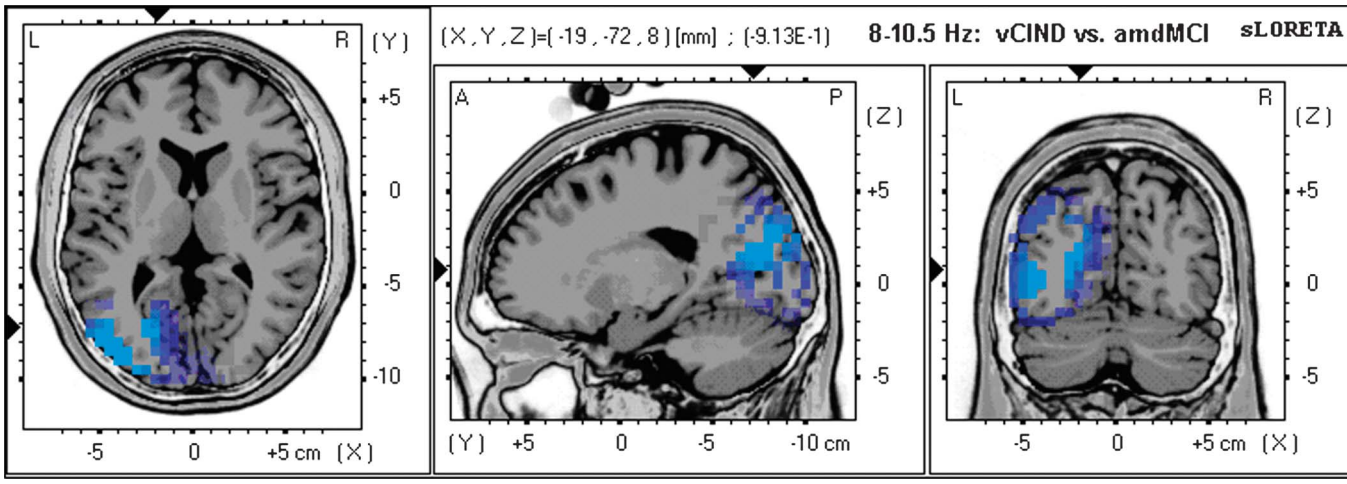

FIG. 2. Statistically significant decrease in alpha 1 source activity in vascular cognitive impairment, no dementia compared with mild (nonvascular) cognitive impairment as evidenced by statistical nonparametric mapping based standardized low-resolution brain electromagnetic tomography in the left cuneus, precuneus, middle occipital gyrus, posterior cingulate gyrus, and inferior occipital gyrus.

cerebrovascular impaired cognitive normal control/TIA) on EEG source activity estimated by sLORETA.

Our study has limitations. First, scalp EEG has an excellent temporal but a poor spatial resolution. A variety of methods exist to solve the inverse solution and estimate the localization of electrical neuronal generators. Several studies reviewed by Pascual-Marqui et al. (2002) have cross-validated accuracy and reliability of the localizing value of low-resolution electromagnetic tomography. Second, because of a small sample size, this is obviously an exploratory analysis and not an attempt to demonstrate diagnostic value for individual patients. Third, control subjects were deliberately selected from a more naturalistic setting instead of from a normative database. This may allow clinically more relevant comparisons as the "hyperhealthy'' subject from a normative database might not be frequently encountered in general clinical practice (Coburn et al., 2006). The cerebrovascular impaired cognitive normal control group consisted of patients presenting with an acute, transient, presumed cerebrovascular event, complete recovery of symptoms, normal clinical neurological examination, negative diffusion weighted magnetic resonance imaging, absence of epileptiform graphoelements on the EEG and no apparent other cause for the event, clinically labeled as TIA patients. Similarly, patients were diagnosed with amdMCI based on operationally defined clinical and psychometric criteria without etiopathogenetic certainty. The −1.5 SD cutpoint might be of limited value in routine clinical practice to determine cognitive impairment in highly educated individuals, where impairment might reflect a decline from a superior to an average cognitive performance (Luis et al., 2003). To account for individual age and education effects in this study, neuropsychological test results were transformed to Z scores. However, we cannot exclude the possibility of including more severely affected highly educated individuals in the vCIND and/or amdMCI groups. The vCIND and amdMCI groups were balanced in terms of age and Mini Mental State Examination score. Homogeneity in global memory functioning between the two groups in our study was post hoc

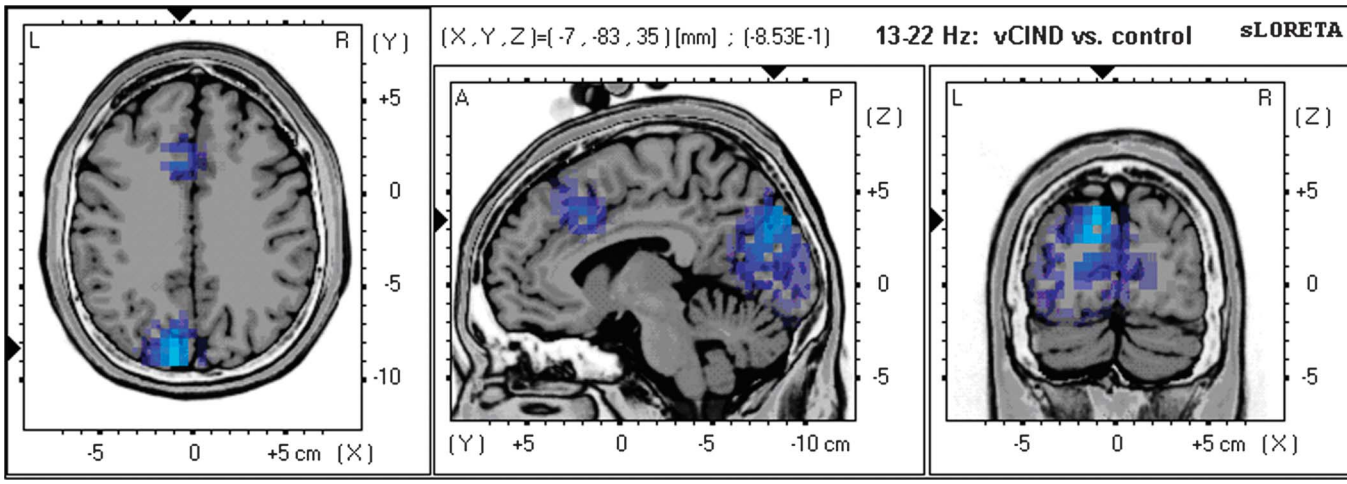

FIG. 3. Statistically significant decrease in beta 1 source activity in vascular cognitive impairment, no dementia compared with cerebrovascular impairment without cognitive impairment as evidenced by statistical nonparametric mapping–based standardized low-resolution brain electromagnetic tomography in cuneus, precuneus, middle occipital gyrus, posterior cingulate gyrus, and inferior occipital gyrus on the left.

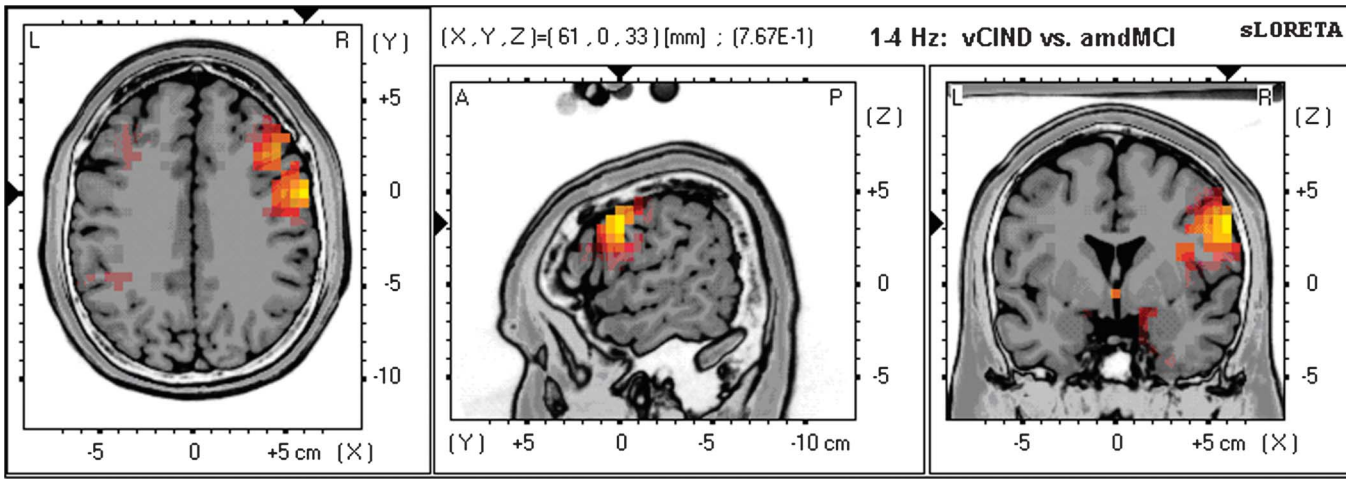

FIG. 4. Statistically significant increase in delta activity in vascular cognitive impairment, no dementia compared with mild (nonvascular) cognitive impairment as evidenced by statistical nonparametric mapping–based standardized low-resolution brain electromagnetic tomography in the right precentral gyrus, middle frontal gyrus, and inferior frontal gyrus.

confirmed by absence of a significant difference in mean global Wechsler Memory Scale-III score. Nonetheless, research methodology in MCI needs to be refined and standardized (Luis et al., 2003; Portet et al., 2006).

Patients with amdMCI did have vascular risk factors as indicated in Table 1 and small presumably nonsignificant vascular microlesions were allowed. It has been shown that there is a relationship between the presence of cerebrovascular risk factors and the occurrence of focal and diffuse EEG abnormalities (Logar et al., 1993). This may have contributed to a decrease in sensitivity that, from a practical point of view, might be controlled for by adequate history, clinical and neuropsychological examination, risk stratification, and structural neuroimaging.

This essentially pragmatic design was specifically implemented to extrapolate our findings more directly to routine clinical practice in which vascular risk factors are more prevalent.

Despite the above-mentioned limitations, consistent significant differences in parietooccipital alpha1 (8 to 10.5 Hz) relative power current density between vCIND and amdMCI and between vCIND and TIA suggest that sLORETA might be a useful supplementary technique to indicate vascular cognitive decline.

Our results add to the findings in vascular dementia (Babiloni et al., 2004) by demonstrating that alterations in this frequency range and localization even occur at the earliest clinical stage of vascular cognitive impairment. This finding, however, is not specific for vascular cognitive impairment because mild AD patients actually had a decline of lower alpha relative power current density compared with patients with vascular dementia (Babiloni et al., 2004). The apparent discrepancy with our results may be at least partially explained in the study by Babiloni et al., 2004 that patients with vascular dementia also had a widespread increase of theta source activity compared with healthy controls and mild AD. First, upper

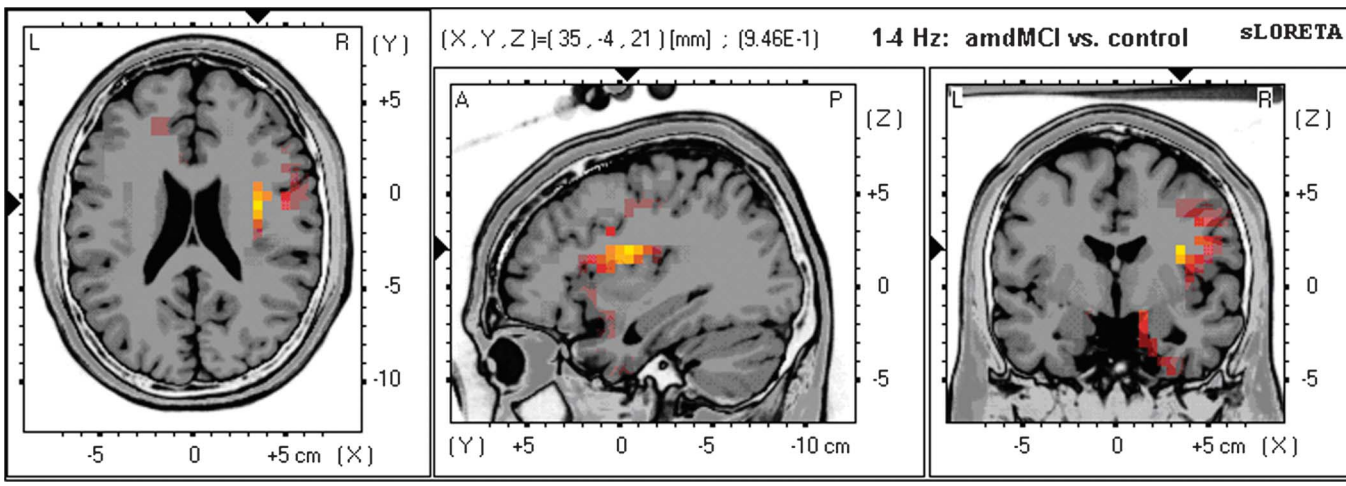

FIG. 5. Statistically significant increase in delta activity in mild (nonvascular) cognitive impairment compared with cerebrovascular impairment without cognitive impairment as evidenced by statistical nonparametric mapping–based standardized low-resolution brain electromagnetic tomography in the right anterior cingulate gyrus, parahippocampal gyrus, uncus, and insula.

theta might coincide with lower alpha activity. Second, our findings suggest that at the initial stage of cognitive decline, alpha1 relative power current density decreases more profoundly in vascular cognitive decline compared with nonvascular amdMCI. At a later stage of cognitive decline, occipital alpha 1 sources show a stronger decline in mild DAT compared with vascular dementia (Babiloni et al., 2004). At this stage, distributed theta sources were found to be largely abnormal in vascular dementia but not in mild DAT (Babiloni et al., 2004). This also suggests that EEG/sLORETA-based discrimination between DAT and vascular cognitive impairment should take the severity of cognitive decline into account. Further longitudinal studies are needed to investigate more specifically a possibly different temporal evolution in frequency-specific source activity in vascular cognitive decline and in DAT.

Parietal and occipital alpha 1 sources were lower in patients with amnesic MCI compared with healthy elderly controls, and occipital alpha1 source amplitude was higher in subjects with subjective memory complaints compared with patients with amnesic MCI (Babiloni et al., 2008a).

Parietal alpha1 sources were higher in subjects with a high white matter vascular lesion load (Babiloni et al., 2008b), whereas no differences were found in other frequency bands. However, the MCI patients with a high vascular load cannot be regarded as typical vascular cognitive decline patients because these patients did not show a typical neuropsychological pattern of vascular cognitive decline with no statistically significant differences in executive function, visuospatial performance, or differences in the memory or language domains (Babiloni et al., 2008b).

The patients with vCIND in our cohort performed significantly worse in working memory, on verbal fluency (executive tasks), and on matrix reasoning (a visuospatial task) compared with amdMCI. Concordantly, we found a statistically significant decrease in resting alpha relative power current density in patients with vCIND compared with cerebrovascular impaired (TIA) patients and amdMCI in regions involved in visuospatial processing and executive functions: precuneus, cuneus, middle occipital gyrus, and posterior cingulate gyrus.

The precuneus is located in the posteromedial cortex of the parietal lobe and has been implicated in a variety of cognitive and behavioral processes (Cavanna and Trimble, 2006). Of special interest, in relation to the observed neuropsychological deficits in vCIND is the role of the precuneus in spatial working memory performance (Berryhill and Olson 2008; Wallentin et al., 2006), verbal fluency (Fu et al., 2006; Gauthier et al., 2009), and verbal episodic memory retrieval (Krause et al., 1999; Shallice et al., 1994; Tulving et al., 1994). The cuneus is activated in visuospatial encoding (Tzagarakis et al., 2009) and spatial associative memory retrieval (de Rover et al., 2008). The posterior cingulate cortex is implicated in associative and relational aspects of memory, spatial orientation, and spatial working memory (Sutherland et al., 1988; Vogt et al., 1992; Whitlock et al., 2008). Involvement of these structures have been found in MCI (Huang et al., 2002; Qi et al., 2010; Ries et al., 2006; Zhou et al., 2008), Alzheimer disease (Ding et al., 2008; Hirono et al., 1998; Zhou et al., 2008), diffuse Lewy body disease (Albin et al., 1996), and vascular dementia (Di Piero et al., 2001; Kerrouche et al., 2006; Waragai et al., 2008).

In EEG recordings, during a modified Sternberg task, an increase in alpha activity during working memory retention was found in the ventral part of the precuneus in subjects with increased upper alpha activity generated in the cuneus, while in subjects with decreased lower alpha activity with increasing workload, the cortical generator for this decreased activity was located in the precuneus (Michels et al., 2008). Although the difference in study design and methodological settings does not allow for a direct comparison with our study, these results indicate that alpha activity in cuneus and precuneus may play an important role in working memory.

Regions with statistically significant alterations in this study are associated with the brain's DMN implicated in internally focused cognitive tasks and task engagement (Buckner et al., 2008; Greicius et al., 2003; Hayden et al., 2009; Raichle et al., 2001). A core network underlying a variety of DMN cognitive domains was evidenced between medial temporal lobe, precuneus, posterior cingulate, retrospenial and temporoparietal junction (Greicius et al., 2009; Hayden et al., 2009; Spreng et al., 2009). A partial correlation analysis of functional connectivity during both rest and at working memory task has implicated a pivotal role for the precuneus and posterior cingulate cortex within the DMN (Fransson and Marrelec, 2008). In normal aging, functional magnetic resonance imaging resting state activity in the DMN was significantly reduced compared with younger subjects, with a significant correlation between less effective executive function/processing speed and activity in the anterior part of the DMN, encompassing the superior and middle frontal gyrus, posterior cingulate, bilateral middle temporal gyrus, and bilateral superior parietal region in elderly subject (Damoiseaux et al., 2008). The DMN is strongly associated with alpha and beta power (Balsters et al., 2011; Jann et al., 2009; Laufs et al., 2003; Mantini et al., 2007).

Cognitive processes are reflected by beta activity in parietal areas (Ray and Cole, 1985). Significantly less resting state power was observed in MCI exclusively and in Alzheimer disease primarily in the beta frequency range (12 to 22 Hz) (Baker et al., 2008). In a simultaneous functional magnetic resonance imaging and EEG study, during resting wakefulness, power in the 17 to 23 Hz beta activity range was positively correlated with blood oxygen level dependent functional magnetic resonance imaging activity in posterior cingulate cortex, precuneus, temporoparietal junction, dorsomedial prefrontal cortex, suggesting that spontaneous cognitive operations during conscious rest, that is, in the default mode of brain function is mediated by 17 to 23 Hz beta activity (Laufs et al., 2003).

In line with these findings, reduced alpha1 and beta1 relative power current density in vCIND in the current study may indicate impaired attention and spontaneous cognition in vCIND, clinically manifesting as a typical lacunar state of apathy, slowness, and executive dysfunction.

Our findings indicate that significant alterations in resting state relative power current density in cognition-related regions can be demonstrated at a very early phase in silent small vessel vCIND compared with both a cognitive and a cerebrovascular control group.

Although our study design does not allow to draw firm conclusions, it appears that decreased resting activity in the DMN, especially in the precuneus and posterior cingulate cortex, may be implicated in vCIND compared with two control groups.

We did not find statistically significant differences in the alpha2 as opposed to the alpha1 band among the different groups. Lower alpha activity is associated with attentional demands to task performance, whereas upper alpha activity is particularly sensitive to semantic memory demands (Klimesch 1997; Vogt et al., 1998). In resting state and in the task-activated paradigm, significant correlations between EEG activity and performance on the Wisconsin Card Sorting test which relies on attention, working memory, and visual processing to assess executive functioning were in general restricted to lower alpha power (Cicek and Nalcaci, 2001). Accordingly, we did not observe a statistically significant difference in verbal memory, while patients with vCIND performed significantly worse on

attentional driven tests (verbal fluency, matrix reasoning, and working memory).

We did not find statistically significant differences in source density power in the theta frequency band between patients with vCIND and TIA or between patients with vCIND and amdMCI. Resting state global theta activity was found to be decreased in patients with MCI compared with healthy controls and was associated with decreased performance on tests of global cognition, memory, language, and executive functioning (Moretti et al., 2007a; Moretti et al., 2008a; Moretti et al., 2008b; van der Hiele et al., 2007). In patients with MCI, the global theta/gamma frequency ratio has been associated to atrophy of the amygdalo–hippocampal complex and associated to conversion in dementia (Moretti et al., 2009a; Moretti et al., 2009b). Using low-resolution electromagnetic tomography, the magnitude of delta and theta EEG sources in parietal, occipital, and temporal areas were found to be increased in patients with MCI compared with healthy controls (Babiloni et al., 2007). Because vascular white matter lesions induce a widespread increase of delta and theta power (d'Onofrio et al., 1996; Moretti et al., 2007a; Szelies et al., 1999), the lack of a significant difference in localized theta activity in vCIND might be attributed to the selection of amdMCI and TIA patients as control groups. As mentioned above, however, we deliberately selected these clinically relevant entities as control groups.

In our amdMCI patients, we found a statistically significant increase in low frequency (1 to 4 Hz) resting state relative power current density localized to regions comprising the limbic system as follows: insula/hippocampus, parahippocampal gyrus, uncus, and anterior cingulate involved in memory formation and retrieval. This localized slow activity is compatible with accelerated hippocampal and entorhinal cortex atrophy in stable and progressive amnesic MCI (Devanand et al., 2007; Jack et al., 2000; Jack et al., 2005; Wang et al., 2009). Slow activity in MCI was found to increase as a function of temporal and frontal atrophy (Babiloni et al., 2006; Fernandez et al., 2003; Moretti et al., 2007a). In our amdMCI patients, delta source activity was lateralized to the right. In a 3-dimensional magnetic resonance imaging mapping study, more severe atrophy of the right hemisphere both in amnesic MCI and mild AD groups was observed (Apostolova et al., 2007).

We found a significant increase in frontal delta relative power current density in vCIND subjects compared with MCI subjects compatible with the hypothesis that executive dysfunction in subcortical small vessel ischemic cognitive decline reflects disruption of frontosubcortical circuits (Cummings, 1994). We did not find a difference in delta relative power current density between vCIND and cerebrovascular impaired patients without cognitive decline. Disruption of frontal areas in vCIND may not be very specific for cognitive decline but might rather reflect cerebrovascular impairment.

In conclusion, we have shown that resting state lower alpha relative power current density in vCIND is significantly decreased in regions implicated in the DMN compared with cerebrovascular impaired cognitive normal patients and patients with amdMCI. Together with the observed neuropsychological deficits in this cohort, reduced lower alpha and reduced lower beta activity may indicate impaired attention and spontaneous cognition in vCIND, clinically manifesting as a typical lacunar state of apathy, slowness, and executive dysfunction.

In agreement with the available data in the literature, the observed alpha and beta decrements may merely reflect cognitive decline and are not specific for vascular cognitive impairment. Instead, the typical limbic pattern of increased cortical delta source activity in amdMCI compared with cognitive normal controls and the frontal delta source increment in vascular cognitive impairment compared with amdMCI (nonvascular) may be useful to differentiate the most common causes of cognitive decline at clinical presentation.

In a setting with limited resources, standard routine EEG with source localization may allow an easy, inexpensive, and reliable evaluation of cognitive dysfunction at an early stage. The results from this exploratory study should be confirmed in a larger population.

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