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EEG MEASURES FOR CLINICAL RESEARCH IN MAJOR VASCULAR COGNITIVE IMPAIRMENT: RECOMMENDATIONS BY AN EXPERT PANEL

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HIGHLIGHTS

EEG/ERP measures are consistently abnormal in major VCI patients.

Main EEG abnormalities affect delta, theta, and alpha rhythms.

Main ERP abnormalities include delayed “oddball” N200/P300 peaks.

Those EEG measures are not diagnostic but promising as predictors and endpoints.

ABSTRACT

Vascular contribution to cognitive impairment (VCI) and dementia is related to etiologies that may affect the neurophysiological mechanisms regulating brain arousal and generating electroencephalographic (EEG) activity. A multidisciplinary expert panel reviewed the clinical literature and reached consensus about the EEG measures consistently found as abnormal in VCI patients with dementia. As compared to cognitively unimpaired individuals, those VCI patients showed (1) smaller amplitude of resting state alpha (8-12 Hz) rhythms dominant in posterior regions; (2) widespread increases in amplitude of delta (< 4 Hz) and theta (4-8 Hz) rhythms; and (3) delayed N200/P300 peak latencies in averaged event-related potentials, especially during the detection of auditory rare target stimuli requiring participants' responses in "oddball" paradigms. The expert panel formulated the following recommendations: (1) the above EEG measures are not specific for VCI and should not be used for its diagnosis; (2) they may be considered as "neural synchronization" biomarkers to enlighten the relationships between features of the VCI-related cerebrovascular lesions and abnormalities in neurophysiological brain mechanisms; and (3) they may be tested in future clinical trials as prognostic biomarkers and endpoints of interventions aimed at normalizing background brain excitability and vigilance in wakefulness.

BACKGROUND

Dementia or major neurocognitive disorder (NCD) is characterized by significant decline in two or more cognitive domains with the loss of independence in activities of daily living (American Psychiatric Association, APA, 2013; McKhann et al., 2011) The epidemiological and economic burden of dementia is enormous and research into its early diagnosis and treatment is required to mitigate this burden.

Cerebrovascular disease (CVD) is the second most common cause of major NCD after Alzheimer's disease dementia (ADD) in Western populations (Fratiglioni et al., 2000; Kalaria et al., 2008), and the first in some Asian countries (Rizzi et al., 2014). After Hachinski et al.'s (1975) definition of vascular causes of dementia, many criteria were proposed in later years for vascular contribution to cognitive impairment and dementia (VCI) by neurological institutes, including those from the Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC; Chui et al., 1992), the National Institute of Neurological Disorders and Stroke –Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN; Roman et al., 1993), the Diagnostic and Statistical Manual of Mental Disorders, 4th and 5th editions (DSM-IV, 1994, and DSM-V, 2013), the Vascular Behavioral and Cognitive Disorders (VASCOG; Sachdev et al., 2014), the American Heart Association/American Stroke Association (Gorelick et al., 2011), and Vascular Impairment of Cognition Classification Consensus Study (VICCCS-2; Skrobot et al., 2018). In this regulatory context, the term "Vascular Dementia (VaD)" has been commonly used to refer to a severe cognitive impairment due to CVD, but the American Heart Association and the American Stroke Association have published a statement stressing the concept that VCI is a preferable term, collectively including patients with mild cognitive impairment (MCI) of probable vascular etiology (VaMCI) and VaD (Gorelick et al., 2011). In this line, "mild VCI" denotes VaMCI patients while "major VCI" denotes VaD patients (Sachdev et al., 2019). Figure 1 illustrates the classification of the diverse types of VCI conditions according to the VICCCS-2 Workgroup (modified from Skrobot et al., 2018).

Please insert Figure 1 around here

The VICCCS guidelines have proposed that neuroimaging techniques such as magnetic resonance imaging (MRI) may be a "gold-standard" examination for the diagnosis of VCI due to its relatively high sensitivity and specificity (Skrobot et al., 2018). Probable mild VCI or probable major VCI may represent the recommended diagnostic terms if only those neuroimaging markers are available (Skrobot et al., 2018). More specifically, the following MRI biomarkers, evaluated by semi-quantitative scales, may demonstrate clinically relevant parenchymal alterations thought to arise from

small vessel pathology in VCI patients (Hachinski et al., 2006; Iadecola et al., 2019; Wardlaw et al. 2013). T1-weighted volumetric sequences may be used to measure brain atrophy including estimates of general atrophy, ventricular size, and medial temporal lobe atrophy (especially useful in the differential diagnosis with neurodegenerative dementing disorders), while T2-weighted sequences may map white matter hyperintensities (WMH) as well as infarctions and hemorrhages classified for number, dimension, and topography. In research contexts, susceptibility weighted imaging (SWI) and diffusion-weighted imaging (DWI) may contribute to map hemorrhages as well.

In research contexts, new MRI techniques may enrich clinical diagnosis by providing quantitative volumetric readouts for WMH and infarcts (Iadecola et al., 2019; Skrobot et al., 2018). Furthermore, diffusion tensor imaging MRI, or DTI, which quantifies the diffusion of water molecules across brain tissue, may provide informative quantitative biomarkers of increased extracellular water content and altered WM fiber structure (Duering et al., 2018). On the flipside, functional MRI may represent related abnormalities in brain neural transmission brain structural networks (Du and Xu, 2019). Notwithstanding, neurophysiological, and neurobiological interpretation of specific MRI findings requires careful correlation with clinical and neuropsychological data since imaging alone cannot inform whether clinical symptoms are due to MRI abnormalities. More details about the use of MRI markers and their clinical value in VCI patients are available in Wardlaw et al. (2013) and Wollenweber et al. (2019), highlighting that a tight temporal, qualitative and quantitative correlation between MRI abnormalities and clinical features should be demonstrated before a diagnosis of VCI can be made.

Although the above neuroimaging techniques can adequately reveal morphologic brain vascular lesions, they cannot stand for pathologic sequelae at the neural metabolic level to probe neurodegeneration of synaptic contacts and neural loss. To this purpose, F-18 Fluorodeoxyglucose positron emission tomography (FDG-PET) in the resting state condition can complement MRI markers, detecting hypometabolism of cortical gray matter regions as a reflection of that neurodegeneration (Heiss, 2018; Heiss and Zimmermann-Meinzingen, 2012).

In research contexts, additional PET tracers (e.g., Pittsburgh Compound-B) can map brain amyloidosis as a support in the differential diagnosis of VCI and ADD, the latter being expected to be associated with more significant accumulation of amyloid in the brain (Heiss, 2018).

Electroencephalographic (EEG) measures

While the above neuroimaging techniques can directly map relevant neuropathological substrates underlying VCI, their use may be limited due to relatively high costs and invasiveness, especially for longitudinal recordings and studies to be developed in lower- and middle-income

countries. Of note, VCI is related to etiologies that may affect the neurophysiological mechanisms regulating brain arousal and generating electroencephalographic (EEG) activity. Therefore, EEG techniques may be of interest for the heuristic and clinical research carried out in VCI patients, as they are non-invasive, repeatable without significant learning effects, globally available, and cost-effective. Scalp-recorded EEG recordings allow the investigation of neurophysiological mechanisms underlying cortical neural ionic current flows and related voltages with ***low-moderate spatial scale*** (i.e., some centimeters) but ***better time resolution*** (i.e., < 1 ms) as compared to imaging techniques to investigate dynamic features of brain activity, namely oscillatory behavior, and millisecond-based time evolution (Pfurtscheller and Lopes da Silva, 1999).

Several methods allow human EEG activity to be recorded and visualized in wakefulness. In the ***frequency domain***, measures of EEG ***rhythms*** potentially unveil mechanisms of neural synchronization and desynchronization of the activity in cortical pyramidal neurons regulating brain arousal, vigilance, and many cognitive functions in humans. In clinical neurophysiology research, the most popular experimental condition of the study of EEG rhythms is the resting state condition (Babiloni et al., 2020a; Schomer and Lopes da Silva, 2018). In clinical contexts, ***eyes-closed resting state EEG (rsEEG) rhythms*** are typically recorded from 19-25 scalp electrodes placed according to the International 10-20 system (Babiloni et al., 2020a; Bocker et al., 1994). Quiet wakefulness is achieved asking participants to let their mind wander freely, without any oriented mental operations such as focused attention, memory recall, planning, etc. The explored brain function investigated in this state is the maintenance of quiet vigilance. This is consistent with the working hypothesis that brain disorders may affect ascending neural systems that underpin specific functions (Babiloni et al., 2020a).

The most popular method for the analysis of rsEEG rhythms has traditionally been the spectral analysis of artifact-free EEG waveforms based on the Fast Fourier Transform (FFT; Babiloni et al., 2020a). It allows the separation of rhythms at different frequencies that are difficult to see with the naked eyes as several rhythms occur simultaneously. Parameters that can be extracted through this procedure at a given scalp electrode include the peak frequency, the absolute power density of a specific rhythm, the relative power or ratio between two of them, reactivity to eyes opening (Babiloni et al., 2020a), and some synoptic index of the total spectrum such as the mean frequency (Arnaldi et al., 2017). Spatial analysis of rsEEG rhythms for clinical neurophysiology investigations may be performed by the study of its scalp topography or estimation of cortical sources (Babiloni et al., 2020a, 2020b).

In the eyes-closed resting state condition, dominant posterior ***alpha rhythms*** are the most prominent oscillations (about 8-12 Hz), which reduce in amplitude or disappear in the transition from

eyes closed to eyes opening in association with the activation of visual-spatial cortical systems (Babiloni et al., 2020a; Schomer and Lopes da Silva, 2017). In fact, simultaneous EEG-fMRI and near infrared spectroscopy (NIRS) studies have confirmed an alpha rhythm related "deactivation" of visual cortex – accompanied by an activation of the thalamus (Moosmann et al., 2003).

Low-frequency alpha rhythms (about 8-10 Hz) show high amplitude in relation to low levels of general brain arousal, attention, and readiness in quiet vigilance (Babiloni et al., 2013; Klimesch, 1996; Klimesch et al., 2006). In the same line, posterior high-frequency alpha (about 10-12 Hz) and low-frequency beta (about 12-20 Hz) rhythms show high amplitude in association with low levels of perceptual, sensorimotor, and memory processes in the condition of quiet vigilance (Becker et al. 2008,2011; Freyer et al., 2013; Haegens et al., 2014; Klimesch, 1996; Klimesch et al., 2006; Pfurtscheller and Lopes da Silva, 1999; Reinacher et al., 2009) and deactivation of underlying cortical regions in fMRI (Ritter et al. 2009). This amplitude decreases during physiological and pathological aging (Babiloni et al., 2017).

During sensorimotor and cognitive events, parallel changes in rsEEG rhythms occur. During sensorimotor events, Rolandic alpha and beta (mu) rhythms reduce in amplitude (i.e., desynchronize) and are replaced by faster cortical oscillations around gamma (40 Hz) rhythms (Pfurtscheller and Lopes da Silva, 1989). Furthermore, sensorimotor parietal alpha rhythms reduce in amplitude as well (Babiloni et al., 1999). During cognitive events, posterior alpha rhythms are replaced by faster cortical oscillations, namely high-frequency beta (20-30 Hz) and gamma (30-70 Hz) rhythms, mainly prompted by (i) forebrain cholinergic direct inputs to hippocampus and cerebral cortex and (ii) thalamocortical projections (Steriade, 2003). Oscillations in low-frequency bands such as ***delta*** (1-4 Hz) and ***theta*** (4-7 Hz) ***rhythms*** typically show small amplitudes in the resting state condition and exhibit complex patterns of changes during sensorimotor and cognitive events (Srinivasan et al., 2006). In this framework, brain neurophysiological dysfunctions may be associated with (i) small changes in amplitude of those EEG rhythms during sensorimotor and cognitive events and (ii) no sharp EEG power peak in the alpha frequency range and ample widespread delta and theta rhythms in the resting state condition (Babiloni et al., 2020a, 2020b; Musaeus et al., 2018).

Event-related changes in amplitude of EEG rhythms can be expressed as percent changes using the event-related desynchronization/synchronization method (ERD/ERS; Pfurtscheller and Lopes da Silva, 1999). Specifically, these changes are expressed as percentage decrease (ERD) or increase (ERS) in the power density of EEG rhythms at a certain frequency band during sensorimotor or cognitive events when compared to a pre-event baseline period (Pfurtscheller, 1992). ERD and ERS at alpha and beta frequencies typically reflect event-related and non-phase-locked cortical activation and inhibition in large cortical regions, respectively (Pfurtscheller and Lopes da Silva,

1999). In contrast, gamma ERS typically reflects event-specific activation in circumscribed cortical regions (Matsunaga et al., 2008; Pfurtscheller and Lopes da Silva, 1999). Overall, ERD/ERS measures at a given electrode may roughly reflect the desynchronization/synchronization of oscillatory activities of large local cortical neural populations generating the EEG activity recorded at that electrode (Pfurtscheller and Lopes da Silva, 1999).

Another popular approach in the frequency domain investigates the relationship between the phase of the EEG activity recorded at one electrode and the phase of the EEG activity recorded at another electrode, namely the "phase-synchronization" of EEG activities at an electrode pair (Babiloni et al., 2020a). With significant limitations in the spatial accuracy and resolution due to head volume conduction effects, such a statistical relationship may reflect the interrelatedness of EEG activities generated by relatively distant cortical sources (Babiloni et al., 2016; Ritter et al., 2008; Freyer et al., 2009)[1]. Noteworthy, it is important to distinguish the concept of "synchronization" used in the analysis of ERS at a given electrode, reflecting a local increase in amplitude/power of EEG rhythms, with the concept of "phase-synchronization" analyzed at a given electrode pair, reflecting an interdependence between two EEG signals related to brain networking.

An important development in the quantitative analysis of EEG signal is the estimation of its cortical source activity and functional connectivity using mathematical and biophysical models of the head volume conductor, active cortical neural populations, as well as propagation of neural ionic currents and related changes of electric fields in the scalp comportment (Srinivasan et al., 2006). Those methods are used to solve the (non)linear inverse problem of EEG based on assumptions, so no unique solution is available for that problem (Srinivasan et al., 2006). Despite the confounding influence of inflated solutions due to head volume conductor effects, these measures may provide insights about cortical neural networks underpinning the regulation of vigilance and active information processing during sensorimotor events and cognitive tasks (Babiloni et al., 2020a).

General topological features of these models of cortical neural networks can be estimated using ***graph theory*** indices (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010), which use as an input measures of interrelatedness of EEG activity at scalp electrode pairs or EEG source connectivity. Some graph theory indices are termed "information circulation", "network robustness

[1] In the present article, we report relevant findings of several studies in VCI patients using techniques for the computation of "interrelatedness of scalp EEG signals and EEG source connectivity" measures. Those studies used several linear and nonlinear measures for this purpose such as spectral coherence, synchronization likelihood, (directed) phase lag index, phase-synchronization, Granger causality, and directed transfer function as the most used. These measures aim to compute either the statistical interrelatedness of EEG time series at electrode pairs/arrays of electrodes or functional connectivity between estimated cortical sources of EEG activity. They are based on mathematical and physical assumptions about the reciprocal correlations or causal relationships between those EEG time series or underlying cortical generators. In the present article, we also reported relevant findings of some studies in VCI patients using measures of "complexity" of EEG time series based on field theories referring to chaos, entropy, random fractal, and auto-mutual information. Due to the clinical nature of this article, few notions were reported to characterize those measures here. More information about them can be found in the original papers cited. A recent overview about applications of those measures in Clinical Neurophysiology can be found in the position paper by Babiloni and others (2020a).

and adaptation to pathological disturbances", "modularity and functional specialization of subnetworks", and "small-worldness", with the latter defined as a balance between intense local connectivity and effective "hubs" for remote connectivity (Bullmore and Sporns, 2009). This approach may be relevant for characterizing neurocognitive disorders as brain disconnection syndromes, but the heterogeneity of the methodological approaches makes the comparison of the previous clinical EEG studies difficult and motivates the establishment of future consensus initiatives to standardize the methodology (van Diessen et al., 2015, 2016).

In the ***time domain***, measures of EEG activity include the analysis of ***sensory-evoked*** or ***event-related*** potentials (EPs/ERPs). EPs/ERPs reflect the summed activity of postsynaptic potentials generated by neural populations that fire in synchrony in response to sensory stimulation or cognitive-motor events. Technically, artifact-free short periods of EEG of a few hundreds of milliseconds related to single events (i.e., EEG epochs) are averaged after the alignment to the event onset, to produce EPs/ERPs phase-locked to those events (indeed, the nonphase-locked components of on-going EEG activity cancel each other during the averaging procedure). Of note, EPs/ERPs show a sequence of peaks of positive (P) and negative (N) voltage maxima that are typically expressed as a function of their post-stimulus latency, amplitude, and topographic scalp voltage distribution.

In clinical neurophysiology research, one of the most extensively used ERP paradigm is represented by the "oddball" paradigm. In a ***2-simulus*** "oddball" paradigm (Hillyard and Kutas, 1983; Polich, 2007; Squires et al., 1975), participants receive a train of many "frequent" (80-70% of probability) and "rare" (20-30%) stimuli intermingled with each other. The task is to ignore the frequent stimuli and react (e.g., counting them or pressing a button) to the rare ones as "targets". Artifact-free EEG epochs are averaged separately for "frequent" and "rare" stimuli. Compared to the ERPs for "frequent" stimuli, those for "rare" stimuli show a prominent posterior positive component peaking at about 300-400 ms post-stimulus, the so-called ***"posterior P300"*** or ***"P3b"*** related to cognitive processes including conscious attention allocation, working memory update, and context closure (Donchin, 1987; Polich, 2007; Rushby et al., 2005). This ERP component may mainly origin from a brain network spanning cortical frontal and temporal-parietal areas and subcortical basal ganglia and hippocampal regions (Rektor et al., 2004; Huang et al., 2015). Furthermore, it has been extensively used to explore abnormalities in cognitive brain systems in patients with cognitive deficits (Duncan et al., 2009; Hedges et al., 2016; Polich and Corey-Bloom, 2005).

In a ***3-stimulus*** "oddball" paradigm (Polich, 2007), a third class of sensory stimuli "rare but to be ignored" is delivered among those mentioned above. Each of the "rare but to be ignored" stimuli is presented only one time during an experiment to generate the experience of "novelty". ERPs for those stimuli show a prominent anterior positive component peaking at about 250 ms post-stimulus,

namely the ***"P3a"*** (i.e., a type of anterior P300). This ERP component may reflect cognitive functions including focal attention handling novelty in sensory stimuli and inhibition processes (Huang et al., 2015; Jeon and Polich, 2001; Polich, 2007; Rushby et al., 2005). Analysis of P3 peaks in the oddball paradigms is typically performed at scalp electrodes, but its spatial analysis implies an estimation of cortical sources, especially based on EEG recordings using 48 or more electrodes (Michel et al., 2004, Michel, 2019).

A combined analysis of EEG activity in time and frequency domains measures the so-called ***"sensory-evoked or event-related EEG oscillations"*** (EOs/EROs). According to the definition of Başar and colleagues (1999), EOs/EROs result from the decomposition of EPs/ERPs into the parallel delta, theta, alpha, beta, and gamma oscillatory responses phase-locked to stimuli or cognitive-motor events (Başar et al., 2001; Başar and Stampfer, 1985; Başar-Eroğlu et al., 2001, 1992). These responses complement ERD/ERS, the latter being expected to be affected also by neurophysiological oscillatory processes non-phase-locked to the neural elaboration of sensory stimuli and cognitive-motor events (Pfurtscheller and Lopes da Silva, 1999). An extensive study by Bernat et al. (2007) showed that major operating EROs of oddball P300 or other ERP components were mainly observed at delta and theta frequencies (Başar et al., 2001; Başar-Eroğlu et al., 1992; Demiralp et al., 1999; Spencer and Polich, 1999; Yordanova et al., 2000). Concerning the neurophysiological basis of ERD/ERS, it has been hypothesized that as compared to ERD/ERS, phase-locked cortical activity is more dependent on the signal transmission from relay thalamocortical neurons to cortical pyramidal neurons (Pfurtscheller and Lopes da Silva, 1999). Furthermore, recent evidence in rats showed that hippocampal and cortical P3-like and/or ERO theta responses to oddball target stimuli were modulated by cholinergic systems (Laursen et al., 2014; Annoui et al., 2018).

A main advantage of the EEG measures mentioned above is their high temporal resolution for identification of the disturbance of brain dynamics associated with cognitive impairments that occur in neurocognitive disorders (Nuwer, 1997). The neurophysiological mechanisms involved in neural synchronization and desynchronization in the cerebral cortex may depend on efficient functional connectivity and underpin information transmission within both local and long cortico-cortical neural circuits (Mantini et al., 2007) Therefore, it is thought that EEG measures are sensitive to abnormalities in the vasculature of brain white matter "connecting" tracts and subcortical structures projecting to cerebral cortex, namely the main generator of EEG activity (Moretti et al., 2007, 2008; Pantoni et al., 2010). Indeed, those abnormalities in VCI patients likely may cause disconnection among neural cells, damage to cortico-cortical and cortico-subcortical pathways as well as the loss of myelinated axons resulting in reduced neural signaling and synaptic activity at the cerebral cortex level.

THE AIM OF THIS ARTICLE AND GENERAL PROCEDURES USED TO REVIEW THE LITERATURE

Due to the huge amount of information embedded in scalp EEG waveforms and the gray zone between signal and biological/instrumental noise, there are uncertainties about the value of EEG measures for clinical trials in VCI patients. To address this issue, the Steering Committee of Electrophysiology Professional Interest Area (EPIA) of The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART), Alzheimer's Association (AA; https://www.alz.org/), and Global Brain Consortium (GBC; https://globalbrainconsortium.org), encouraged the formation of a large multidisciplinary Expert Panel to review the literature and provide recommendations about candidate EEG measures for the ***stratification of VCI patients*** and ***exploring neurophysiological mechanisms of their brain function*** in clinical trials. Specifically, the Expert Panel addressed the question ***"What EEG measures most consistently reveal abnormalities across studies in mild and major VCI patients in comparison with age-matched cognitively unimpaired (CU) persons? Are they suitable for use in future clinical trials?"*** An ancillary question was about the specificity of those abnormalities to be addressed by comparing changes in EEG measures in other age-related neurocognitive disorders such as Alzheimer's and Parkinson's diseases. The members of the Expert Panel cover different disciplines (i.e., neurology, psychiatry, and neuroimaging of dementias; clinical neurophysiology and quantitative EEG of dementias; and cognitive and systems neurosciences) strictly related to this general question.

The authors' recommendations were based on a comprehensive review of the literature conducted using Web of Science (Core Collection) and PubMed databases, using a combination of different key words for the "population of interest" and for the "EEG measures of interest": ("vascular cognitive impairment" OR "vascular contribution to cognitive impairment and dementia" OR "vascular dementia" OR "subcortical ischemic vascular disease" OR "small vessel disease" OR "multi-infarct dementia") AND (electroencephalography OR "resting state EEG" OR "ongoing EEG" OR "background EEG" OR "quantitative EEG" OR "brain rhythms" OR "brain oscillations" OR "evoked potentials" OR "event-related potentials" OR "oddball paradigm" OR P300 OR P3 OR "event-related oscillations" OR "evoked oscillations" OR "event-related desynchronization" OR "event-related synchronization").

The selection of studies was based on several pre-defined inclusion criteria. We included peer-reviewed articles in English on EEG studies carried out in VCI patients without restrictions in the year of publication. These studies included both resting state and task-based experiments and could use several data analysis techniques as listed in the following: a) visual analysis and description of well-known graphoelements observed on ongoing rsEEG traces; b) synchronization, reflecting the

time evolution of the synchrony of the activity of a local cortical neural population at a spatial scale of few centimeters required to generate recordable EEG rhythms; c) complexity, referring to the complex dynamics underlying temporal patterns at one scalp electrode or spatiotemporal patterns across many scalp electrodes (Jeong, 2004); and d) interrelatedness of EEG activity at scalp or EEG source connectivity. Regarding the experimental designs of interest, we included: a) longitudinal studies, cohorts of patients with VCI; b) cross-sectional studies, samples of VCI patients with different severity and disease duration; and c) classification studies, accuracy of EEG measures in the discrimination between CU persons, patients with VCI and/or other types of cognitive impairment at individual level.

In addition and in order to ensure the high quality of the studies, all selected articles were critically reviewed by some authors (i.e., C.B., A.B., M. K., G.Y., B. G., and F.N.) using a sub-set of criteria reported in Jelic and Kowalski (2009) with some modifications: a) study population should have been recruited from the clinical research settings or well defined population based cohorts, and all patients should have passed uniform and extensive diagnostic procedure, including structural neuroimaging; b) all the patients should have been diagnosed according to the established consensus clinical diagnostic criteria used as a "gold standard"; c) ten or more participants should have been included at least in VCI diagnostic group and control groups should match in demographic variables; d) disease severity should have been quantified according to the universally accepted global cognitive or clinical rating scales; and e) EEG recording procedure and analyzing methods including classification algorithms should have been appropriate and described in detail.

Based on that material and procedure, those authors produced a full draft narrative review with a focus on EEG measures revealing most consistent abnormalities across clinical studies in mild and major VCI patients. The draft was circulated among the other authors for further discussions for the sake of reaching a consensus about the recommendations and clinical guidance to deliver. Integrations, adaptations, and amendments were part of the project workflow. For that purpose, the original draft was repeatedly circulated and discussed across all authors for about two years (between 2018 and early 2020) before being completed in May 2020.

Noteworthy, the terms and methodological procedures discussed in this article may not correspond to those used in the daily medical practice supplied in services of clinical neurophysiology, and we do not recommend that neurologists and psychiatrists should necessarily use the present terms and methodological procedures in their practice for diagnostic, prognostic or monitoring purposes. Indeed, this paper is ***not*** a collection of guidelines for the application of techniques of clinical neurophysiology in daily medical practice. As mentioned above, this article is focused on EEG measures potentially useful for future clinical research in VCI patients.

As this manuscript was not designed to suggest revisions to diagnostic criteria but to reach consensus recommendations on next steps for the use of EEG measures into a broader spectrum of clinical trials, the present revision of the literature was not based on standard procedures typically adopted by international biomedical societies for the revision of the medical intervention and practice (e.g., among them, see the "GRADE" Handbook to address the so-called "PICO" health care questions, https://gdt.gradepro.org/app/handbook/handbook.html). The authors hope that the field will soon reach the maturity for the involvement of international biomedical societies for that purpose.

RESULTS OF THE REVIEW

Overview of included studies

We identified 390 studies, 381 from the database search and 9 through other methods such as review of reference lists of relevant articles. After removing duplicates, screening by title and abstract, and revising full text, 218 articles were excluded and 92 were finally included in the review (see Figure 2 for the pathway of the studies included). Of these 92 articles, 61 were classified as studies of resting state EEG measures and 37 as event-related EEG measures[2]. In the following description of the results, we termed as "abnormal" an EEG activity showing statistical differences with that recorded in cognitively unimpaired adults matched as age.

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Evolution of diagnostic terms in EEG literature in VCI patients

It is well known that diagnostic terms and semantics to denote VCI patients evolved in the last decades (van der Flier et al., 2018). It is only after the publication of NINDS-AIREN criteria in 1993 that the term VaD was progressively replaced by that of multi-infarct dementia (MID), Later developments led to the understanding that not only multiple cortical infarcts, but small vessel disease can also lead to dementia (O'Brien and Thomas, 2015).

Earlier literature linked the concept of VCI with that of MID, thus missing other possible causes of cerebrovascular lesions. In a similar vein more recent literature conceivably tends no longer to identify VCI with small vessel ischemic disease (SIVD) (Erkinjuntti and Gauthier, 2009; Roh and Lee, 2014).

This shift of attention over the years may partly reflect differences in interpreting neuroimaging findings. Recent years have brought a distinct lexicon of neuroimaging findings

[2] Adding the results for both categories resulted in more than 92 articles, since some of the studies included both analyses of resting state EEG and event-related EEG. The same is true for the different sub-categories within the two general categories.

corresponding to cerebral small-vessel disease (cSVD) as key factor for SIVD, including small subcortical infarcts that formerly could have been associated with MID (Wardlaw et al., 2013).

The recent VICCCS-1 study proposed that the major forms of VCI (VaD) should be classified into four main subtypes: (i) post-stroke dementia (PSD); (ii) subcortical ischemic vascular dementia (SIVaD); (iii) multi-infarct (cortical) dementia (MID); and (iv) mixed dementias (further subdivided according to additional neurodegenerative pathologies).

Another clear issue in revision of the literature is the heterogeneity of clinical diagnoses in VCI patients, creating a gray zone between VaMCI or VaD in several cases (mild or major VCI, respectively, with newer terminology) due to SIVD and MID.

Finally, another critical aspect is that most EEG studies in VCI patients included "mixed" diseases belong to cognitive impairment and dementia, including AD and other neurodegenerative diseases. Future EEG studies in VCI patients may include the evaluation of diagnostic biomarkers of AD neuropathology (i.e., amyloidosis or tauopathy in the brain) or α–synucleinopathy. To date, cerebrospinal (CSF) analysis may allow to rule out the possible confounding effects of mixed neuropathology in future EEG studies focused on VCI patients.

Keeping in mind the above issues in the interpretation of the literature results, the present expert panel did not evaluate EEG measures as a function of different diagnostic classes of VCI. Rather, we systematically used "mild and major VCI" in this report. When appropriate, we added between brackets the original diagnostic classes of VCI patients in the articles revised (e.g., VaD, MID, cSVD, etc.).

Resting state EEG measures in VCI patients

Visual analysis of resting state EEG (rsEEG) waveforms (12 studies reviewed)

According to Jonkman (1989; 1997), the literature up to 1996 showed no consensus on the utility of visual analysis of rsEEG waveforms to distinguish ADD from MID patients. This position was based on earlier studies by Bucht et al. (1984), Erkinjuntti et al. (1987, 1988), Ettlin et al. (1989), Harrison et al. (1979), Sloan et al. (1995), Soininen et al. (1982), and Wagner et al. (1985). Those studies did not find important differences between the groups or in the classification figures based on abnormalities in rsEEG waveforms. The most common results were a slowing of the predominant background frequencies more frequent in ADD than in MID, and more usual focal disturbances in MID. Moreover, about other neurodegenerative conditions, also patients affected by Parkinson's disease or parkinsonian disorders could show a significant slowing of the dominant EEG rhythm. However, the main conclusion was that EEG waveforms could be valuable in differentiation of dementia patients from age-matched CU participants, but differentiation between MID and ADD was

not reliable using rsEEG activity alone. Although visual abnormalities in the EEG waveforms are not useful for separating dementia types, Gur et al. (1994) showed that non-demented patients with first-ever ischemic stroke and abnormal EEG waveforms at baseline had 2.6 times more risk of developing dementia at two years than those with normal EEG activity.

Afterward, Gawel et al. (2009, 2007) showed that visual EEG analysis was not able to differentiate major VCI (probable subcortical VaD) from age-matched CU individuals. Finally, Liedorp et al. (2009) performed a large retrospective study in more than one-thousand patients with cognitive disorders. They reported differences in patterns of rsEEG waveforms among several types of clinical diagnoses through an elaborate combination of focal abnormalities such as slow wave activity, epileptiform discharges, and diffuse abnormalities, such as background activity below 8 Hz, spatially widespread delta or theta rhythms, and diminished reactivity of posterior alpha rhythms during the eyes opening. Results showed that the co-occurrence of both focal and diffuse abnormalities in different periods of rsEEG waveforms was associated with an increased prevalence of all types of dementia due to VCI, dementia with Lewy Bodies (DLB), and ADD; however, only diffuse disturbances were associated with ADD (Liedorp et al., 2009).

Keeping in mind the above data and methodological limitations about the heterogeneity of vascular lesions and lack of diagnostic biomarkers of mixed neurodegenerative diseases in the VCI cohorts considered, visual analysis of rsEEG waveforms cannot be recommended as a main measure for clinical trials in VCI patients. This conclusion may be revised in future studies using a combination of neuroimaging evidence of VCI and (i) high-resolution EEG electrode montages (Seeck et al., 2017), (ii) advanced scoring systems for EEG waveforms (Beniczky et al., 2017) and (iii) EEG topographic mapping.

Quantitative spatial and frequency analysis of rsEEG rhythms (51 studies reviewed)

Most of the earlier rsEEG studies in VCI patients used ***measures of EEG power density*** computed by well-known standard fast Fourier transform (Babiloni et al., 2020a). Compared with age-matched CU persons as a control group, major VCI patients showed the following abnormalities of EEG power density: (i) slowing in frequency of the peak posterior alpha frequency, (ii) a reduction in power density of dominant occipital alpha rhythms, (iii) an increase in power density of fronto-central alpha rhythms (i.e., the component in the alpha range of sensorimotor mu rhythms, Crone et al., 1999), and (iv) a topographically widespread increase in power density of theta and delta rhythms (d'Onofrio et al., 1996; Erkinjuntti et al., 1988; Moretti et al., 2004, 2012; Neto et al., 2015; Saletu et al., 1991, 1992; Signorino et al., 1995, 1996; Sheorajpanday et al., 2013; Sloan et al., 1994; Wu et al.,2014). Szelies et al. (1999) showed that delta and theta power were inversely, and alpha power

was positively correlated with glucose metabolism in major VCI patients. In some studies, major VCI (MID and cSVD) patients also showed a decrease in beta power density associated with the above changes in delta, theta, and alpha power density (Holschneider and Leuchter, 1995; Martín-Loeches et al., 1991; Neto et al., 2015; Saletu et al., 1991; van Straaten et al., 2012). Partanen and colleagues (1997) reported reduced alpha amplitude ratio between eyes closed and eyes open condition in major VCI patients as compared to age-matched CU persons. Loring et al. (1985) reported a decrease in 40 Hz activity at rest in major VCI (MID) patients compared to age-matched CU persons, whereas Lv et al. (2020) showed an increase of power of gamma for the same comparison.

Compared with patients with other dementing disorders as a control group, VCI patients showed specific abnormalities in rsEEG measures. In this sense, Martin-Loeches et al. (1991) showed a significantly higher power for delta and theta frequency bands in ADD compared to MID patients during eyes open, especially over the central-parietal and occipital regions bilaterally. In addition, Saletu et al. (1992, 1991) found less beta activity over frontal areas in MID than in ADD patients. Moreover, MID patients revealed an increased in power asymmetry in the delta/theta range over the frontal regions, in the alpha range over the parietal region and in the beta range fronto-polarly (Saletu et al., 1992). Furthermore, Moretti et al. (2004) revealed that as compared to ADD patients, major VCI patients exhibited "slowing" in frequency of the power density peak in the alpha range and globally higher theta power density. In the same vein, Gawel et al. (2009, 2007) reported that the alpha/delta plus theta power density ratio, and the global rsEEG mean frequency, were higher in major VCI patients compared with an ADD group. Moreover, distributed theta cortical source activations were abnormally greater in major VCI patients but not mild ADD patients (Babiloni et al., 2004a). In comparison to control stroke patients who had completely recovered from transient ischemic attacks, Sheorajpanday et al. (2013) reported that mild VCI patients were characterized by a decrease in widespread alpha (including sensorimotor and visual-spatial components) and beta source activations, while delta sources increased in activation in comparison to amnesic MCI patients possibly suffering from AD.

Drug effects on the EEG (Pharmaco-EEG) of VCI patients were also studied. Saletu et al. (1992) studied the effect of denbufylline on both ADD and MID patients, showing in both groups a significant increase of fast alpha activity and alpha adjacent beta activity over the right central region, as well as over the left occipito-temporal area as compared to placebo-treated ones. Saletu et al. (1995) also showed positive effects on EEG in MID patients treated with nicergoline, showing a significant decrease in delta and theta, and an increase in alpha 2 and beta activity. Moreover, these positive effects of nicergoline on the EEG of MID patients were positively correlated with a clinical improvement (Saletu et al., 1997). In two experiments, Muresanu et al. (2008, 2010) showed that

cognitive deficits (ADAScog score) of major VCI patients were positively correlated with delta-theta power and negatively correlated with alpha power. Furthermore, cerebrolysin treatment improved cognitive status, reduced delta power, and increased alpha activity (Muresanu et al., 2008) in major VCI patients. These authors also reported that positive effect of cerebrolysin treatment lasted at least 12 weeks after treatment (Muresanu et al., 2010). The positive effect of galantamine treatment was reported by Sorokina et. al. (2007) since after treatment slow-wave power decreased and alpha power increased.

Complexity measures of the rsEEG rhythms were derived by information theory or nonlinear dynamical theory to account for the brain as a system characterized by complex spatiotemporal dynamics of neural networks (Gao et al., 2011). Kim et al. (2000) employed a test of Wackermann's global Ω complexity and found decreased complexity in major VCI patients compared with age-matched CU persons. Using the nonlinear dynamical measures including dimensional complexity and Lyapunov exponents, Jeong et al. (2001) found that the values of the complexity measures in rsEEGs were pathologically increased in several electrodes of major VCI patients, whereas the complexity measure values in most electrodes were decreased in ADD patients. Furthermore, most of the VCI patients showed an uneven distribution of the complexity values in rsEEG rhythms over widespread scalp regions compared with ADD patients and age-matched CU individuals. This result suggests that different patterns of EEG complexity measures across the scalp regions between VCI and ADD patients can be a potentially useful indicator for the diagnosis of VCI and ADD.

Previous rsEEG studies in VCI patients have used heterogeneous methodologies to measure ***interrelatedness of rsEEG rhythms between electrode pairs***. Although some studies have failed to find differences between ADD and major VCI patients in spectral coherence measures (Sloan et al., 1994), Leuchter et al. (1994b, 1992, 1987) reported that major VCI (MID) patients were characterized by abnormally low rsEEG ***spectral coherence*** (i.e., the most popular linear measure of such interrelated rsEEG rhythms, typically derived by FFT) at a large frequency range over Rolandic areas, whereas a similar reduction was observed in ADD patients between anterior and posterior scalp areas overlying long cortico-cortical neural fibers. Leuchter and colleagues interpreted those findings as indicating a neocortical "disconnection syndrome" in ADD patients in which there may be a loss of cortico-cortical tracts. In contrast major VCI patients may be affected by impairment of broad complex ***networks of cortico-subcortical and cortico-cortical fibers***, especially vulnerable to widespread subcortical vascular damage as that revealed by periventricular WMH (Leuchter et al., 1994a, 1992). This interpretation agrees with a study (Babiloni et al., 2004b) showing that the most distinguishing feature in ADD patients with respect to major VCI (VaD) patients was a more prominent reduction of interrelatedness of rsEEG rhythms as revealed by ***synchronization likelihood***

between fronto-parietal electrodes at low frequency alpha rhythms (a measure sensitive to both linear and nonlinear interrelatedness of rsEEG activity). In the same vein, Babiloni et al. (2008a, 2008b) investigated rsEEG measures in two groups of ADMCI patients (matched as cognitive deficits) with high versus low cerebrovascular disease load as revealed by WMH. As compared with age-matched CU persons, ADMCI group with low and high WMH load showed lower activity of posterior alpha sources and reduced parietal-to-fronto directional interrelatedness of rsEEG rhythms as revealed by ***directed transfer function*** (a multivariate measure derived from Granger causality sensitive to linear directional interrelatedness of rsEEG activity) between electrode pairs for theta, alpha, and beta rhythms (Babiloni et al., 2008a, b). Furthermore, in relation to the ADMCI group with low WMH load, those with high WMH load showed greater activity of posterior alpha sources (Babiloni et al., 2008a) and higher parietal-to-fronto directional interrelatedness of rsEEG rhythms as revealed by ***directed transfer function*** between those electrode pairs and frequencies (Babiloni et al., 2008b), thus suggesting a greater sensitivity of those rsEEG features to AD neurodegeneration than cerebrovascular brain neuropathologies in the explanation of cognitive deficits in MCI patients.

Van Straaten et al. (2015) applied techniques for analysis of the directionality of interrelatedness of rsEEG rhythms between electrode pairs. They found clear phase gradients from anterior to posterior electrodes in all rsEEG frequency bands except in the delta band in the age-matched CU group whereas this pattern was significantly different without a clear direction in the group of patients with major VCI (van Straaten et al., 2015).

It should be noted that some negative results have been reported. van Straaten et al. (2015) found no differences between major VCI patients and age-matched CU persons in the interrelatedness of rsEEG rhythms between electrode pairs as revealed the Phase Lag Index and directed Phase Lag Index (measures sensitive to nonzero lag phase interrelatedness of rsEEG activity). Concerning the specificity of EEG interrelatedness measures, Sloan et al. (1994) showed no significant differences in rsEEG spectral coherence between ADD vs. major VCI (MID) patients with reduced regional cortical blood flow. Lv et al. (2020) reported decreased gamma-band connectivity in mild major VCI group compared with an age-matched CU group.

Concerning the ***specificity of rsEEG measures of VCI***, several ***correlation*** studies showed encouraging associations between rsEEG measures and both clinical features and neuroimaging markers (i.e., WMH) of cerebrovascular lesions. Specifically, some studies showed an association between rsEEG measures and clinical features in VCI patients such as disease severity (Sheorajpanday et al., 2014), progression of symptomatology (Sheorajpanday et al., 2013, Shibata et al., 2014), and cognitive deficits (Gawel et al., 2007; Leuchter et al., 1993), in comparison with patients with other forms of neurocognitive disorders (Erkinjuntti et al., 1988; Moretti et al., 2012;

Neto et al., 2015). Moretti et al. (2007) in a study comparing a cohort of mild VCI patients in four sub-groups based on subcortical CVD as scored by the age-related white matter changes scale (ARWMC) showing that the severity of the cerebrovascular WMH load was related to increased global delta power density and decreased global alpha power density in mild VCI patients. Moreover, theta/alpha1 power ratio was the most sensitive EEG marker of cerebrovascular damage, showing a significant increase in moderate and severe cerebrovascular WMH load groups, as compared to mild and no damage groups, related with the individual extent of CVD.

Interestingly, mild VCI (subcortical CVD) patients with executive function deficits exhibited lower fronto-parietal spectral coherence of rsEEG rhythms at low-frequencies when compared with age-matched CU persons and MCI patients with prodromal AD and episodic memory deficits (Moretti et al., 2008).

Concerning the ***accuracy of rsEEG measures in the discrimination of VCI and ADD patients at an individual level***, some earlier investigations produced promising positive findings.

Leuchter and Walter (1989) showed that EEG topographical spectral ratios were useful at discriminating between ADD and major VCI (MID) patients. In a later study, Leuchter et al. (1992) reported an accuracy of 76% in the classification between ADD and major VCI (MID) individuals considering the ratio of the rsEEG spectral coherence between near and far electrode pairs. However, Leuchter et al. (1993) showed no large differences in the classification of ADD and major VCI (MID) for relative or absolute powers, slow-wave ratio, and alpha ratio. In comparisons between normal persons and patients, the proportion of participants correctly classified was high for the absolute power measures (77% of ADD, 81% of MID), and low for the alpha ratios (63% of ADD, 67% of MID). Seal et al. (1998) showed that alpha and beta relative power in central and parietal electrodes allowing a correct classification between ADD and major VCI between 85-90% for eyes closed, open and the subtraction of both. Szelies et al. (1994) reported that the relative theta power density discriminated ADD and major VCI (MID) patients from age-matched CU persons, while the ratio between occipital and frontal alpha power density distinguished ADD from major VCI patients.

These results were confirmed even at the level of ***MCI status***. Sheorajpanday et al. (2014) showed an overall classification accuracy of 95% using verbal fluency and (delta + theta)/ (alpha +beta) power density ratio as independent diagnostic predictors in the discrimination of MCI patients possibly due to AD and mild VCI patients.

The above results were confirmed using more sophisticated classifiers based on ***artificial intelligence methods including artificial neural networks and other leaning machines***. Anderer et al. (1994) obtained a classification rate of 90% through an ***artificial neural network*** as a classifier in the discrimination between major VCI and ADD patients using the topographic distribution of

absolute delta and theta power density as input features. In the same line, Snaedal et al. (2012) developed a step-wise classification procedure using ***support vector machines*** as classifiers and several rsEEG spectral features (i.e., power density and coherence) in the discrimination between age-matched CU persons, MCI patients who remained stable for more than 24 months, and several subgroups of neurocognitive disorders, namely ADD, major VCI, DLB/Parkinson's disease dementia (PDD), fronto-temporal dementia (FTD), and depression mimicking mild dementia. This procedure reached an accuracy of 75% for the classification of ADD and major VCI individuals.

An important aspect of the basic clinical question in the current article is the value of ***rsEEG measures of disease progression*** in VCI patients. Unfortunately, only a few ***longitudinal*** studies have published findings on this matter. Therefore, most of the candidate rsEEG markers of disease progression to be tested in future studies may be suggested by ***cross-sectional*** studies with VCI patients with different severity of cognitive deficits (e.g., mild and major VCI). Concerning longitudinal studies, an early investigation followed age-matched CU persons, ADD, major VCI (MID), and functional psychiatric patients over a 2-year period (Sloan and Fenton, 1993)[3]. There was to ***no change*** in rsEEG power density over time in the major VCI group (Sloan and Fenton, 1993). Another early longitudinal study (Dunkin et al., 1994) showed that the rsEEG spectral coherence between electrode pairs overlying Rolandic areas, likely reflecting short cortico-cortical and cortico-subcortical connections, was stable as a "trait" marker in both groups of ADD and major VCI (MID) patients. In contrast, the rsEEG spectral coherence between electrode pairs in the anteroposterior scalp axis, e.g. possibly reflecting long cortico-cortical connections, exhibited stability in major VCI (MID) and age-matched CU persons at 1-year follow-up, while ADD patients showed great variability in rsEEG spectral coherence indicating both "state" and "trait" features (Dunkin et al., 1994).

Concerning ***cross-sectional*** studies, Gawel et al. (2007) developed an investigation comparing some rsEEG features in subgroups of ADD and VCI patients at mild, moderate, and severe stages of dementia. They reported that: (i) mean frequency of rsEEG activity in temporal electrodes was lower in ADD than VCI patients at mild and moderate stages of cognitive deficits; (ii) global alpha/delta power density ratio was lower in ADD than VCI patients with moderate dementia; and (iii) the alpha/delta plus theta power density ratio, and the mean frequencies of rsEEG activity from temporal electrodes were lower at the most severe stages of cognitive deficits in patients with both neurocognitive disorders. Finally, some studies have investigated the effect of different ***risk factors*** for the development of VCI, such as diabetes and coronary artery disease, on rsEEG differences

[3] Although the study of Sloan and Fenton (1993) did not fulfil one of the quality criteria by Jelic and Kowalski (2009), i.e., enough sample size, we decided to include it anyway because of the importance of longitudinal studies and the scarcity of this type of studies in the literature.

between individuals with and without cognitive impairment. Abo Hagar et al. (2018) have found higher alpha 2 power and decreased alpha 1 power in MCI patients with diabetes compared both with diabetes patients without MCI and age-matched CU persons. On the other hand, Tarasova et al., (2018) in a regression model reported that theta/alpha ratio, theta rhythm in the frontal and occipital areas of the left hemisphere in eyes closed, and alpha 2 power with eyes open in the frontal areas of the right hemisphere, were the predictors more associated with an increased risk for MCI in patients with coronary artery disease, sensitivity of the model being 90.5%.

Table 1 reports the most relevant findings among those reported above, supporting the value of spectral rsEEG measures in the characterization of brain functions in VCI patients.

Please insert Table 1 around here

Event-related EEG measures in VCI patients

Oddball event-related EEG potentials (ERPs) analyzed in the time domain (20 studies reviewed)

In contrast to the many oddball ERP studies carried out in ADD and amnesic MCI patients (Güntekin and Başar; 2016; Yener and Başar, 2013), the literature is relatively scarce in VCI patients, however converging results have been obtained. Specifically, oddball ERP studies in major VCI patients reported similar results using different modalities (auditory, visual, or somatosensory) of oddball tasks (Chen et al., 1997; Hanafusa et al., 1991; Ito, 1994; Kedhr et al., 2009; Neshige et al., 1988; Muscoso et al., 2006; Oishi et al., 1996; Sloan et al., 1994; Xu et al., 2012; Yamaguchi et al., 2000). There was a significant delay of posterior P3b peak ***latency*** when detecting targets in major VCI patients compared with age-matched CU persons. Other oddball ERP studies showed effects also in posterior P3b peak ***amplitude*** (Ito, 1994; Kedhr et al., 2009; Xu et al., 2012) or peak-to-peak amplitude of N2 and P3b components (van Harten et al., 2006). Moreover, some ERP studies have found a delayed N2 peak preceding the posterior P3b (Kedhr et al., 2009; Neshige et al., 1988; van Harten et al., 2006), and even peak delays in more exogenous components such as N1 and P2 (Kedhr et al.,2009).

It is an open question if the above abnormalities in peak latency and/or amplitude of oddball ERP components in VCI patients may be disease ***specific***, as similar oddball ERP findings were reported in other types of neurocognitive disorders (e.g., ADD patients; Bonanni et al, 2010; Onofrj et al., 2003; Polich and Corey-Bloom, 2005). In favor of the specificity of the oddball ERP effects, Muscoso et al. (2006) reported that major VCI patients were characterized by a selectively prolonged auditory P3b compared with changes in latency in many oddball ERP components in ADD patients. The P3b peak latency showed 59% sensitivity and 93% specificity in the discrimination of major VCI

patients versus age-matched CU persons, while P2 peak latency reached even better discriminant values, namely 79% sensitivity and 98% specificity (Muscoso et al., 2006).

In favor of some specificity of the above oddball ERP components, Podemski et al. (2008) showed that mild VCI patients with leukoaraiosis and cortical atrophy had longer N2 and P3b peak latencies in relation to cognitive deficits compared with MCI patients with cortical atrophy only. Similarly, Jiang et al. (2014, 2013) showed significantly longer auditory P3b peak latency in mild VCI patients in relation to frontotemporal lesions and leukoaraiosis, as compared with age-matched CU persons and patients who had suffered from stroke but without any cognitive impairment. This prolonged P3b latency was even higher for mild VCI patients with hyper-homocysteinemia (Jiang et al., 2014). Finally, Yamaguchi et al. (2000) showed that the auditory P3a peak latency for rare distracters was longer and the amplitude lower in major VCI (VaD) patients than control ADD and age-matched CU groups. Furthermore, the scalp topography of the P3a peak was also different in the three groups; its maximum amplitude was frontal in age-matched CU persons, central in ADD patients, and parietal in major VCI patients (Yamaguchi et al., 2000).

An auditory deviant-standard-reverse oddball paradigm to elicit the *mismatch negativity* (MMN) was used by Jiang et al. (2017) to compare mild VCI patients, mild ADD patients and age-matched CU persons. The MMN reflect an automatic detection mechanism at the pre-attentive stages of information processing. The results showed a significant decrease of the mean MMN amplitude between both patients' groups and age-matched CU persons, and the MMN peak latency in mild VCI patients was significantly shorter than in age-matched CU persons and ADD patients. However, no differences between prodromal VCI and ADD patients were found.

Regarding pharmaco-EEG studies using oddball paradigm, Saletu et al. (1995, 1997) demonstrated a significantly shortened P300 latency under nicergoline treatment in both ADD and MID patients. Paci et al. (2006) also showed a reduction of P300 latency in major VCI patients after one month of treatment with donepezil. Moreover, Liu et al. (2016) reported the same result plus increased P300 amplitude in major VCI patients after treatment with donepezil and acupuncture.

The studies regarding the relation between ERPs and risk factors for VCI are scarce. In this vein, Mecklinger et al. (2006) examined the relationship between the integrity of cerebrovascular microcirculation and ERPs in a nonclinical group of participants with arterial hypertension. The authors reported that latencies of the P3a and the P300 showed a reliable correlation with the measures of vascular pathology.

The application of nonlinear measures for analyzing oddball ERPs is limited. Xu et al. (2012) applied complexity measures of approximate entropy in the analysis of visual oddball ERPs in major VCI (VaD) patients versus elderly and young CU persons. The major VCI patients showed greater

values of approximate entropy (as a measure of signal complexity) than those seen in age-matched CU persons.

Overall, the most consistent findings were longer N2 and posterior P3b peak latency during the detection of auditory oddball targets in major VCI patients (Chen et al., 1997; Hanafusa et al., 1991; Kedhr et al., 2009; Neshige et al., 1988; Muscoso et al., 2006; Oishi et al., 1996; Sloan et al., 1994; Xu et al., 2012; Yamaguchi et al., 2000).

Oddball event-related EEG measures analyzed in the frequency domain (6 studies reviewed)

Few studies in VCI patients have analyzed oddball event-related EEG data in the frequency domain. Lou et al. (2011) used novel multichannel linear descriptors of EEG oscillations in major VCI patients involved in the detection of oddball targets. As compared to age-matched CU persons, major VCI patients showed greater spatial complexity and lower field strength in event-related EEG oscillations at delta frequencies, thus suggesting the involvement of more cortical areas during task performance (Lou et al., 2011). In another study, Xu et al. (2011) reported a decrease in delta power density (i.e., ERS) at frontal, central, and parietal electrodes during the detection of oddball targets in major VCI patients compared with age-matched CU persons. Central and parietal delta ERS was also lower in CU elderly as compared with young persons, thus suggesting some specificity for the effect in frontal areas in major VCI patients (Xu et al., 2011). However, it should be considered that similar changes in delta rhythms during the detection of oddball targets have been repeatedly reported in patients with ADD, AD-MCI, PDD and other brain disorders (Başar et al., 2016; Başar and Güntekin, 2008; Güntekin and Başar, 2016), thus hinting that different neuropathological substrates may affect neurophysiological oscillatory mechanisms underpinning oddball event-related EEG activity at delta frequencies.

Reports in VCI patients investigating the interrelatedness of oddball event-related EEG rhythms between electrode pairs are also quite limited. Wang et al. (2014) showed that compared with healthy persons, major VCI patients were characterized by decreased strength of information flow measures in oddball EEG activity, through directed transfer function from parietal to anterior electrodes at delta, theta, and alpha bands. Furthermore, the directed transfer function showed that those major VCI patients were also characterized by reduced inter-hemispheric interrelatedness of delta and theta rhythms as well as reduced interrelatedness of delta rhythms from parietal to anterior electrodes during the pre-stimulus period (Xu et al., 2015). In parallel, interrelatedness of EEG rhythms increased in both pre-stimulus and post-stimulus periods, as a possible "compensatory" function (Xu et al., 2015). Those EEG data were also used as an input to a topological graph analysis of cortical neural networks underpinning oddball target detections (Wang et al., 2016). Graph indices

showed that compared with healthy persons, the major VCI patients were characterized by weakened topological patterns of outgoing information flow (i.e., an out-degree index) estimated from EEG rhythms recorded at parietal electrodes, with this region losing its "hub" status in cortical neural networks in relation to cerebrovascular lesions (Wang et al., 2016).

Noteworthy, the studies mentioned above computed interrelatedness of rsEEG activity at electrode pairs, so any explanation at underlying cortical areas should be taken with extreme caution due to head volume conduction effects.

Finally, Wang et al. (2019) studied the same measure, interregional directed connectivity derived from directed transfer function, to differentiate major VCI patients from age-matched CU persons. They used three different machine learning methods, including linear discriminant analysis, error back-propagation neural networks, and support vector machine. Those authors reported that major VCI patients could be identified from healthy persons using error back-propagation and support vector machine classifiers. Furthermore, they found that combining support vector machine with feature choice by Fisher score, the accuracy reached 86.11%, sensitivity 86.67 % and specificity 85.71%.

Non-oddball event-related EEG measures (12 studies reviewed)

The presence of cognitive deficits in VCI patients has mainly motivated the use of "cognitive" oddball paradigms, but a few non-oddball EP-ERP and frequency domain studies were published. Loring et al. (1985) compared the 40 Hz activity (gamma band) among ADD patients, major VCI (MID) patients and age-matched CU persons in both a verbal and a visual-spatial cognitive task. Despite ADD patients showing less 40 Hz activity under the two cognitive tasks when compared to CU persons, MID patients showed a decrease in 40 Hz activity just under the verbal task. In addition, MID patients showed more 40 Hz activity than ADD patients in the two conditions. In the same line Seal et al. (1998) aimed to discriminate between ADD and major VCI patients based on spectral power on two active conditions, an odor detection task, and a subtraction task. They used a discriminate function analysis and reported a 95% correct classification for both ADD and VCI patients using a combination of delta, theta, alpha and beta bands relative power during the odor detection task, and 91% for the subtraction task.

Few works have studied the evoked potentials in the auditory, visual, and somatosensory modalities in vascular cognitive literature. In this vein, Tachibana et al. (1989) reported differences between major VCI (MID) patients and age-matched CU persons in different components of the brainstem auditory evoked potentials (BAEPs). MID patients showed significant prolonged inter-peak latencies between waves I and V compared to normal persons, but not differences between MID

and ADD patients. Regarding visual evoked potentials (VEPs), Sloan et al. (1994) performed visual flash and pattern reversal recordings and failed to find any difference among major VCI (MID) and ADD. However, using a simple visual checkerboard paradigm, Rosengarten et al. (2007) showed a reduction of N75-P100 responses in major VCI patients as compared to ADD and age-matched CU persons. Interestingly, Huneau et al. (2018) used a flickering checkerboard stimulation to compare VEPs in preclinical VCI patients (asymptomatic CADASIL) and age-matched CU persons and did not find any significant difference at this preclinical stage.

More prolific has been the study of somatosensory evoked potentials (SEPs). Kato et al. (1990) comparing major VCI (MID) patients, patients with multiple infarcts without dementia, and age-matched CU persons, and found a prolongation of central conduction time (CCT) measured by median nerve SEPs in MID patients compared with both groups. Later, Ito et al. (1994) studied SEPs in major VCI patients compared with patients with other neurocognitive disorders. They also reported prolonged CCT (from N13 peak to N20 peak) and delayed N20, N140, and P200 peak latencies in major VCI patients compared with patients of the ADD and PDD groups. Comparing major VCI (both cortical and subcortical) with different severity levels and healthy persons, Tsiptios et al. (2003) reported a latency delay in N13, a decreased amplitude in N19 and P27, and a prolongation of N11-P27 conduction time in severely demented patients in comparison to age-matched CU persons. However, mild VCI patients did not differ from the other groups of persons in any one of the measurements. Paradowski et al. (2007) also showed prolonged latencies of N13 responses in major VCI patients compared with an age-matched CU group. Finally, Polak et al. (2009) measuring the vagus somatosensory evoked potentials did not find any difference between major VCI patients and age-matched CU persons, contrary to the results for ADD patients.

Two articles have studied ERPs in cognitive tasks other than oddball paradigm in VCI patients. Wranek and Ladurner (1993) analyzed the P300 component in a size discrimination task in major VCI patients and an age-matched CU group. Although the latency of P300 was longer in VCI patients, the repetition of the task lead to a learning effect in both groups reflected by a significant decrease in P300 latency. Using a memory workload task, Beuzeron-Mangina et al. (2009) reported a delay in the latency of a P300-like component (P450) over pre-frontal and frontal regions in major VCI patients compared to age-matched CU participants, but not differences between VCI and ADD patients. However, the amplitude of P450 was larger for ADD than for VCI and age-matched CU group especially at posterior areas, and no differences were found between VCI patients and age-matched CU persons.

Table 2 reports the most relevant findings among those reported above, supporting the value of event-related EEG studies, especially those with oddball paradigms, in understanding brain dysfunctions underpinning cognitive deficits in VCI patients.

Please insert Table 2 around here

NEUROPATHOPHYSIOLOGICAL BASIS OF EEG MEASURES IN VCI PATIENTS

In our review of the literature, major VCI patients with different vascular lesions showed the most consistent abnormalities in rsEEG rhythms at delta-theta and alpha bands as well as in the prolongation of N2 and posterior P3b peak latencies during the detection of oddball auditory targets (Tables 1 and 2). These abnormalities may reflect, at least in part, the effect of cortical and subcortical vascular lesions on distributed neural networks involved in the generation of cortical EEG activity. Those networks may be formed by basal forebrain, basal ganglia, and bidirectional thalamocortical neurophysiological circuits (Crunelli et al., 2015; Dey et al., 2016; Hughes and Crunelli, 2005), with a special role of thalamocortical functional connectivity during active event-related information processing accompanying ERPs (Pfurtscheller and Lopes da Silva, 1999). In this framework, the importance of thalamocortical functional connectivity is confirmed by converging evidence of prolonged central conduction time and delayed short-term EPs in VCI patients as compared to those with other neurocognitive disorders (Ito, 1994; Rosengarten et al., 2007).

More specifically, cerebrovascular lesions in VCI patients may affect transmission of action potentials in subcortical white matter bundles connecting the mentioned cerebral circuits (with an emphasis on those between thalamus and cerebral cortex), possibly inducing delays in that neurotransmission with the following sequential impact: (i) abnormal timing of synchronization and desynchronization of neural activity, (ii) prolonged and less effective temporal summation of post-synaptic potentials in cortical neural populations, and (iii) alteration in the time evolution of scalp-recorded EEG activity at several frequencies (Crunelli et al., 2015; Dey et al., 2016; Hughes and Crunelli, 2005; Gawel et al., 2007; Pfurtscheller and Lopes da Silva; 1999). As a result, such an abnormal (de)synchronization of cortical neural activity in VCI patients may explain the increase in the peak latencies of EPs and oddball ERPs (Mecklinger et al., 2006; van Harten et al., 2006), the event-related reduction in delta and theta responses reported in several studies in VCI patients (Xu et al., 2011; Wang et al., 2014), as well abnormal increase of rsEEG delta and theta rhythms and a decrease or slowing of alpha rhythms underpinning vigilance as a pillar for cognitive processes such as attention, executive functions, and others (Tsuno et al., 2004; Walker et al., 2000).

Based on *in-vivo* intracerebral EEG recordings and pharmacological manipulations in *in-vitro* electrophysiological recordings in rodent brain neurons, this derangement of neural synchronization

and connectivity may involve: (i) glutamatergic and cholinergic neurons, (ii) thalamocortical high-threshold, GABAergic interneurons, (iii) thalamocortical relay-mode, and (iv) cortical pyramidal neurons (Crunelli et al., 2015; Dey et al., 2016; Hughes and Crunelli, 2005; Gawel et al., 2007).

Of note, a previous study evaluated the changes of EEG in the vascular damage of the cholinergic system (Moretti et al., 2008) correlating the brain rhythmicity with the cerebrovascular damage of long-range (capsular tract) and short-range (medial and perisylvian tracts) cholinergic pathways in ninety-four patients with mild cognitive impairment. Results show different brain oscillations changes due to the cholinergic pathway involved. A significant increase of delta and theta power band was found in patients with the highest total cholinergic burden as well as in patients with highest capsular pathway damage; total load of cholinergic damage was also associated with decreased gamma power band. Alpha frequency was differentially affected: decrease of alpha3 power band was associated with the greatest damage of the capsular pathway whereas increase of alpha3 power band was associated with the greatest damage of the perisylvian pathway.

RECOMMENDATIONS

In this article, a multidisciplinary panel of experts reviewed the field literature and reached consensus about the EEG measures more consistently found as abnormal in VCI patients when compared to cognitively healthy persons. These measures were obtained in major VCI patients tested in two main experimental conditions. In the first experimental condition (i.e., eyes-closed resting state), participants had to maintain quiet vigilance for few minutes, while in the second experimental condition they had to respond to rare auditory target stimuli and ignore frequent auditory stimuli (auditory "oddball" paradigm), namely a cognitive task based on cognitive processes including conscious attention and short-term memory.

In the eyes-closed resting state condition, major VCI patients showed reduced amplitude of prominent alpha (8-12 Hz) rhythms in posterior regions and a widespread increase in the amplitude of delta (< 4 Hz) and theta (4-8 Hz) rhythms, associated with reduced interrelatedness of those rhythms at electrode pairs. These EEG measures of interest were able to classify major VCI and CU persons with a moderate discriminant accuracy > 80%. These EEG measures were those receiving the major number of converging experimental confirmations (Figure 3).

Please insert Figure 3 around here

In auditory "oddball" paradigms, major VCI patients showed delayed N2/P3b peak latencies during the detection of target stimuli (Figure 4).

Please insert Figure 4 around here

In the reviewed clinical trials, those EEG measure did not show specific relationships with cerebrovascular lesions in individual major VCI patients. Therefore, they ***should not be used for diagnostic purposes in VCI patients***. In the instrumental assessment of VCI patients, neuroimaging biomarkers may supply more direct and objective measurements of cerebrovascular lesions (Adamis et al., 2005; Smith, 2005).

The present multidisciplinary expert panel also reached consensus about the recommendations regarding the use of the EEG measures more consistently found as abnormal in major VCI patients.

For heuristic purposes, those measures may be used to better understand the relationships between (i) the etiology, localization, and extension of the cerebrovascular lesions in the brain and (ii) the topographical, frequency, and/or latency features of the EEG measures obtained in major VCI patients.

For future clinical trials, those measures may be ***tested as prognostic biomarkers*** and ***endpoints of pharmacological and non-pharmacological*** (e.g., noninvasive transcranial brain electric or magnetic stimulations) ***interventions*** targeting brain excitability. Indeed, taking equal the diagnosis of major VCI based on clinical and neuroimaging markers, major VCI patients with the greatest alterations of those EEG measures may present the fastest clinical decline over time. Furthermore, the major VCI patients with the smallest alterations of those EEG measures (then most preserved neurophysiological systems") may present the greatest beneficial effects of interventions targeting brain excitability.

The present multidisciplinary expert panel recommend international experimental initiatives aimed to (i) design and carry out further prospective cross-validation studies and (ii) cross-validate the proposed use of the EEG measures more consistently found as abnormal in major VCI patients at both group and individual levels. On the one hand, those studies at the group level may relate the EEG measures of interest to (i) qualified markers of cerebrovascular lesions derived from in-vivo neuroimaging and post-mortem neuropathology for heuristic purposes and (ii) the effect of ***interventions*** targeting brain excitability for clinical trials. On the other hand, those studies at the individual level may test prognostic value of the EEG measures of interest for clinical applications.

Those future studies in major VCI patients may also explore further paradigms used to investigate neurophysiological mechanisms underlying sensory, motor, and cognitive (e.g., executive) functions such as recordings of steady-state evoked potentials accompanying serial sensory stimulations, "expectancy" contingent negative variations, movement-related potentials and sensorimotor mu rhythms, and potentials related to go/no-go decision making (Schomer and Lopes da Silva, 2017).

A limitation of the mentioned EEG measures of interest is that they were validated by a relatively low number of multi-centers, prospective, and longitudinal studies performed in major VCI patients. Therefore, future studies are needed to qualify EEG measures of disease progression in major VCI patients. Good examples of international initiatives for this purpose are PharmaCog (www.pharmacog.org) and ENIGMA (www.enigma.ini.usc.edu). A notable example in the field of neuroimaging is Alzheimer's Disease Neuroimaging Initiative (ADNI, www.adni.loni.usc.edu).

The present multidisciplinary panel of experts recommend future investments on the following promising research lines.

Prospective population-based screening studies of EEG measures of interest in general aged people may be informed by genetics of VCI (O'Brien and Thomas, 2015; Schrijvers et al., 2012). Indeed, large-scale studies have established genetic vulnerability markers for VCI, for example the MTHFR vascular gene related to homocysteine metabolism. By screening prospective cohorts for genetic VCI liability, their resting state or oddball EEG measures of interest may be traced over long periods, the most sensitive of those EEG measures identified, and conversion into major VCI condition predicted for high genetic risk individuals. These investigations may be combined with large-scale genetic studies of the EEG parameters (Malone et al., 2014a, 2014b; Smit et al., 2018) and lifestyle/environment (UK Biobank) such as Cam-Can https://www.cam-can.org/). In those studies, a multimodal virtual brain bank may be updated over time (https://www.cam-can.org/index.php?content=strategy) and may inform how disease progression can be slowed.

Recent developments exploited EEG techniques for constraining generative brain network models that allow to infer the underlying neurophysiological processes in the healthy brain (Ritter et al.,2013, Becker et al.,2015, Schirner et al., 2019) and in diseases, i.e., utilization as mechanistic markers for diagnosis differentiation and disease trajectory prediction in encephalopathy (Symmonds et al., 2018) and different forms of dementing diseases (Solodkin et al., 2017; Stefanovski et al., 2019). The consortium Virtual Brain Cloud (https://tvb.virtualbraincloud-2020.eu/tvb-cloud-main.html) uses this brain network modeling approach in combination with data from several large-scale cohorts (including the above mentioned) to further exploit noninvasive imaging measures like rsEEG with respect to their potential for dementia risk assessment and differentiation based on the underlying causal neurobiological processes.

A THEORETICAL FRAMEWORK OF EEG MEASURES IN VCI PATIENTS

In the view of the present panel of experts, the potential role of EEG measures as biomarkers in major VCI patients may be inspired by seminal publications of the International Working Group for New Research Criteria for the Diagnosis of Alzheimer's Disease (IWG-2; Dubois et al., 2014)

and the Working Group of the National Institute on Aging - Alzheimer Association Research Framework (NIA-AA Research Framework, Jack et al., 2018).

On the one hand, the IWG-2 suggested two classes of biomarkers for the assessment of ADD (Dubois et al., 2014), namely the ***"diagnostic"*** biomarkers (i.e., those measuring the pathophysiological hallmarks of the disease such as the cerebral amyloidosis and the amount of total or phospho-tau in the cerebrospinal fluid or directly within the brain by PET) and the ***"progression or topographical"*** biomarkers (i.e., those measuring progression of region-specific neurodegeneration with characteristic "AD-signatures", such as FDG-PET and structural MRI). Furthermore, other promising candidates as progression biomarkers are currently under evaluation (i.e., diffusion tensor imaging and resting-state functional MRI).

On the other hand, the Working Group of the NIA-AA Research Framework (Jack et al., 2018) suggested: (i) ***"diagnostic Alzheimer's disease"*** biomarkers measuring cerebral amyloidosis (i.e., "A" biomarkers) and phospho-tau (i.e., "T" biomarkers) by CSF or PET techniques and (ii) **"*neurodegenerative/progression"*** biomarkers (i.e., "N" biomarkers) measuring total tau by CSF sampling, FDG-PET hypometabolism, and structural MRI markers of brain atrophy.

Keeping in mind the above theoretical qualification of AD biomarkers, the present panel of experts posits the introduction of another class of biomarkers in the instrumental assessment of major VCI patients. These biomarkers may probe the brain vulnerability or resilience of ***subcortical and thalamocortical neural (de)synchronization mechanisms*** in relation to primary cerebrovascular lesions. These biomarkers would be represented by the rsEEG, EPs, and auditory oddball measures (time and frequency domains) consistently found as abnormal in major VCI patients in independent scientific studies, reviewed in the present article.

Keeping in mind the ***"neurophysiological"*** meaning of the mentioned EEG biomarkers, the term **"*neural synchronization" biomarker*** may be used in the instrumental assessment of major VCI patients. These biomarkers would complement the standard neuroimaging and sonographic ***"diagnostic"*** and ***"topographical"*** biomarkers of primary vascular pathology (e.g., reactivity of the cerebral vasculature, O2-uptake capacity) and the routine assessment of clinical manifestations of the disease (Adamis et al., 2005; Smith, 2005).

The present panel of experts posits that even with intrinsic low-moderate spatial resolution, those "neural synchronization" EEG biomarkers may significantly enrich the assessment of major VCI patients measuring an abnormal functional neural synchronization and connectivity in the brain regions affected by vascular neuropathology (Babiloni et al., 2008a, 2008b; Leuchter et al., 1992; Szelies et al., 1994; van Straaten et al., 2012, 2015).

Such a conceptual expansion of the biomarker panel for major VCI patients would be aligned with the effort to accomplish a systems-level integration of pathophysiological dynamics, from molecular pathways up to the downstream effect on large-scale brain networks, across a clinical continuum from resilience to functional failure and symptoms. Therefore, multimodal biomarkers for multidimensional information – including the EEG measures of interest recommended in the present article– could be integrated to identify clusters of major VCI patients sharing biological and neurophysiological features for precision medicine-oriented diagnostic and therapeutic approaches (Hampel et al., 2019a, b).

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Conflicts of interest

No relevant conflict of interest for the co-Authors in the present article.

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TABLE LEGENDS

Table 1. Most relevant studies using resting state electroencephalographic (rsEEG) measures in patients with vascular contribution to cognitive impairment and dementia (VCI).

Table 2. Most relevant studies using evoked potentials (EPs) and event-related potentials (ERPs) analyzed in time domain and derived measures of event-related EEG analyzed in frequency domain in patients with vascular contribution to cognitive impairment and dementia (VCI).

FIGURE LEGENDS

Figure 1. The vascular cognitive impairment subtypes according to the Vascular Impairment of Cognition Classification Consensus Study (VICCCS-2) (changed from Skrobot et al., 2018). Abbreviations = VCI: vascular cognitive impairment or vascular contribution to cognitive impairment and dementia; VaMCI: vascular mild cognitive impairment; VaD: vascular dementia; AD: Alzheimer's disease; DLB: dementia of Lewy bodies.

Figure 2. Flow diagram of study selection followed in the review process. Abbreviations = VCI: vascular contribution to cognitive impairment and dementia; EEG: electroencephalography.

Figure 3. An example of the decomposition of resting state eyes-closed (spontaneous) electroencephalographic (rsEEG) rhythms typically observed at delta (< 4 Hz), theta (4-7 Hz), alpha (8-12 Hz), and beta (13-30 Hz) frequencies in cognitively unimpaired adults. The illustrated rsEEG rhythms are produced by a digital filtering based on fast Fourier transform (FFT) of the recorded rsEEG activity. In these rsEEG rhythms, the dominant component is observed at alpha frequencies and posterior scalp areas, as a reflection of a widespread pattern of cortical neural inhibition due to the lack of significant visual, visuospatial, and somatomotor information processing. Indeed, resting state condition is characterized by a quiet and relaxed wakefulness in a subject at eyes closed kept in a silent environment. It is speculated that rsEEG rhythms may be generated at the cortical level as a reflection of neurophysiological oscillatory mechanisms of brain neural synchronization involving reticular ascending activating systems, reciprocal thalamocortical-corticothalamic, and cortico-cortical systems. It is also speculated that in VCI patients, there are delays in neural transmission and abnormalities in functional connectivity in those systems. These abnormalities may induce a decrease in dominant alpha rhythms in posterior scalp areas and an increase in widespread delta and theta rhythms in VCI patients resting in quiet wakefulness.

Figure 4. An example of auditory oddball event-related potentials (ERPs) typically observed in cognitively unimpaired adults. The illustrated oddball ERPs are produced averaging artifact-free EEG epochs related to auditory target stimuli followed by subject's counting or hand motor responses. Those target stimuli (20% of probability to occur) are intermingled with frequent auditory stimuli to be ignored (80% of probability to occur). Normally, hundreds of auditory stimuli are delivered in this oddball paradigm, to enhance the signal-to-noise ERP responses. In these averaged ERPs, dominant components are negative ERPs peaking at about 200 ms after the target stimulus onset (N200). Afterward, there is a late positive component peaking at about 300 ms after the target stimulus onset (P300). It is speculated that rsEEG rhythms may be generated at the cortical level as a reflection of neurophysiological oscillatory mechanisms of brain neural synchronization involving reticular ascending activating systems and, mainly, thalamocortical and cortico-cortical systems. It is also speculated that in VCI patients, there are a variable delay stimulus-by-stimulus in neural transmission and abnormalities in those neural circuits, especially thalamocortical and cortico-cortical ones. In VCI patients, these abnormalities may induce a delay in the latency of N200 and P300 peaks.

Table 1

EEG feature	Sample comparisons	EEG biomarkers	Main findings	Related references
Synchronization	VCI (MID/SIVD) vs age-matched controls	Alpha frequency Delta, theta, alpha, beta, gamma power Delta and theta sources	Slowing of alpha frequency Decrease in alpha, beta and gamma power Widespread increase in theta and delta power Decreased alpha amplitude ratio between eyes closed/eyes open	D'Onofrio et al. (1996); Erkinjuntti et al. (1988); Holschneider and Leuchter, (1995); Martín-Loeches et al. (1991); Moretti et al. (2004, 2012); Neto et al. (2015); Muresanu et al (2008, 2010); Partanen et al. (1997); Saletu et al. (1991, 1992, 1995); Signorino et al. (1995, 1996); Sheorajpanday et al. (2013); Sloan et al. (1994); Szelies et al. (1999); van Straaten et al. (2012); Wu et al. (2014)
	VCI (MID/SIVD) or VaMCI vs ADD	Alpha frequency Delta, theta, alpha and beta power Theta sources	Slowing of alpha frequency and higher EEG mean frequency Higher theta (eyes closed) and alpha 2 power Lower delta and theta (eyes open) power Less beta activity Increased in power asymmetry in delta/theta Widespread increase in theta power Higher alpha/delta plus theta power Higher ratio occipital/frontal alpha power Higher (delta + theta)/ (alpha +beta) ratio	Babiloni et al. (2004a); Gawel et al. (2007, 2009); Martin-Loeches et al. (1991); Moretti et al., (2004); Saletu et al. (1991, 1992); Sheorajpanday et al. (2014); Szelies et al. (1994)
Complexity	VCI, vs ADD and age-matched controls	EEG dynamics complexity	Increase of complexity of brain dynamics Decreased global Ω complexity (vs controls)	Jeong et al. (2001); Kim et al. (2000)
Connectivity	VCI (MID) vs ADD and age-matched controls	Alpha connectivity (SL), coherence, directed phase lag, gamma connectivity	Decrease in coherence in Rolandic areas Higher fronto-parietal SL in alpha 1 band Reduction of anterior to posterior phase gradients in theta, alpha, and beta bands Decreased gamma-band connectivity (vs controls)	Dunkin et al. (1994); Babiloni et al. (2004b); Leuchter et al. (1987, 1992, 1994a); Lv et al. (2020); van Straaten et al. (2015)

Table 2

EEG feature	Sample comparisons	EEG biomarkers	Main findings	Related references
EP/ERP synchronization	VCI (MID/SIVD/VaMCI) vs age-matched controls	P300 latency/amplitude	Latency prolongation of P300, N200 and or MMN	Chen et al. (1997); Hanafusa et et al. (1991); Ito (1994); Jiang et al. (2013, 2014); Jiang et al. (2017); Kato et al. (1990); Kedhr et al. (2009); Muscoso et al. (2006); Neshige et al. (1988); Podemski et al. (2008); Sloan et al. (1994); Tachibana et al. (1989); van Harten et al. (2006); Xu et al. (2012); Yamaguchi et al. (2000)
		N200 latency	Amplitude reduction of P300 and MMN	
		MMN amplitude and latency	Latency prolongation of N140 and P200 components of SERPs	
		Sensory SEP/ERP latencies	Latency prolongation of CCT (N20-N13), and N20 component of SSEP	
			Latency prolongation N13-N30 and N20-P40 of auditory SEPs	
			Latency prolongation of waves I and V of BAEPs	
	VCI (MID/SIVD) vs ADD	P3a latency/amplitude	Latency prolongation of P3a	Rosengarten et al. (2007); Yamaguchi et al. (2000)
		SEPs amplitude	Amplitude reduction of P3a	
			Amplitude reduction of N75 and P100	
ERP complexity	VCI vs age-matched controls and young controls	ERP dynamics complexity	More complex ERP waveforms and higher approximate entropy	Xu et al. (2012)

Figure 1

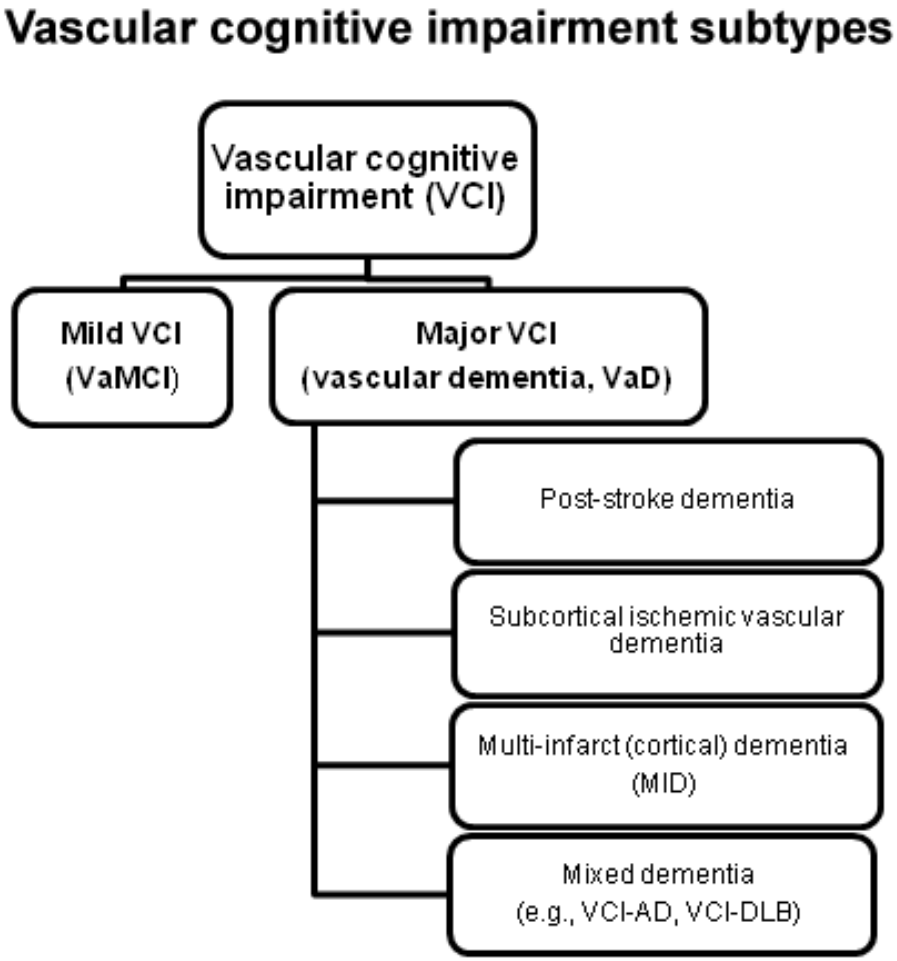

Vascular cognitive impairment subtypes
Vascular cognitive impairment (VCI)
Mild VCI (VaMCI)
Major VCI (vascular dementia, VaD)
Post-stroke dementia
Subcortical ischemic vascular dementia
Multi-infarct (cortical) dementia (MID)
Mixed dementia (e.g., VCI-AD, VCI-DLB)

Figure 2

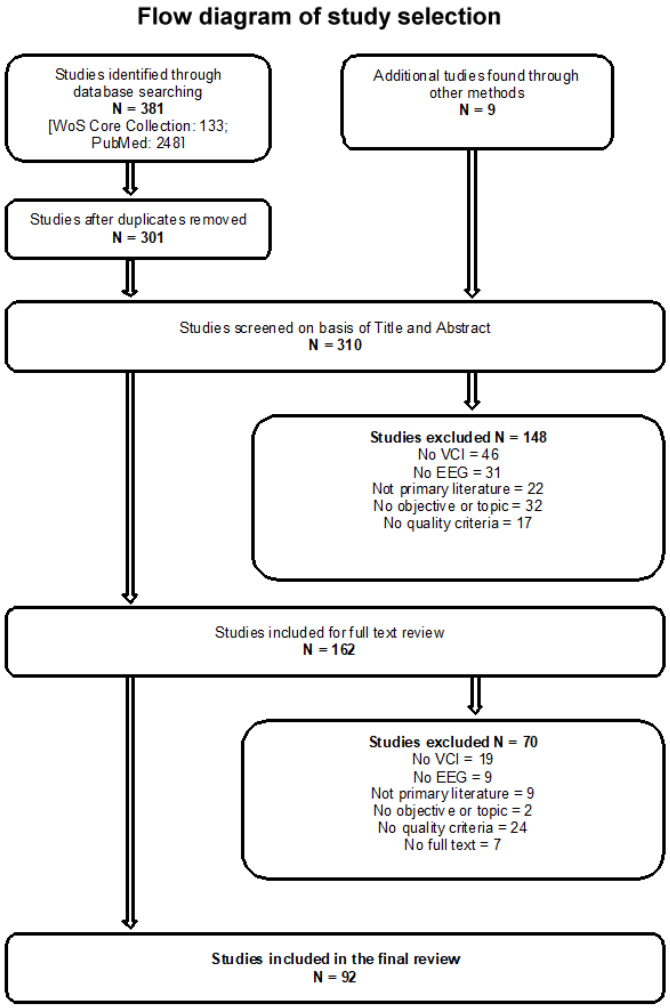

Flow diagram of study selection
Studies identified through database searching
N = 381
[WoS Core Collection: 133; PubMed: 248]
Additional tudies found through other methods
N = 9
Studies after duplicates removed
N = 301
Studies screened on basis of Title and Abstract
N = 310
Studies excluded N = 148
No VCI = 46
No EEG = 31
Not primary literature = 22
No objective or topic = 32
No quality criteria = 17
Studies included for full text review
N = 162
Studies excluded N = 70
No VCI = 19
No EEG = 9
Not primary literature = 9
No objective or topic = 2
No quality criteria = 24
No full text = 7
Studies included in the final review
N = 92

Figure 3

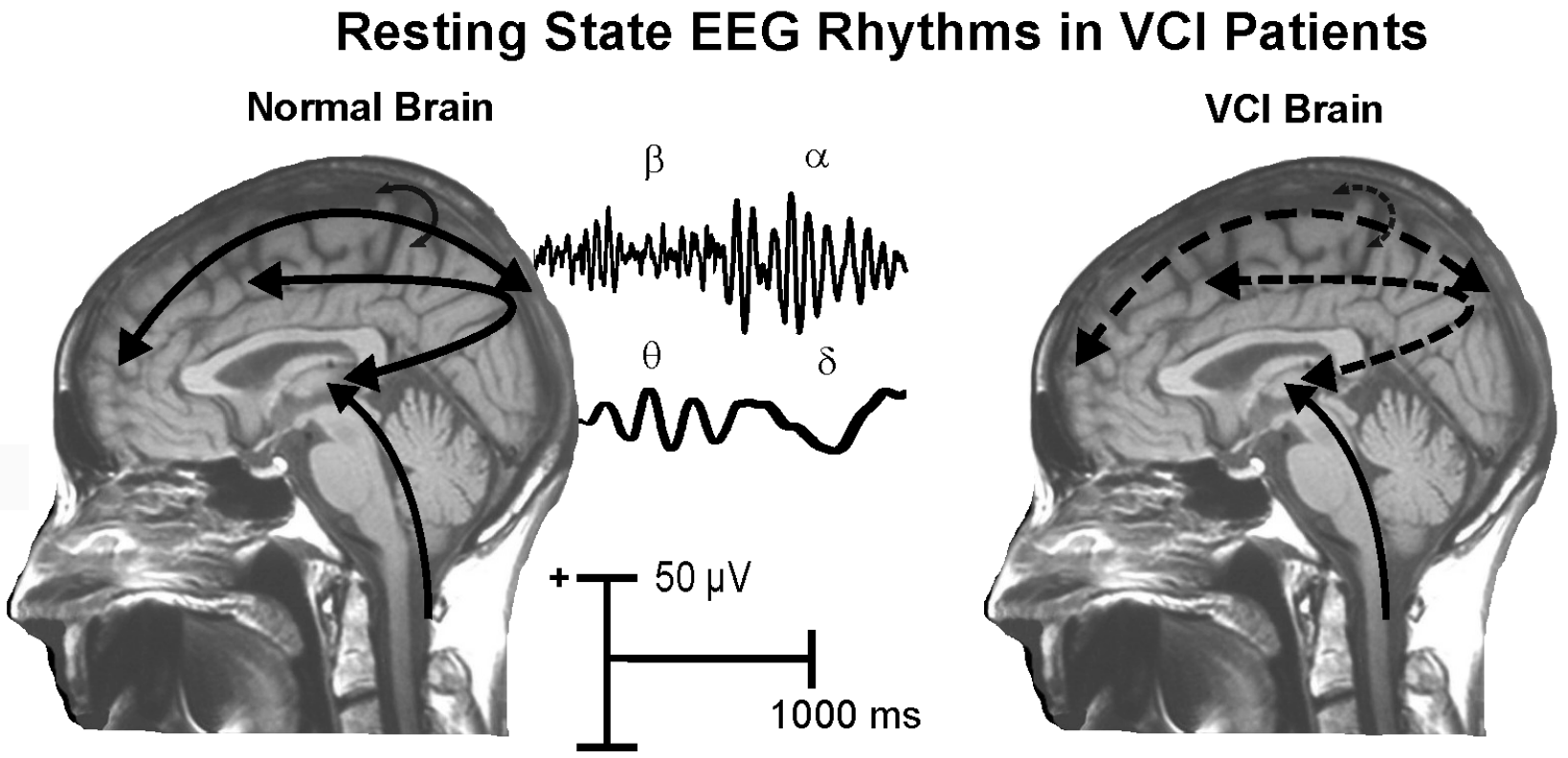
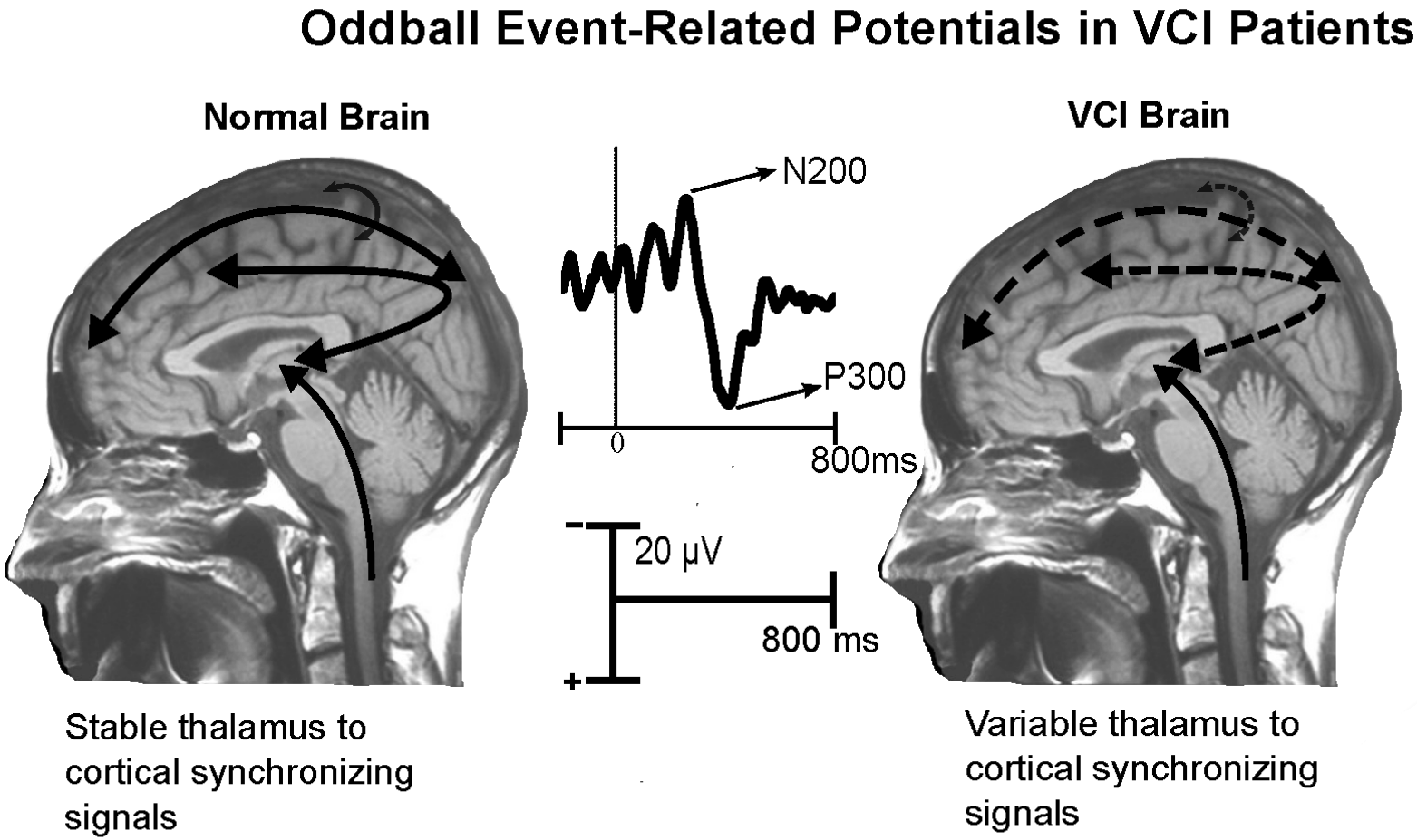

Resting State EEG Rhythms in VCI Patients
Normal Brain
VCI Brain
β
α
θ
δ
+
50 µV
1000 ms
Alpha dominant
thalamocortico-corticothalamic
synchronizing signals
Delta-Theta dominant
thalamocortico-corticothalamic
synchronizing signals

Figure 4


Oddball Event-Related Potentials in VCI Patients
Normal Brain
VCI Brain
N200
P300
0
800ms
20 µV
800 ms
–
+
Stable thalamus to cortical synchronizing signals
Variable thalamus to cortical synchronizing signals