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VASCULAR DEMENTIA: FROM CLINICAL TO BIOCHEMICAL AND NEUROPHYSIOLOGICAL MARKERS

Tesi di Dottorato

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To my son and to my father

ACRONYMS AND ABBREVIATIONS

AD: ALZHEIMER'S DISEASE

CADASIL: CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY'

CSP: CONTRALATERAL SILENT PERIOD

EMG: ELECTROMYOGRAPHIC

GABA: GAMMA AMINO-BUTYRIC ACID

ICF: INTRACORTICAL FACILITATION

ISI: INTER STIMULUS INTERVAL

ISP: IPSILATERAL SILENT PERIOD

M1: PRIMARY MOTOR CORTEX

MEP: MOTOR EVOKED POTENTIAL

NMDA: N-Methyl-D-aspartate

rMT: RESTING MOTOR THRESHOLD

SAI: SHORT-LATENCY AFFERENT INHIBITION

SICI: SHORT-INTERVAL INTRACORTICAL INHIBITION

SIVD: SUBCORTICAL ISCHEMIC VASCULAR DEMENTIA

TMS: TRANSCRANIAL MAGNETIC STIMULATION

VaD: VASCULAR DEMENTIA

VCI-ND: VASCULAR COGNITIVE IMPAIRMENT-NO DEMENTIA

WMLs: WHITE MATTER LESIONS

ABSTRACT

BACKGROUND: Vascular Dementia can be considered the second most common cause of dementia after Alzheimer's disease. However, unlike the degenerative dementias, it's possible to carry out preventive strategies. Recently, neurophysiological techniques and in particular transcranial magnetic stimulation have been tested in patients with dementia in order to pick up early cerebral functional changes. The present research aimed to investigate cortical excitability in non-demented elderly patients with leukoaraiosis

METHODS: Motor cortex excitability, transcallosal inhibition, intracortical inhibition and facilitation and central cholinergic function were evaluated in patients with a vascular cognitive impairment-no dementia.

RESULTS: No differences were found for measures of motor cortex excitability and transcallosal inhibition between patients and controls. A significant enhancement of intracortical facilitation was observed in patients. Moreover central cholinergic circuits seem to be spared in patients.

DISCUSSION AND CONCLUSION: This study provides the first evidence of functional changes in intracortical excitatory neuronal circuits in patients with vascular cognitive impairment-no dementia. Central cholinergic functioning seems to be spared in these patients. This functional integrity differs from that reported in patients with Alzheimer's disease or mild cognitive impairment, underlying the distinctive involvement of the cholinergic pathway in degenerative dementia and vascular form, even in their early or preclinical stage.

Key words: Brain stimulation, Cognitive impairment, Cortical excitability, Motor dysfunction, Intracortical circuitry

INTRODUCTION

Dementias and other neurodegenerative disorders that affect memory, cognition and behavior are a public health priority across the developed world (European Parliament resolution on a European initiative on Alzheimer's disease and other dementias[1]). With an aging population, it has been estimated that the number of people with dementia will double every 20 years (Sosa-Ortiz *et al.*, 2012). The impact of dementias on health, quality of life, autonomy and dignity of people with the condition are well recognized (Mioshi & Hodges, 2009; Arrighi *et al.*, 2010; Leroi *et al.*, 2012). Increasingly, national and international agencies are taking into account the potential consequences of the increase of these diseases for the financial sustainability of health and social protection systems[2], (Dorsey *et al.*, 2013).

The most pressing challenge is the difficulty in discriminating the different forms of dementia and of recognizing the earliest stages from normal brain aging.

So far, the exact mechanism that leads to dementia or to the maintenance of the integrity of cognitive function are not well understood, although it has been proposed the existence of endogenous compensatory mechanisms, both at a cellular level and at the level of neuronal networks (Park & Reuter-Lorenz, 2009).

Today the diagnosis of dementia, whether at a late or early stage, is mostly based upon the clinical evaluation of the subject. The need for screening and early diagnosis tools have focused the search to identify precocious biological and instrumental markers of each dementing illness. Moreover, unlike the degenerative dementias, in the case of Vascular Dementia (VaD) is possible to carry out a preventive strategy with a closer and more accurate control of vascular risk factors. The identification of patients in an early stage of dementia, with the use of specific

[1] http://www.europarl.europa.eu/sides/getDoc.do?type=TA&language=EN&reference=P7-TA-2011-0016

[2] http://www.consilium.europa.eu/ueDocs/cms_Data/docs/pressData/en/lsa/104778.pdf

clinical and biological markers, is advocated in an attempt to prevent the progression of vascular-related cognitive impairment into a picture of overt dementia.

Immunocytochemistry and electron microscopy unveiled the involvement of the different neuronal populations and neurotransmitters in the genesis of dementia (Jellinger, 2012; Taipa *et al.*, 2012; Weiner, 2013).

Van der Flier and Scheltens have produced an overview on the different diagnostic strategies in dementia. They took into consideration several diagnostic aids including the contribution of electroencephalography, but did not consider other neurophysiological tests (Van der Flier & Scheltens, 2005). Indeed, neurophysiological techniques, especially Transcranial Magnetic Stimulation (TMS), have emerged as valuable tools for the functional evaluation of cerebral cortex in those patients. Since its introduction, nearly 30 years ago (Barker *et al.*, 1985), TMS has increasingly been used to provide novel insights into the pathophysiology of the neural circuitry that underlies several neurological and psychiatric diseases.

With this assumption, VaD and the relatively recent concept of Vascular Cognitive Impairment-No Dementia (VCI-ND), as well as the most relevant TMS measures are discussed below. Finally, motor cortex excitability and cholinergic circuitry functioning are evaluated in VCI-ND patients.

Capitolo 1
VASCULAR COGNITIVE IMPAIRMENT-NO DEMENTIA AND VASCULAR DEMENTIA: A PREDICTABLE CONTINUUM?

Despite the large phenotypic and pathogenetic variability that has resulted in a lack of consensus on its diagnostic criteria (Román *et al.*, 2002), VaD can be considered as the second most common cause of dementia after AD.

VaD results from ischaemic, hypoperfusive, or hemorrhagic brain lesions that are manifest as numerous clinical syndromes as indicated in Table 1.

To characterize VaD, criteria of State of California Alzheimer's Disease Diagnostic and Treatment Centers and the National Institute for Neurological Disorders and Stroke-Association Internationale pour la Recherche et I'Enseignement en Neurosciences are commonly used (Román *et al.*, 1993)

The Subcortical Ischemic Vascular Dementia (SIVD) related to small-artery disease and hypoperfusion, has attracted increased attention, both for its wide prevalence (as it is the most common form of VaD) and for its substantial clinical, radiological and pathophysiological homogeneity.

1.1 **Subcortical ischaemic vascular dementia**

1.1.1 *Definition*

SIVD is a small-vessel dementia because changes in cerebral microcirculation have a central role in its pathogenesis (Pantoni & Garcia, 1995; Román *et al.*, 2002).

In fact two main pathophysiological pathways are involved: the occlusion of the arteriolar lumen due to arteriolosclerosis that leads to the formation of lacunes, resulting in the *état lacunaire* and the incomplete infarction of deep white matter with a clinical picture of Binswanger's disease.

1.1.2 *Epidemiology*

The risk factors for VaD are the same for stroke. The risk factors for stroke can be divided into: non-modifiable (e.g. age, sex, genetic factors, etc.) and modifiable (e.g. hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking, obesity, etc.). Hypertension has been shown to be the most common modifiable risk factor for stroke. A history of stroke leads to a twofold increase in the risk of dementia in the population older than 65 years.

Whereas the link between hypertension and VaD, through the well-established relationship between hypertension and stroke, may seem self-evident, it is often overlooked that in many cases of VaD there is no clear history of stroke. To be more precise, cortical stroke, which is often symptomatic and therefore more easily recognized, is not the most prevalent cause of VaD. VaD is most often caused by lacunar infarcts (e.g., multi-infarct dementia) or severe white matter disease, both related to small vessel disease, and these are frequently clinically unrecognized as acute stroke.

In clinical studies, the proportion of VaD caused by small-vessel disease ranges from 36% to 67% (Chui, 2001). In the population-based Cardiovascular Health Study, about a quarter of 3660 participants aged 65 or older had one or more lacunes on magnetic resonance imaging (MRI). Most lacunes (89%) were clinically silent or were manifest as gait problems and subtle cognitive impairments that were not recognised as stroke (Longstreth *et al.*, 1998). White matter lesions (WMLs) may be observed in young subjects, but their prevalence increases sharply with age, occurring in at least 70% of individuals over the age of 70 years (O'Brien *et al.*, 2003). Although they may be present in older individuals with normal cognitive function, the WMLs are of crucial clinical relevance as they are linked to cognitive decline (de Groot *et al.*, 2001). In addition, the non-cognitive consequences such as depression, apathy, gait disturbances and urinary disorders are frequent and persistent and reduce the quality of life (Bella *et al.*, 2010). Depending on the location of these vascular lesions, their extent, and the patient's cognitive reserve, these silent lesions can, however, have sufficient impact to cause VCI or VaD.

1.1.3 *Neuropathology*

Dementia is caused by the ischaemic injury, which includes both complete infarction (lacunar infarcts and microinfarcts) and incomplete infarction of deep cerebral white matter. Lacunar infarcts or lacunes are small cavitated ischaemic infarcts of less than 15 mm in diameter. They are typically located in the basal ganglia, internal capsule, thalamus, pons, corona radiata, and centrum semiovale. White-matter lacunes can overlap with non-confluent areas of ischaemic white-matter changes. Microinfarcts are mostly noncavitated and are found in cortical and subcortical structures. Their size can range from a few microns to about one-tenth of the size of lacunes. Pathological features of white-matter lesions in Binswanger's disease include: diffuse myelin pallor (that spares U fibres, astrocytic gliosis, widening of perivascular spaces (état crible)., and lacunes in the basal ganglia and pons; loss of oligodendrocytes leading to rarefaction, spongiosis (vacuolisation), and loss of myelin and axons without definite necrosis (incomplete white-matter infarction), which finally culminates in white-matter necrosis and lacunes.

SIVD incorporates the two old neuropathological and clinical conditions, the lacunar state (état lacunaire) and Binswanger's disease.

In addition to lengthening and tortuosity, the lumen of medullary arterioles in elderly individuals is progressively reduced due to arteriolosclerosis. The cause of this senile arteriolosclerosis remains unknown. It begins late in the fourth decade of life, increases in severity with age, is more prominent in the frontal lobe, and is followed by arteriolosclerosis in the parietal, occipital, and temporal lobes. The severity of WMLs in patients with Binswanger's disease increases in direct proportion to the degree of stenosis due to arteriolosclerosis of medullary arterioles.

Subependymal lesions in the immediate vicinity of the ventricles correspond to decreased myelin, loss ependymal cells, reactive gliosis, and increased extracellular fluid. Lacunes result from occlusion of lenticulostriate, thalamoperforating, and long medullary arterioles and must be distinguished from dilated perivascular spaces.
SIVD is commonly associated with cortical hypometabolism and hypoperfusion, which result in cortical and hippocampal atrophy.

1.1.4 *Pathophysiology of ischaemic brain injury*

Numerous pathophysiological mechanisms involving the microcirculation are related to the genesis of SIVD such as haemorheological factors, increased resistance to flow, decreased autoregulation, endothelial changes, dysfunction of the blood–brain barrier and dilatation of perivascular spaces. Their combined effects result in hypoperfusion and incomplete infarction of deep white matter.

Damage to the blood–brain barrier and chronic leakage of fluid and macromolecules, particularly in hypertensive patients, could contribute to white-matter injury. Increased concentrations of CSF proteins were found in individuals with white-matter lesions detected by brain imaging and in brains from patients with Binswanger's disease at autopsy. Increased concentrations of proteases, complement, immunoglobulins, and inflammatory cytokines may also contribute to glial and axonal damage (Román *et al.*, 2002).

1.1.5 *Coexistence of Degenerative and Vascular Changes in SIVD*

Dementia in SIVD correlates with hippocampal and cortical atrophy. Hippocampal atrophy may result from a mixture of ischemic and degenerative pathologies. The cause of diffuse cortical atrophy is not known, but may be partially indexed by the severity of white matter hyperintensities (Fein *et al.*, 2000)

1.1.6 *Clinical features*

The clinical features of SIVD include motor and cognitive slowing, memory impairment, mood changes and urinary symptoms. Dysarthria and pseudobulbar palsy may be also be present. Gait disturbance in SIVD has been traditionally classed as "marche à petits pas"—a short-stepped, wide-based, apraxic gait with a tendency to fall. In clinical practice, however, most patients with SIVD present with a gradual course punctuated by acute deficits leaving residual subtle focal signs (arm drift, central facial weakness, and reflex asymmetry) as well as parkinsonian signs, small-step gait, unsteadiness, or unilateral incoordination.

Loss of executive function is the major component of cognitive disability and dementia, due to the loss of planning capacity, working memory, attention, concentration, stimuli discrimination, abstraction, conceptual flexibility, and self-

control. Some patients are unable to initiate the required behaviour, whereas others fail to inhibit irrelevant behaviours. Memory disturbances are less severe than in AD, and mainly include forgetfulness and problems with spontaneous recall that improve with cues and prompting. Language, calculation ability, and other higher cortical functions are preserved. Intact recognition and verbal fluency separate SIVD from Alzheimer's disease (AD). Personality and mood disorders include apathy, irritability, and so-called vascular depression (Bella *et al.*, 2010).

As the disease progresses, patients with SIVD limit their field of interest, show emotional instability, attentional loss, decreased ability to make associations, and difficulties in shifting from one idea to another, resulting in perseveration.

These manifestations probably result from ischemic interruption of parallel circuits from the prefrontal cortex to the basal ganglia and corresponding thalamo-cortical connections, circuits known to be involved in executive control of working memory, planning, language, mood, attention, constructional skills, motivation, and socially responsive behaviours Interruption of the dorsolateral prefrontal-subcortical loop results in executive dysfunction; orbitofrontal-subcortical circuit lesions preclude frontal inhibition of the limbic system and are manifested by uninhibited behaviours, impulsivity, and personality change. The anterior cingulate (medial frontal) cortex mediates motivation, thus lesions of this circuit commonly result in apathy, abulia, and even akinetic mutism (Bonelli & Cummings, 2007).

The clinical picture of acute single-strategic lacunar dementia is characterised by the abrupt onset of cognitive impairment. This impairment is in many cases associated with confusion, apathy, psychomotor retardation, inattention, abulia, and other features of frontal-lobe dysfunction but with mild focal findings (eg, hemiparesis, central facial weakness, or dysarthria). This clinical picture is in most cases the result of lacunar strokes involving the inferior genu of the internal capsule, thalamus,or caudate nucleus (Román *et al.*, 2002).

1.1.7 *Neuropsychological assessment*

The commonly used bedside tests for dementia screening overlook executive dysfunction whereas the use of appropriate tests, indicates that frontal system involvement predominates in cerebrovascular cognitive disorders. In this line, the

Montreal Cognitive Assessment (MoCA) has revealed to be a valuable screening test sensitive to the milder forms of cognitive impairment that often accompany cerebrovascular disease (Koski, 2013).

1.1.8 *Imaging*

Brain imaging is crucial as a confirmatory test for SIVD since silent lesions commonly occur. A diagnosis of VaD can rarely be reached in the absence of vascular lesions (stroke, lacunes, and white-matter changes) as shown on brain imaging. Lacunar infarcts and white-matter lesions can be detected by computed tomography (CT) and MRI of the brain. WMLs are seen as bilaterally symmetrical areas of hypodensity on CT and as hyperintensities in the periventricular or deep subcortical white matter on FLAIR or T2-weighted MRI. MRI has higher sensitivity than CT for the detection of white-matter lesions. Lacunar infarcts are seen as round or oval cavitated lesions with a diameter less than 15 mm. In radiological studies, a limit of 3–20 mm is generally used, although the size of a radiologically detected lacunar infarct is slightly larger than that found at autopsy. In the chronic stage, lacunar infarcts are hypodense on CT scans, hyperintense on FLAIR or T2-weighted MRI, and hyperintense relative to CSF on proton-density MRI.

Most of the CSF-isointense lesions on proton-density MRI at the level of anterior commissural or inferior putamen are perivascular spaces or état criblé. Lesions smaller than 1-2 mm are more likely to be enlarged perivascular spaces than infarcts.

1.2 **The Vascular Cognitive Impairment continuum**

Currently, the definition of “dementia” requires an overt impairment of memory functions, implying that the patient is identified only after a substantial damage of cognitive functios has occurred. With this approach, it is not possible to identify cases in the early stage for a possible therapeutic intervention. For this reason, Hachinski and Bowler have introduced the term of Vascular Cognitive Impairment (VCI) to identify the continuum of patients with cognitive impairment following a stroke, from those at high risk, but without a clear cognitive decline (the stage of "brain at risk") up to the severe dementia (Hachinski & Bowler, 1993).

Vascular cognitive impairment (VCI) is a heterogeneous group of cognitive disorders that share a presumed vascular cause and a specific cognitive profile in which memory is preserved and executive function impaired (Hachinski & Bowler, 1993). VaD can be considered as the most severe form of VCI.

The broad concept of VCI has been revisited (Ingles *et al.*, 2002) (Hachinski *et al.*, 2006) because subcortical cerebrovascular disease may be frequently associated with mild cognitive impairment, not yet defined as dementia. This clinical condition is indicated by the acronym VCI-ND (vascular cognitive impairment-no dementia) and it is characterized by the loss of some cognitive functions without, however, a substantial decline of the functional autonomy and evidence of a overt dementia (Román *et al.*, 2004; Moorhouse & Rockwood, 2008).

1.2.1 *Epidemiology*

VCI can be deemed the most common form of cognitive impairment (Román *et al.*, 2004). In the Canadian Study of Health and Aging, the VCI-ND was the subtype of VCI with the highest prevalence among the population aged ≥ 65 years (Rockwood *et al.*, 2000).

1.2.2 *Pathophysiology*

The pathophysiology of VCI continues to be investigated. A mechanistic approach separates VCI associated with large vessel disease from that associated with small vessel disease, including subcortical ischaemic vascular disease, and non-infarct ischaemic changes. Although cognitive impairment due to large vessel disease is clinically important, it is seldom found in isolation. In older patients, small vessel disease (overt or covert) is ubiquitous and can accelerate the clinical progression of AD. Small vessel disease includes leukoaraiosis, subcortical infarcts, and incomplete infarction associated with cognitive impairment, and might be the most common cause of VCI (Román *et al.*, 2002). Not all the neuropathology in VCI involves frank infarction but is more probably a continuum of processes related to ischaemia. Non-infarct ischaemia is accepted as an integral part of the disease process that affects both presentation and outcomes.

1.2.3 *Coexistence of Degenerative and Vascular Changes*

Degenerative and vascular mechanisms may coexist at the pathological level in patients with cognitive impairment, particularly in older age. Patients with SVD have various degrees of brain atrophy. It is uncertain whether this reflects the aging process, the concomitant presence of a degenerative mechanism, or is related to subcortical vascular changes. A significant synergistic interaction was found between WMLs and atrophy measures in overall cognitive performance across time and the rate of cognitive decline. A synergistic effect was also observed between baseline lacunar infarcts and all measures of atrophy on change in psychomotor speed. (Jokinen *et al.*, 2012b). Moreover, in SVD patients, there was a significant association between brain volume and executive function (Nitkunan *et al.*, 2011).

1.2.4 *Diagnosis*

VCI is a clinical diagnosis. The harmonisation standards recommend a detailed account of the cognitive complaint that includes an account by the patient or informant of cognitive domains such as memory, speed of thinking or acting, mood, and function. Information about vascular risk factors, such as hypertension, hyperlipidaemia, diabetes mellitus, alcohol or tobacco use, and physical activity, should be sought. History taking should also include checks for cardiovascular disease, transient ischaemic attacks or strokes, and endarterectomy, hypercoagulable states, migraine, and depression (Hachinski *et al.*, 2006).

Physical examination should include blood pressure, pulse, body mass index, waist circumference, and examination of the cardiovascular system for evidence of arrhythmias or peripheral vascular disease. Neurological examination should note focal neurological signs and assess gait initiation and speed.

1.2.5 *Neuropsychological assessment*

The pattern of cognitive deficits in patients with VCI varies considerably. Single strategic infarcts can lead to specific cognitive profiles, whereas subcortical lesions are often associated with abnormalities of information processing speed, executive function, and emotional lability.

Standard cognitive assessments, such as the Mini Mental State Examination (MMSE), are insensitive to these abnormalities. In patients with VCI, diffusion tensor imaging-measured white matter microstructural damage is more related to MoCA than MMSE performances. MoCA is suited for the cognitive screening of patients with small vessel disease (Pasi *et al.*, 2014).

1.2.6 *Imaging*

Neuroimaging studies require a clinical correlation in the assessment of people with memory complaints; however, VCI shows no pathognomonic neuroimaging features. Infarct location often does not correlate with the cognitive profile, and neuroimaging cannot reliably confirm the chronology of lesions and cannot inform the relative contribution of neurodegenerative versus ischaemic processes to the clinical presentation. For a diagnosis of probable VaD, the NINDS‐AIREN and the California criteria require evidence of cerebrovascular disease seen with neuroimaging and that infarcts and leukoaraiosis fit specific criteria with regard to their location and the amount of white matter affected. These criteria have proved to be insensitive in practice, however, which makes their use problematic for the routine clinical diagnosis of VC. Increasing recognition of the importance of incomplete infarction and hypoperfusion inform the understanding that VCI might be present in the absence of neuroimaging abnormalities. Patients with VCI who do not have lesions on neuroimaging can have a particularly poor prognosis (Rockwood *et al.*, 2007).

Although CT is widely available, and in many parts of the world is a pragmatic choice for patients, it is less sensitive than MRI. Newer MRI-based neuroimaging techniques continue to advance our knowledge of the pathophysiology of VCI. The results of diffusion tensor MRI studies have enhanced our understanding of lesion location in relation to clinical presentation, and suggest that such white matter changes are not necessarily ischaemic. In general, white matter disease is associated with loss of neuronal integrity, which leads to higher mean diffusivity and lower fractional anisotropy. Diffusion tensor MRI techniques might eventually enable measurement of the number of fibres per tract and the functional areas connected by white matter. The importance of atrophy in VCI is increasingly recognised and might

show a stronger association with disease progression and depressive symptoms than whitematter changes. Medial temporal atrophy is emerging as an important correlate of cognitive dysfunction, including executive dysfunction. Likewise, even small amounts of white matter abnormalities are associated with significant memory and language impairments.

1.2.7 *Disease progression and treatment possibilities*

It has been shown that even mild forms of VCI-ND are associated with a poor outcome, probably as a result of early motor involvement, disorders of balance and gait, postural instability, urinary problems, or the early impact on executive functions (Ingles *et al.*, 2002). In particular, a follow-up of 5 years, conducted to evaluate the progression of cognitive and functional decline, showed that 52% of patients with VCI-ND had died and 46% had developed dementia (Ingles *et al.*, 2002). In addition, patients with VCI-ND have an increased risk of death and institutionalization (Rockwood *et al.*, 2000) and a higher risk of dementia after stroke (Serrano *et al.*, 2007). Because VCI is common and its treatment costly, it is a target for further study, and progress in this field is evident.

Capitolo 2
TRANSCRANIAL MAGNETIC STIMULATION

TMS may give information about the excitability of the human brain cortex, the conduction along cortico-spinal tract (Chen *et al.*, 2008), as well as the functional integrity of intracortical neuronal structures and callosal fibers (Kobayashi & Pascual-Leone, 2003). In particular, TMS has a strong talent to unveil motor system impairments in their pre-clinical phase.

Although not always clearly clinical evident, the involvement of motor areas in dementia has been shown by compelling clinical, neuropathological and neuroimaging studies as discussed below. Changes in motor areas may be secondary to the direct structural alterations caused by the disease process, or more often the consequence of indirect remodeling mechanisms.

Moreover, the integrated approaches using neurophysiological techniques together with structural and functional imaging have allowed the study of connectivity across motor and non-motor areas (Rossini *et al.*, 2007). By evaluating the effects of agonists or antagonists for specific neurotransmitters, it has been shown that TMS can selectively and non-invasively explore the function of glutamatergic, gabaergic and cholinergic cortical circuits (Paulus *et al.*, 2008).

Although the physiological abnormalities revealed by TMS are not disease-specific (Kobayashi & Pascual-Leone, 2003), there may be specific neurophysiological changes that co-segregate in each dementing illness, consistent with the involvement of distinct neurobiological substrates in the pathogenesis of each disease.

TMS can be delivered as single pulse, pairs of stimuli to the same or different brain areas, paired cortical and peripheral stimulation, or as trains of repetitive stimuli at various frequencies. A single TMS pulse, applied to the primary motor cortex (M1) at adequate stimulator intensity, elicits a motor evoked potential (MEP) in contralateral target muscles.

2.1 **The resting motor threshold**

Resting motor threshold (rMT) refers to the lowest TMS intensity able to evoke motor-evoked potentials (MEPs) more than 50 μV in amplitude in muscles at rest in at least five out of 10 trials (Rossini *et al.*, 1994)

rMT is considered as a global parameter of human brain excitability as it is a compound measure of the membrane excitability of cortico-spinal neurons, neural inputs into pyramidal cells within the cortex, as well as the excitability of spinal motor neurons, neuromuscular junctions and muscles (Ziemann *et al.*, 1996; Rossini & Rossi, 2007).

rMT because is increased by drugs that block voltage gated sodium channels (Ziemann *et al.*, 1996) and it is decreased by non- N-Methyl-D-aspartate (NMDA) glutamatergic agent (Di Lazzaro *et al.*, 2003)

2.2 **The contralateral and ipsilateral silent period**

A suprathreshold TMS pulse applied to M1 during a tonic voluntary contraction of contralateral muscles results in a suppression of the electromyographic (EMG) activity of those muscles lasting few hundred milliseconds (Chen *et al.*, 1999). This phenomenon, called controlateral silent period (cSP), is a functional measure of intracortical inhibitory circuits (Cantello *et al.*, 1992; Werhahn *et al.*, 1999). Pharmacological studies using using benzodiazepines revealed that CSP is mainly mediated by gamma amino-butyric acid (GABA)-B transmission.

Conversely, if the pulse is delivered to the ipsilateral M1, an EMG silence with the duration of about 30 ms, which is referred as ipsilateral silent period (iSP), can be recorded and it reflects the capacity of the motor cortex to excite inhibitory interneurons of its contralateral counterpart and seems to be conveyed by transcallosal pathways (Ferbert *et al.*, 1992) (Meyer *et al.*, 1995).

2.3 **Intracortical inhibition and facilitation**

Inhibitory and excitatory interneuronal activity within the human cortex (Kujirai *et al.*, 1993; Ziemann, 2004) can be studied non-invasively using paired-pulse TMS paradigms. Although introduced for the study of motor areas, paired-pulse TMS can

also be applied to non-motor areas. Conventional paired-pulse paradigms utilize a subthreshold 'conditioning stimulus' followed by a suprathreshold 'test stimulus'. By varying the intensity of the conditioning stimulus and the interval between the pair of TMS pulses (the interstimulus interval (ISI)), a number of measures of intracortical interneuronal functions and interactions have been developed. At ISI of 1–4 ms, the conditioning stimulus results in a reduction of MEP amplitude, and has been termed short-latency intracortical inhibition (SICI). At longer ISI (7–20 ms), the effect is an intracortical facilitation (ICF) (Kujirai *et al.*, 1993). The mechanisms behind these phenomena are considered to take place within the cerebral cortex and to be mediated by different neural circuits. SICI is probably mediated by the activity of GABA-A interneurons (Di Lazzaro *et al.*, 1998; Di Lazzaro *et al.*, 2000), whereas the phenomenon of facilitation is more complex (Ziemann 2004).

Long-interval intracortical inhibition is a cortical phenomenon referred to the inhibitory effects of supra threshold conditioning stimulus (Lu *et al.*, 1998) delivered at ISIs of about 50–200 ms before the test stimulus that is likely mediated by the activation of pre-synaptic GABA-B receptors on inhibitory interneurons (McDonnell *et al.*, 2006).

2.4 **Short-latency afferent inhibition**

Short-latency afferent inhibition (SA) is a further TMS-based protocol that reflects the inhibitory modulation on M1 exerted by the sensory inputs (Tokimura *et al.*, 2000). MEPs recorded in the hand muscles can be reduced by an electrical stimulation of the median or ulnar nerve, if the time interval between the peripheral nerve stimulus and the TMS pulse over M1 is 2-8 milliseconds longer than the time needed by the fast-conducting peripheral nerve afferents to reach the cortex (Tokimura *et al.*, 2000). SAI may be considered as a non-invasive way to test central cholinergic activity in vivo, since it has been shown to be reduced or abolished by intravenous injection of the muscarinic receptor antagonist scopolamine (Di Lazzaro *et al.*, 2000) and to be positively modulated by acetylcholine (Di Lazzaro *et al.*, 2005).

Capitolo 3
DEMENTIA THROUGH THE LOOKING GLASS OF TRANSCRANIAL MAGNETIC STIMULATION

3.1 **Vascular Dementia**

The few TMS studies targeting this disorder have focused on SIVD. TMS studies on VaD or cerebrovascular pathology that affects cognition are summarized in Table 2. VaD patients have been selected accordingly to the same diagnostic criteria and have a comparable stage of disease. All the studies conducted so far (Alagona *et al.*, 2004; Di Lazzaro *et al.*, 2008; Pennisi *et al.*, 2011a), but one (Nardone *et al.*, 2008b), showed a reduction of the rMT. No abnormalities have been described for active MT, duration of SP, ICI and ICF. An abnormality of SAI was found only in a small subgroup of patients, which might represent a mixed form of dementia (Di Lazzaro *et al.*, 2008) and in the study of Nardone and coworkers (Nardone *et al.*, 2008b).

CADASIL (acronym for ‘‘cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy’’) is considered a pure genetic model of VaD. CADASIL patients of the included studies (Manganelli *et al.*, 2008; List *et al.*, 2011; Palomar *et al.*, 2013), have been identified accordingly with the genetic criteria, but differ in terms of disease stage. In summary, a single study showed reduced rMT (Manganelli *et al.*, 2008), whereas the reduction of SAI observed in two studies (List *et al.*, 2011; Palomar *et al.*, 2013) supports the hypothesis of a central cholinergic system impairment in CADASIL (Di Lazzaro & Ziemann, 2013). In support of this, there have been positive effects reported for anticholinesterasic drugs in these patients. Moreover, compared to control subjects, CADASIL patients show impaired ICF and, more generally, in sensorimotor plasticity (List *et al.*, 2011; Palomar *et al.*, 2013), although, sensorimotor plasticity is preserved in patients with normal cognitive scores (List *et al.*, 2011).

In the attempt of exploiting rTMS protocols as therapeutic option for VaD, a randomized controlled pilot study showed that one session of high frequency rTMS applied over the left DLPFC improved executive performance, whereas no effects were observed in any other cognitive functions (Rektorova et al., 2005). However, it has to be noted that this study was performed on a small sample of patients suffering of cerebrovascular disease with mild cognitive impairment but without dementia. In the same groups of patients, high-frequency rTMS was shown to be a possible therapeutic option to alleviate depressive symptoms (Fabre et al., 2004; Jorge et al., 2008).

3.2 **TMS in AD**

AD is the most common cause of primary dementia. Motor disorders as gait impairment, rigidity and hypokinesia usually occur in more advanced stage of the disease. Intracellular neurofibrillary tangles, deposits of tau protein and extracellular beta-amyloid, predominantly affects the entorhinal cortex, the hippocampus and the posterior cortical associative areas. However, the density of NFT and plaques in the primary motor cortex seems to be not negligible. In moderate to severe AD, volumetric and diffusion tensor imaging correlated gait dysfunction to the progressive grey matter degeneration of motor and cingulate cortex, the insula and the cerebellum (Olazarán *et al.*, 2013). Moreover, M1 volume has also been associated with gait performance in Mild Cognitive Impairment (MCI) (Annweiler *et al.*, 2013). Alteration of intracortical motor connectivity confirms the involvement of motor areas in the early stage of AD (Vidoni *et al.*, 2012). Most of the studies reported a global enhanced cortical excitability, as evaluated by rMT. Moreover several studies reported a significant reduction of SAI supporting the cholinergic system impairment hypothesis in AD. cSP showed a normal duration in most of the studies. Contrasting results were obtained for SICI whereas no changes in ICF have been reported so far. In conclusion, an increase of motor cortex excitability, as assessed by MTs, and a consistent reduction of SAI seem to be the more robust neurophysiological alterations in early AD (Cantone *et al.*, 2014).

3.3 **Frontotemporal lobar de generation**

FTLDs affect the frontal lobe and/or temporal lobe and occur predominantly with changes in behavior, personality, social conduct and verbal expression. Motor system is often involved, as suggested by the reported genetic and clinical association of FTD with parkinsonism and with motor neuron disease (Espay *et al.*, 2011).

TMS reveals central motor circuit abnormalities (reduced amplitude or absent MEPs, increase of MEPs latency and CMCT) even in the absence of clinical pyramidal involvement. Unlike what has been described in AD, no significant changes in MTs, in intracortical inhibition/facilitation and in central cholinergic activity, estimated by SAI, have been shown (Cantone *et al.*, 2014).

3.4 **Dementia with Lewy bodies**

Dementia with Lewy bodies is a synucleinopathy characterized by fluctuating mental status, an impairmentof attention and visuospatial ability, recurrent complex visual hallucinations and, often, a parkinsonian syndrome without tremor (McKeith *et al.*, 2005). Patients manifesting parkinsonism have a lower regional cerebral blood flow in M1 and in left supplementary motor area (SMA) (Takahashi *et al.*, 2010). In agreement with neurochemical investigations showing cholinergic deficits (Tiraboschi *et al.*, 2000), a significant reduction of SAI was demonstrated in DLB (Di Lazzaro *et al.*, 2007).

3.5 **Dementia in movements disorders**

Cognitive impairments in Parkinson's disease may be related to the cholinergic system degeneration. Accordingly, SAI is significantly decreased in the more affected side, in patients with dementia and MCI.

TMS studies reveal an impairment of callosal function in progressive supranuclear palsy patients tested through the iSP and shorter cSP and disrupted iSP with a structural and/or functional impairment of callosal integrity in corticobasal degeneration (Cantone *et al.*, 2014).

In sporadic olivo-ponto-cerebellar atrophy, a degeneration often associated with Multple System Atrophy (MSA), increased MTs and reduced MEP amplitudes

showed a significant correlation with cerebral hemispheres atrophy (Martinez *et al.*, 1995).

Finally TMS studies revealed MEPs abnormalities in up to 72% of 34 Huntington disease patients correlating with the duration of motor symptoms and the severity of involuntary movements, and increased rMT in 10% of 21 first-degree offspring, in absence of clinical signs (Meyer *et al.*, 1992). A more recent study in pre-manifest and early manifest HD showed higher MTs in patients than in control subjects (Schippling *et al.*, 2009).

Capitolo 4
EVALUATION OF CORTEX EXCITABILITY IN PATIENTS WITH VCI-ND

4.1 **Material and methods**

4.1.1 *Subjects*

The study included 10 patients with VCI-ND (mean age 73.5 ± 6) and 10 age-matched controls (mean age 65.3 ± 2.2) all consecutively recruited from the database based on the Cerebrovascular Disease Center of the University of Catania (Italy). The study was approved by the local ethical committee, and written informed consent was given by all individuals. This study has been conducted in accordance with the Declaration of Helsinki (1964).

4.1.2 *Inclusion critera*

The patients did not meet the Diagnostic and Statistical Manual for Mental Disorders-Forth Edition (Association & DSM-IV.) criteria for dementia but fulfilled the brain imaging criteria for subcortical vascular disease with predominant WMLs (Erkinjuntti *et al.*, 2000). They showed impairment in at least one cognitive domain and normal abilities in activities of daily living, thus assuming a clinical picture of VCI-ND. Controls did not have vascular lesions or other abnormal findings at brain imaging. All participants underwent electroencephalogram to rule out predisposition to seizures.

4.1.3 *Exclusion criteria*

Patients with a history of major neurological disorders (i.e., dementia, stroke, Parkinson's disease, multiple sclerosis, and epilepsy) or major psychiatric illness, head trauma, acute or chronic noncompensated medical illness (such as heart failure, liver cirrhosis, kidney failure, respiratory failure, severe metabolic imbalance, and

diffuse neoplasm), and alcohol or drug abuse were excluded. None of the participants was on antidepressant or other psychotropic drugs.

Additional exclusion criteria included mini-mental state examination (MMSE, 1975) <24, conditions precluding MRI or TMS execution, and use of drugs able to modulate cortical excitability.

4.1.4 *Clinical and neuropsychological evaluation*

All subjects underwent a clinical evaluation, including age, gender, education, presence of cerebrocardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, coronaropathy, atrial fibrillation, and smoking habit), and general and neurological exams. Patients and controls were treated for their vascular risk factors with anti-platelet or anticoagulant medications (aspirin, clopidogrel and warfarin), antihypertensive drugs (angiotensinconverting enzyme inhibitors, angiotensin II receptor antagonist, diuretics, and calcium channel blockers), cholesterol lowering medications (statins), and oral antidiabetic drugs or insulin.

The neuropsychological battery of tests assessed overall cognitive impairment (MMSE), frontal lobe abilities (frontal assessment battery, FAB)(Appollonio *et al.*, 2005), interference task stroop color-word test, depressive symptoms (the 17-item Hamilton depression rating scale) (Hamilton, 1960), apathy (apathy scale), and functional status (activity of daily living and instrumental activity of daily living).

The brain MRI was acquired from patients and controls with a 1.5 T general electric system. The imaging protocol consisted of T1-, T2-, proton density-weighted, and fluid-attenuated inversion recovery scans; slice thickness was 5mm with 0.5mm slice gap. In the patients group, the severity of WMLs was graded according to the Fazekas visual scale (Fazekas *et al.*, 1987).

4.1.5 *TMS technique*

rMT, CSP, ISP, intracortical inhibition and facilitation and SAI were evaluated in 10 patients and 10 controls. MEPs of the right first dorsal interosseous (FDI) muscles were elicited using a Magstim 200 stimulator (The Magstim Company, Whitland, Dyfed) connected to a 70 mm figure-of-eight coil applied with the handle pointing backwards and laterally, at an angle of 45∘ to the sagittal plane, on the optimum site of stimulation which consistently yielded the largest MEP (hot spot). EMG activity

was recorded from a silver/silverchloride surface active electrode placed over the motor point of the target muscle with the reference electrode placed distally at the metacarpophalangeal joint of the index finger. Motor responses were amplified and filtered (bandwidth 3–3000Hz) using a Medelec Synergy (Oxford Instruments) system with gains of 100 μV and 5mV/div.

Resting MT (rMT) was defined, according to the IFCN Committee recommendation (Rossini *et al.*, 1994), as the lowest stimulus intensity able to elicit MEPs of an amplitude >50 μV in at least 5 of 10 trials, with the muscle at rest.

Central motor conduction time was calculated by subtracting the conduction time in peripheral nerves, estimated by conventional F-wave techniques, from MEP latency obtained during moderate active muscle contraction (10–20% of maximum background force), at a stimulus intensity set at 130% of the rMT.

M and F waves were elicited by giving supramaximal electrical stimulation (constant current square wave pulse of 0.2 ms) to the ulnar nerve at wrist. The size of the MEPs was expressed as a percentage of supramaximal M wave amplitude (A ratio). Moreover, in order to assess spinal motor excitability, the mean amplitude of the F wave was measured in the target muscle.

The CSP and ISP were determined with an approximately 50% of maximum tonic voluntary contraction of the FDI muscles, induced by controlateral and ipsilateral single TMS pulses delivered at 130% of rMT, respectively. The mean CSP and ISP durations of 10 rectified trials were calculated. The onset latency of ISP was defined as the time interval from TMS to the decline of tonic EMG activity of more than 70% of mean EMG activity assessed over 100 ms prior to stimulation. ISP duration was measured from the onset of the previously defined decrease of tonic EMG activity to recurrence of mean prestimulus EMG activity.

SICI and ICF have been studied using the conditioning-test paradigm described by Kujirai et al. (Kujirai *et al.*, 1993) applying two magnetic stimuli through a Bistim module (The Magstim Company, Whitland, Dyfed) connected to a CED Micro 1401 interface (Cambridge Electronic Design, Cambridge, UK). The conditioning stimulus was applied at 80% of the subject's rMT, and the intensity of the test stimulus (TS) was set at 130% of the rMT. The ISIs tested were 1, 3, 5, 7, 10 and 15 ms. Ten trials for each ISI, for the conditioning stimulus alone and for test stimulus alone, were

recorded in a random way with an 8-s interval among each trial. The responses were expressed as the ratio between the MEP amplitude produced by paired stimulation and that produced by test stimulation alone.

SAI was studied using the technique of Tokimura (Tokimura *et al.*, 2000). Conditioning peripheral stimuli were single pulses of electrical stimulation (200 μs duration) applied through bipolar electrodes to the ulnar nerve at the wrist (cathode proximal). Conditioning stimulus intensity was set just above the motor threshold necessary to evoke a visible twitch of the thenar muscles. The afferent inhibition induced by the peripheral conditioning stimulus was tested at different interstimulus intervals (ISIs)r. ISIs were determined relative to the latency of the N20 component of the somatosensory evoked potential obtained after stimulation of the right ulnar nerve. To record somatosensory evoked potentials, the active electrode was attached 3 cm posterior to C4 (according to the 10–20 International EEG system) and the reference was 3 cm posterior to C3, respectively. Five hundred responses were averaged to identify the latency of the N20 peak. ISIs from the latency of the N20 plus 2 ms to the latency of the N20 plus 8 ms were investigated in steps of 1 ms. Ten repeats were delivered for cortical stimulation alone and for conditioned stimulation at each ISI in pseudo-randomised order. The amplitude of the conditioned responses was expressed as a ratio of the amplitude of the test response.

All measurements were conducted while subjects were seated in a comfortable chair with continuous EMG monitoring to ensure either a constant level of EMG activity during tonic contraction or complete relaxation at rest. Data were collected on a computer and stored for off-line analysis. Hardware setting, data collection and offline processing/analysis were performed by the tool described in Giordano et al.(Giordano *et al.*, 2012)

4.1.6 *Statistical Analysis*

The variables obtained from patients and controls in the two experimental sessions were compared using the t-test for unpaired datasets and the $\chi 2$ test for categorical variables. A P value less than 0.05 was considered statistically significant.

4.2 **Results**

4.2.1 *Clinical data*

Patients and controls were similar in terms of age, gender, educational level, and cerebrovascular risk factors profile. Soft neurological signs, such as subtle tendon reflex asymmetry, slight postural instability, and sensory disturbances, were reported in some of the patients. As expected, stroop scores were significantly higher, and FAB score was significantly lower in patients compared with controls although without any evidence of functional disability.

4.2.2 *rMT, cSP, iSP*

Both data from the first experimental session showed no statistically significant differences for rMT, cSP and iSP.

4.2.3 *SICI and ICF*

The mean time course of intracortical excitability is shown in Figure 1. Conditioned MEP amplitude at ISIs 10 ms from the left hemisphere was significantly larger in the patient group than in the control group, indicating an increase in ICF ($p < 0.05$). Conversely, ICI did not differ between patients and controls.

4.2.4 *SAI*

As shown in Figure 2, no statistically significant differences was observed for SAI at both ISIs (ISI N20+2 msec: 75.4 % ± 15.7 *vs* 81.1% ± 9.8, *p*=NS; ISI N20+8 msec: 67.7% ± 14.5 *vs* 74.8% ± 18, *p*=NS) between patients and controls.

Capitolo 5
DISCUSSION

5.1 **Motor cortex excitability**

The study provides the first evidence of an enhanced ICF without change of cortical excitability indexed by rMT in patients with VCI-ND [data published in (Bella *et al.*, 2011)].

However the reason of this dissociation remains rather complex. It was hypothesized that rMT depends on glutamatergic synaptic excitability (Paulus *et al.*, 2008) whereas the physiology underlying ICF is less clear. The leading hypothesis is that ICF reflects the state of excitability of distinct excitatory interneuronal circuits within the motor cortex (Kujirai *et al.*, 1993; Ziemann *et al.*, 1998). Moreover the hypothesis that ICF might origin from a recruitment of circuits in addition to those involved in the generation of I-waves might explain the dissociated changes of the two TMS variables (Paulus *et al.*, 2008). Mapping experiments indicated as possible candidates neurons that underlie the ICF phenomenon the numerous cortico-cortically projecting pyramidal cells and their axons, likely to be located in or near the sensorimotor cortex (Ziemann *et al.*, 1998). The different sensitivity to drug administration suggests that they are mediated by the activation of different receptors (Ziemann, 2004; Paulus *et al.*, 2008). In particular, excitatory glutamatergic interneurons within the motor cortex and NMDA receptors appear to influence ICF (Ziemann, 2004).

Finally the net effect of facilitation could be the result of prevailing excitation and weaker inhibition phenomena, involving different neurotransmission pathways. However, the neurochemical network underlying ICF seems to be more complex since ICF involves various neurotransmitters, supporting the hypothesis that ICF is a complex neurophysiological phenomenon, likely to be mediated by glutamatergic

facilitation, tempered by persisting GABAergic inhibition and influenced by the cholinergic, dopaminergic, adrenergic and serotonergic systems.

An impairment of ICF has never been described in patients with AD, in MCI and in the single study performed on SIVD patients at ISI 10 ms (Cantone *et al.*, 2014).

The enhanced ICF provides an electrophysiological support to the hypothesis that age-related WMLs, commonly observed on MRI of non-demented elderly, might result in functional changes of intracortical excitatory neuronal circuits. Whether these changes represent a neurophysiological marker in the brain at risk for dementia or are part of plastic compensatory remodeling process remains unclear.

The role of the white matter in cortical excitability in normal and pathological conditions has been studied combining the use of structural imaging and TMS. Functional MRI (fMRI) studies have shown that cerebral white matter lesions determine cortical changes in motor and non motor areas. fMRI was used to test preclinical functional changes in the motor network organization related to WMH severity. In particular, there was a more widespread activation of non-primary motor areas such as the pre-supplementary motor area and the frontotemporal and occipital regions (Linortner *et al.*, 2012) during a motor task involving the lower limbs. This increased activation of a specific network (motor or neocortical frontal and parietal areas) might represent an adaptive response aiming at limiting the functional consequences of small vessel disease and maintaining a normal level of functioning (Galluzzi *et al.*, 2008).

With this regard, it is well known that the motor cortex hyperexcitability is a relatively stable electrophysiological feature of both AD and VaD. This has been considered part of a plastic compensatory response to neuronal loss (Rossini *et al.*, 2007), supporting the concept of dementia as a dynamic condition and changes of specific TMS parameters as indexes of motor cortex plasticity (Delvendahl *et al.*, 2012). The enhanced cortical plasticity might counteract cognitive decline and shed light on the reasons underlying decline or preservation of cognitive domains. This hypothesis has been demonstrated by means of TMS mapping technique in AD patients who showed a frontal and medial shift of the motor cortical output's center of gravity (CoG), suggesting functional reorganization compensating for disease progression, at least in its early stages (Ferreri *et al.*, 2003).

Recently a TMS study demonstrated that also motor cortex is plastically rearranged in SIVD with a slightly lesser CoG frontal shift compared to AD (Guerra *et al.*, 2014). Then, the motor cortex facilitation observed in our cohort of VCI-ND patients could be the expression of plasticity-related processes, mediated by glutamate-dependent NMDA receptor activation.

In conclusion, there is still much plasticity in VCI–ND, and careful evaluation of patients with this condition who do not progress to dementia or who revert to no cognitive impairment might enhance our understanding of how exposures interact with neuropathology.

5.2 **Transcallosal Inhibition**

No abnormality of interhemispheric connections in terms of TI evaluated by means of iSP was also found, supporting a relative functional CC integrity in this group of patients. The increasing load of age-related WMLs volume was significantly correlated with atrophy of the CC and its subregions in non-disabled elderly subjects with leukoaraiosis, suggesting that WMLs may lead to a gradual loss of CC tissue (Ryberg *et al.*, 2008; Frederiksen *et al.*, 2012). CC atrophy is also significantly associated with impaired motor performance and walking speed and seems to contribute to development of dementia in the elderly independently of WMLs load (Ryberg *et al.*, 2011). However, results from other studies showed that the pure extent of WMLs may be more related to impairment of frontal lobe function rather than that of callosal atrophy (Yamauchi *et al.*, 2000). Indeed, we observed worse cognitive performances in tests evaluating frontal lobe abilities despite a substantial radiological and neurophysiological CC integrity. Conversely, in our patients with an executive dysfunction without impairment of global cognitive status, a normal functioning of transcallosal inhibitory mechanisms is in line with the MRI lack of a significant CC pathology. It can be hypothesized that CC would be spared in non-demented LA patients where the intrahemispheric changes due to deep WMLs may be related to executive dysfunction and the transhemispheric connections might possibly take place via the anterior and posterior commissures. Recent data derived from the LADIS study of longitudinal quantitative MRI on a large cohort of elderly patients with age-related WMLs and no or mild impairment in instrumental activity

of daily living seem to support this view (Jokinen *et al.*, 2012a). The authors showed that the rates of tissue loss in the total CC area and in rostrum/genu and midbody subregions were significantly associated with decline in a compound measure of cognitive speed and motor control, but not in those of executive functions, memory, or global cognitive function. Alternatively, it has been postulated that, in patients with extensive LA, atrophy and reduced diffusion anisotropy of the CC may indicate diffuse hemispheric deep white matter tract damage, which may explain global cognitive impairment and development of vascular dementia (Otsuka *et al.*, 2012).
On the contrary, in degenerative dementia, comprehensive but still subclinical dysfunctions of motor cortical inhibition with strong interactions of intra- and interhemispheric inhibitory phenomena were recently described in terms of significant prolongation of the iSP duration in mild to moderate AD patients compared with controls (Hoeppner *et al.*, 2012). Recently, a combined study using diffusion tensor imaging (DTI) and TMS in AD correlated the iSP and the rMT with fractional anisotropy and mean diffusivity values of the CC and corticospinal tract. Although both TMS and DTI metrics were prominently altered in AD patients, impaired white matter integrity was not associated with increased iSP latency or reduced rMT (Wegrzyn *et al.*, 2013), and, therefore, beside the direct degeneration of the underlying fiber tracts, other pathophysiological mechanismsmay account for the observation of decreased TI and increased motor excitability in AD.

5.3 **Colinergic circuitry**

The second main finding of the study indicate that the central cholinergic circuits seem to be spared in VCI-ND patients. This result is in line with the previous researches in VaD patients (Di Lazzaro *et al.*, 2008; Pennisi *et al.*, 2011b) and different from that observed in AD or MCI patients. Several studies reported a significant reduction of SAI in AD patients (Di Lazzaro *et al.*, 2002; Di Lazzaro *et al.*, 2004; Di Lazzaro *et al.*, 2005; Di Lazzaro *et al.*, 2006; Di Lazzaro *et al.*, 2007; Sakuma *et al.*, 2007; Nardone *et al.*, 2008a; Di Lorenzo *et al.*, 2013), supporting the cholinergic system impairment hypothesis.

Motor cortex excitability in MCI patients has been investigated in only three studies, reporting contrasting results (Sakuma *et al.*, 2007; Julkunen *et al.*, 2008;

Olazarán *et al.*, 2010). However studies seem to indicate SAI measure as a possible tool to identify MCI patients with an increased risk to convert into AD given that SAI was significantly reduced in amnestic MCI patients, while it was not significantly different in non-amnestic patients (Nardone *et al.*, 2012). Our group of VCI-ND patients did not exhibit impairment of the cholinergic system at this stage in a manner similar to that seen in non-amnestic MCI.

Abnormal SAI has also been reported in DLB (Di Lazzaro *et al.*, 2007), a form of dementia that responds to cholinergic medications (Emre *et al.*, 2004) . In contrast, SAI was found to be normal in frontotemporal dementia (Di Lazzaro *et al.*, 2006), a non-cholinergic form of dementia. Therefore, SAI may be a marker of a dysfunction in some circuits related to memory function that are probably cholinergic in nature; SAI testing can be used as a noninvasive test for the assessment of cholinergic pathways in patients with dementia and may represent a useful additional tool in the differential diagnosis between the cholinergic forms and the non-cholinergic forms of dementia at every stage of the disease.

However the role of the cholinergic system in the development of cognitive impairment is still under discussion in VD. Changes in those cholinergic cortical networks that are involved in SAI have been demonstrated in about 70% of patients with a clinical diagnosis of AD. Our data could support the hypothesis of a different involvement of cholinergic system in VaD/VCI-ND as demonstrated in a recent neuroimaging study (Kim *et al.*, 2013). In particular, the study has shown that the loss of cholinergic pathways correlates with cognitive dysfunction in both AD and SIVD but with different mechanisms. The atrophy of the nucleus basalis of Meynert is likely to be the predominant contributor to cognitive impairments in AD, whereas, the cognitive dysfunction of SIVD was associated with compromised subcortical cholinergic fibers not with nucleus itself (Kim *et al.*, 2013).

However TMS studies have shown few VaD patients with SAI abnormalities that could have concomitant neuropathological changes of AD and thus represent the percentage of patients with a mixed form of dementia (Di Lazzaro *et al.*, 2008; Nardone *et al.*, 2008b).

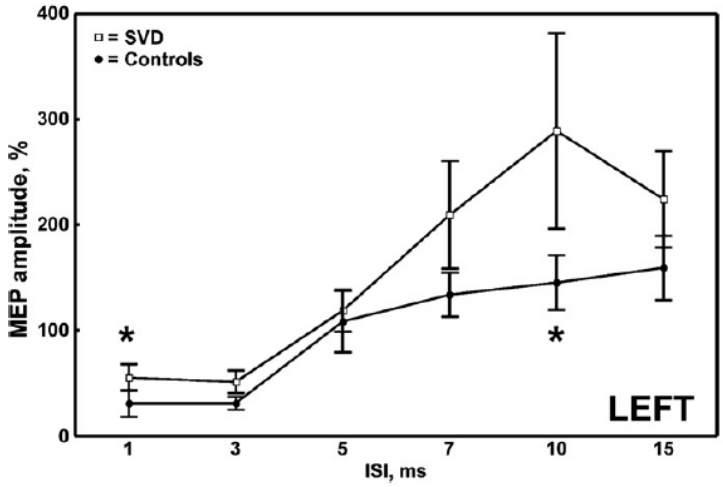
Likely, our patients have been carefully selected according to the diagnostic criteria for VCI-ND and represent an homogeneous sample of subjects who might

develop dementia of the vascular type without significant AD pathology. In particular, they have a clear history of vascular risk factor and in some cases have soft neurological signs, they fulfill the brain imaging criteria for subcortical vascular disease with predominant WMLs (Erkinjuntti *et al.*, 2000) and exhibit a prominent alteration of executive functions according to the typical cognitive profile of pure SIVD (Graham *et al.*, 2004).

5.4 **Conclusion**

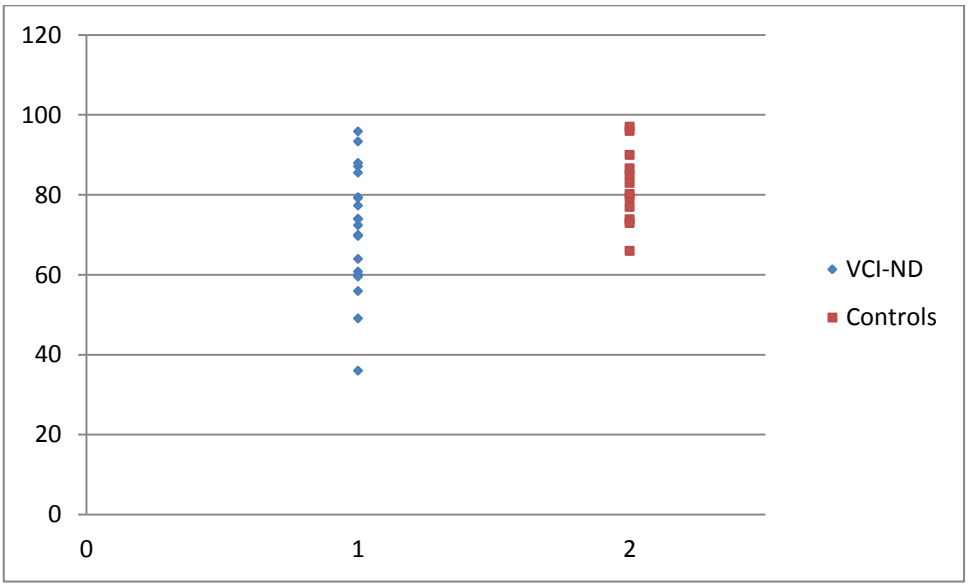
In conclusion, much of the literature agrees on the utility of basic TMS measures like rMT and SAI in patients with dementia. Although a single measure is not sufficient to define a diagnosis, the abnormalities detected in the TMS parameters of interest are, all together, footprints of specific pathophysiological processes that affects motor and non-motor areas in different types of dementia. Hence, not the single alterations, but the whole frame on how all the pieces of the puzzle fit together can help to build a comprehensive knowledge on the diseases, predict their progression and identify the so called ‘‘brains at risk’’.

FIGURE 1



Mean intracortical excitability obtained by the paired conditioning-test stimulus paradigm in VCI patients and controls. Bars indicate standard errors. MEPs are expressed as percentage of the amplitude of the basal MEP evoked by test stimulation alone. *$p < 0.05$.

FIGURE 2



Scatterplot showing individual values of SAI

TABLE 1

Clinico-pathological classification of VaD

Large-vessel vascular dementia

- Multi-infarct dementia—multiple large complete infarcts, cortical or subcortical in location, usually with perifocal incomplete infarction involving the white matter;
- Strategic infarct dementia—a single infarct in functionally critical areas of the brain (angular gyrus, thalamus, basal forebrain, or territory of the posterior cerebral artery or anterior cerebral artery)

Small-vessel vascular dementia

- SIVD (Binswanger's disease; lacunar dementia or lacunar state; multiple lacunes with extensive perifocal incomplete infarctions; CADASIL);
- Cortical-subcortical (Hypertensive and arteriolosclerotic angiopathy; cerebral amyloid angiopathies (including familial British dementia); other hereditary forms; collagen-vascular disease with dementia; venous occlusions).

Ischaemic-hypoperfusive vascular dementia

- Diffuse anoxic-ischaemic encephalopathy;
- Restricted injury due to selective vulnerability;
- Incomplete white-matter infarction;
- Border-zone infarction

Haemorrhagic vascular dementia

- Traumatic subdural haematoma;
- Subarachnoid haemorrhage;
- Cerebral haemorrhage

TABLE 2

Publication	N. of pts (sex M/F)	Age mean ± SD or (range)	Diagnosis and criteria	Disease stage	Therapy with CNS affecting's drugs	A) MEPs//CMCT; B) drugs induced's changes	A) rMT (mean); B) drugs induced's changes	A) SAI (mean); B) drugs induced's changes	A) CSP (mean); B) drugs induced's changes	A) SICI (mean); B) drugs induced's changes	A) ICF (mean); B) drugs induced's changes	Plasticity protocol
Vascular dementia and other cerebrovascular disease that affects cognition												
Alagona et al. (2004)	20 (8/12)	71.8 ± 9.37	Probable VaD[a]	Executive frontal lobe dysfunction (not specified neuropsychological tests)	None	A) NS//- B) -	A) ↓**(32.7 ± 2.61) B) -	A) - B) -	A) NS B) -	A) - B) -	A) - B) -	–
Di Lazzaro et al. (2008)	12 (8/4)	70.9 ± 9.6	VaD[a]	Mild–moderate (MMSE:24.5 ± 4.2; GDS:3.45 ± 1.5)	None	A) -//- B) -	A) ↓*(48.8 ± 8.1) B) -	A) NS B) -	A) - B) -	A) NS B) -	A) - B) -	–
Nardone et al. (2008a,b)	20 (12/8)	70.9 ± 4.4	Probable VaD[a]	Mild–moderate (MMSE:22.0 ± 3.6; DRS:98.4 ± 17.8)	None	A) -//NS B) -	A) NS B) -	A) ↓*(73.5 ± 13.5) B) -	A) NS B) -	A) NS B) -	A) NS B) -	–
Manganelli et al. (2008)	10 (5/5)	61.4 ± 8.5	CADASIL (genetic diagnosis)	Severe/selective cognitive impairment/normal (Battery of test from Ragno et al. (1995))	Not specified	A) NS//NS B) -	A) ↓*(49.4 ± 14.4) B) -	A) ↓**(79.5 ± 21.7) B) -	A) - B) -	A) - B) -	A) - B) -	–
Pennisi et al. (2011a,b)	20 (8/12)	71.8 ± 9.4	Probable VaD[a]	Mild–moderate (MMSE:19.4 ± 3.4)	None	A) ↑**(6.8 ± 1.7) //- B) -	A) ↓**(32.7 ± 2.6) B) -	A) - B) -	A) NS B) -	A) - B) -	A) - B) -	–
List et al. (2011a,b)	12 (4/8)	48.3 ± 8.3	CADASIL (genetic diagnosis)	Only reduced performance in verbal memory test (MMSE:29.3 ± 0.9)	Not specified	A) -//- B) -	A) NS B) -	A) - B) -	A) - B) -	A) - B) -	A) - B) -	PAS → ↑* ctDCS:NS
Bella et al. (2011)	10 (6/4)	70.8 ± 6.3	Vascular cognitive impairment-no dementia (MRI criteria for SVD)	Cognitive impairment-no dementia (MMSE:27.5 ± 1.9; ADL:6; IADL: 7.8 ± 0.2)	None	A) -//NS B) -	A) NS B) -	A) - B) -	A) NS B) -	A) ↓* B) -	A) ↑* B) -	–
Bella et al. (2012)	9 (not specified)	70 (66–84)	Vascular cognitive impairment-no dementia (MRI criteria for SVD)	Cognitive impairment-no dementia (no significant changes at 2-year follow-up: MMSE: − 0.70 ± 1.5; ADL: − 0.2 ± 0.44; IADL: − 0.67 ± 0.8)	None	A) NS//NS B) -	A) ↓** (L - 5.33 ± 3.87) B) -	A) - B) -	A) NS B) -	A) NS B) -	A) NS B) -	–
Palomar et al. (2013)	10 (5/5)	56.9 ± 9.8	CADASIL (genetic diagnosis)	Mild–moderate (MMSE:24.5 ± 5.02)	None	A) -//- B) -	A) NS B) -	A))↓ ** (ISIs 20 and 22 ms) B) -	A) NS B) -	A) NS B) -	A) ↓ ** (ISIs 10 and 12 ms) B) -	PAS → ↓**t0, t15,t30

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