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Potential neurophysiological biomarkers for the diagnosis of age-related neurodegenerative diseases

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Abstract

The global population with dementia is rapidly increasing around the world. The major risk factor for dementia is aging. There is currently no treatment available and the cost of symptomatic treatment is high. There is a growing interest in possible clinical applications of non-invasive methods that are safe and easy-to-perform in diagnosis of dementia. The purpose of this paper is to investigate the usage of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) to diagnose dementia in early stages of the disease. Early diagnosis is needed to reduce the costs of symptomatic care. When investigating the usage of TMS-EEG technology, we will look at how we can distinguish dementia in different neurodegenerative diseases between each other. More research is needed to suggest an accurate parameters for diagnosis of dementia with this type of technology.

Key words: dementia, Alzheimer’s disease, frontotemporal dementia, TMS-evoked potentials, motor-evoked potentials, mild cognitive impairment, aging, diagnosis

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List of the abbreviations

Abbreviation	*Definition*
AD	Alzheimer's disease
CNS	Central Nervous System
WHO	World Health organization
NINCDS-ADRDA	National Institute of Neurological, Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
TMS	Transcranial magnetic stimulation
EEG	Electroencephalography
TEP	TMS evoked potential
MEP	Motor evoked potential
TS	Test stimulus
SICI	Short-interval intracortical inhibition
LICI	Long-interval intracortical inhibition
MTL	Medial temporal lobe
LLD	Late-life depression
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
BPSD	Behavioral and psychological symptoms of dementia
NPS	Non-cognitive neuropsychiatric symptoms
FTD	Frontotemporal dementia
PDD	Parkinson's disease dementia

DLB	Dementia with Lewy bodies
VD	Vascular dementia
M1	Motor cortex
fMRI	Functional magnetic resonance imaging
EMG	Electromyography
NFT	Neocortical neurofibrillary tangles
MCI	Mild cognitive impairment
D - wave	Direct wave
I - wave	Indirect wave
CSP	Cortical silent period
SAI	Short-latency afferent inhibition
ICF	Intracortical facilitation
GABA	γ-aminobutyric acid
NMDA	N-methyl-D-aspartate
AP	Anterior - posterior
PA	Posterior - anterior
rMT	resting Motor Treshold
MoCA	Montreal Cognitive Assessment
MMSE	Mini - Mental State Examination

1. Introduction

'When it comes to neurodegenerative conditions such as dementia, ... treatment options are lacking. Encouragingly, the evidence-base for lifestyle as therapy is emerging.'

'I can think of no other disease that has such a profound effect on loss of function, loss of independence, and the need for care. I can think of no other disease so deeply dreaded by anyone who wants to age gracefully and with dignity. I can think of no other disease that places such a heavy burden on families, communities, and societies. I can think of no other disease where innovation, including breakthrough discoveries to develop a cure, is so badly needed.'

—Dr Margaret Chan, Director-General of the World Health Organization, at the Conference on Global Action Against Dementia, March 2015
(Thompson et al., 2017)

1.1 The importance of Dementia

Dementia is characterised by cognitive and behavioural changes including deficits in memory, disruption in cognition, personality and sensorimotor functions. The major risk factor of dementia is aging and most patients with dementia are older than 65 years (Elahi & Miller, 2017). Dementia is observed in most people with neurodegenerative diseases like Alzheimer's disease (AD). Neurodegeneration in dementia is characterized by loss of neurons in the central nervous system (CNS) mainly in the hippocampus and in the neocortex and is considered to be a major cause of motor and cognitive dysfunction (Jeong, 2017).

According to the World Health organization (WHO), the global population with dementia is expected to be three times higher reaching 152 million patients in 2050. The cost of medical care, social care as well as informal care is going to double in ten years (WHO, 2017). There is currently no treatment available. Biomedical approaches to treat neurodegenerative diseases failed in

the past and diseases like Alzheimer's disease are treated only on a symptomatic level. This approach has very little effect on the progression of the diseases (Bredesen, 2014).

Environmental factors can reduce the risk of dementia. Encouragingly, there is evidence that healthy lifestyle can be a form of therapy. Research suggest that a personalised therapeutic program may improve cognitive performance as well as short term memory. The therapeutic program may include a balanced healthy diet with the uptake of vitamins and antioxidants, regular exercise few times a week, good quality sleep and others (Bredesen, 2014). These factors have some influence on the overall well-being reducing the risk and effect of dementia. For example obesity is linked with cognitive impairment and is associated with increased risk of developing dementia (Beilharz et al., 2015). Magnetic resonance images of older adults without dementia show increased hippocampal volume in an aerobic exercise group compared to a stretching control group. An increase in the volume of hippocampus is associated with an improved memory function (Erickson et al., 2011). Hippocampal increase was also observed in magnetic resonance imaging scans of medical students after an exam compared to three months earlier suggesting that learning can induce structural changes in the brain (Draganski et al., 2006).

Substantial effort is made to improve the diagnosis of neurodegenerative diseases. Laboratory tests cannot be used for the diagnosis. Nowadays neurologists use tests based on the National Institute of Neurological, Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) that can identify the cause of dementia (Mckhann et al., 1984).

Brain imaging techniques like magnetic resonance imaging (MRI) or positron emission tomography (PET) can be used for the diagnosis of neurodegenerative diseases. Structural changes including atrophy can be observed using MRI and different patterns of distribution of cerebral glucose metabolism related to neurodegenerative dementia can be identified (Del Sole et al., 2016). However, these methods for diagnosis can reveal

neurodegeneration in an advanced progressive stage that might be too late to reverse into normal brain functioning.

Potentially we could find ways to predict dementia or make a diagnosis early before the onset of the disease. In this thesis, I investigate the possibility to use transcranial magnetic stimulation (TMS) combined with electroencephalography (EEG) to diagnose neurodegeneration in early stages or even before the structural and behavioural changes occur. The reason why I chose this type of technology is the fact that changes related to movement, that can be investigated using TMS - EEG, are one of the early signs of cognitive decline in AD dementia and precede memory impairment (Alberts et al., 2016).

1.2 Aim of the Current Review

The aim of this review is to investigate the usage of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) and possibly electromyography (EMG) for the diagnosis of dementia. The following questions need to be addressed:

1. What are the differences in TMS evoked potentials (TEPs) between healthy controls and patients with dementia as part of some neurodegenerative disease?
2. How does the motor evoked potentials (MEPs) differ between healthy participants and people with dementia?
3. What are differences in measurements using TMS protocols in people with dementia compared to healthy controls?

The major task of this review is to analyze and compare four groups of participants: healthy young individuals, old healthy individuals, patients with mild cognitive impairment and patients with dementia. We can assess the presence, amplitude of peaks, latency, duration and distribution of TMS evoked potentials and motor evoked potentials. Before the actual comparison, we will also address some environmental factors that could influence the data obtained with TMS-EEG.

Aside from comparing mainly the TEPs, we can also look at differences between TMS induced motor evoked potentials (MEPs) related to movement. A number of studies suggest an increased excitability of MEPs when switching from rest to a motor-task condition (Nikulin et al., 2003). We can examine properties like amplitude and latency of MEPs where amplitude is a sign of excitability of corticospinal pathways (Vaseghi et al., 2015).

First, we will look at TMS evoked potentials in healthy subjects looking at the cortical dynamics. Transcranial magnetic stimulation (TMS) can be used as non-invasive method to activate the human cortex investigating the cortical integrity, inhibitory and excitatory processes. We can also evaluate the plasticity combining the TMS with electromyography (EMG) in the motor cortex

(Farzan et al., 2013). There is an increasing amount of TMS-EEG studies that investigate the EEG correlates of either single or paired pulse TMS paradigms in the motor cortex mainly during rest (Farzan et al., 2013).

Second, we will explore the characteristics of TEPs in elderly healthy participants, patients with mild cognitive impairment and patients with dementia. As we will see further, dementia is common among neurodegerative diseases like Alzheimer's disease. Patients experience decline in cognitive function when examining person's performance. Patients have decreased semantic and episodic memory, attention or visuospatial function (Borland et al., 2020). However, some studies suggest that there is a change in TEP components with aging. Elderly experience decline in cognitive and sensorimotor functions and the variability between them is very high (Houde et al., 2018). The decline also correlates with changes in cortical excitability in the motor cortex (Levin et al., 2014).

Third, we will look at different TMS protocols that are used to measure the excitation and inhibition in the motor cortex (Tremblay et al., 2019). We will look at different types of intracortical inhibition and facilitation TMS protocols with paired-pulse TMS. The test stimulus (TS) elicits motor evoked potentials (MEPs) and TMS protocols can influence their size with a conditioning stimulus (CS). Depending on the interval between the stimuli we can use short-interval intracortical inhibition (SICI) or long-interval intracortical inhibition (LICI) protocol (Hermans et al., 2019).

2. An Overview of Dementia

2.1 Characteristics of Dementia

Dementia is one of the major health problems that our society has to face affecting more that 47 million people around the world. It is a source of social, personal and financial burden for the dementia patients. The cognitive impairment is detected at the beginning of diagnosis of dementia (Corriveau & Roderick et al., 2017). According to the standard criteria, two significant requirements need to be assessed. First, the cognitive functioning needs to be severely damaged to negatively interfere one own's daily life and social functioning. Second, patients have to suffer from a specific memory impairment (McKhann et al., 1984). The most prevalent dementia diagnosis is Alzheimer's disease (AD) that makes up two thirds of dementia cases (Corriveau & Roderick et al., 2017).

Dementia is described as a clinical syndrome with cognitive and intellectual impairment that significantly affects the functional independence of an individual. The early stages of dementia are difficult to differentiate from aging but the cognitive impairment and functional disability are clearly seen in mild to moderate stages of dementia (Bahar-Fuchs et al., 2019). The earliest cognitive signs of dementia due to Alzheimer's disease include deficits in episodic memory function. The AD pathology is characterized as delayed recall of events observed even several years before the actual diagnosis of AD (Weintraub et al., 2012). This type of memory impairment is linked to the dysfunction of medial temporal lobe (MTL) memory system, limbic and hippocampal regions. The pathology spreads to the neocortical regions with dementia progression which results in worsening of cognition (Maass et al., 2018).

The diagnosis of dementia is made based on the progressive decline in cognition (agnosia, apraxia, or executive dysfunction) and memory impairment. A widely available cognitive screening test Mini-Cog is used to measure cognitive changes before we can determine a definitive diagnosis. It consists of clock drawing test and delayed, three-word recall task. Individuls

with a positive result for cognitive impairment are further investigated (Seitz et al., 2018). The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) has developed diagnostic criteria for Alzheimer's disease. The criteria for Alzheimer's disease include experience of memory loss, severe loss of mental functioning and decline in cognitive abilities (Rossor et al., 2010).

According to the National Institute of Neurological and Communicative Disorders and Stroke (2019), patients may have problems with decision-making and language skills. They state that Alzheimer's disease is a non-reversible brain disorder for which we have no cure so far. A well - advanced disease is hard to stop, and it means we should aim for specific early diagnosis which is the core question of my thesis.

Other studies describe the behavioral and psychological symptoms of dementia (BPSDs) that have a negative impact on the prognosis of patients. The symptoms of AD patients include anxiety, depression, delusions, apathy and very common disturbed sleep (Kazui et al., 2016). MRI study of AD patients with Late-life depression (LLD) found atrophy in many brain structures for example amygdala, hippocampus, thalamus and frontal areas (frontal orbital, frontal superior, frontal middle, frontal medial superior) compared to non-demented controls. The duration of LLD was positively correlated with the tissue volume in the parahippocampal area. However, smaller volumes in the frontal areas were also correlated with older age (Andreescu et al., 2008). Among more surprising symptoms are hallucinations and euphoria (Kazui et al., 2016). These non-cognitive neuropsychiatric symptoms (NPS) affect 98% of patients with dementia creating a huge amount of stress and difficulties in daily life. A rapid disease progression is associated with untreated NPS. Therefore, early symptomatic treatment should be applied (Kales et al., 2015).

Non-pharmacologic treatment reduces the symptoms, operates as a prevention mechanism and provides a relief from stress not only for the patients but also for the caregivers (Kales et al., 2015). Non-pharmacological therapy includes cognitive behavioral therapy helping mainly with anxiety, music therapy for depression and other group therapies (Kazui et al., 2016).

2.2 Other causes of dementia

Alzheimer's disease is not the only cause of dementia and other causes that are less frequent remain poorly recognized. These include Frontotemporal dementia (FTD), Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB) and Vascular dementia (VD). These other causes of dementia are globally underdiagnosed because it is often hard to differentiate them even though diagnostic criteria also exist. The clinical symptoms are often overlapping which makes the diagnosis particularly challenging (Nardone et al., 2018). The importance of clear and early diagnosis differentiating among different dementia syndromes is high. Reducing the number of dementia patients is highly favorable (Corriveau et al., 2017).

Frontotemporal dementia (FTD) is a heterogenous type of dementia characterised by frontal and temporal neurodegeneration. The behavioral variant shows changes in personality and impaired social functioning. The other two progressive aphasia types are marked with decline in language functioning and motor symptoms (Bott et al., 2014). Patients with frontotemporal dementia experience lack of empathy, executive dysfunction and compulsions (Olney et al., 2017).

The rate and timing of cognitive decline in Parkinson's disease dementia varies a lot affecting the functioning and quality of life of patients of all age groups. The prevalence of dementia is around 30% as reviewed by studies from 1990s onwards. There is a full spectrum of cognitive decline ranging from early mild, moderate and severe dementia (Aarsland et al., 2018). Parkinson's disease is considered as a movement "parkinsonian" disorder characterised by an inability to move on command (Dickson, 2012). The main pathophysiology of PD is the dysfunction of motor cortex (M1) for example increase in tremor - related activity in M1 measured with functional magnetic resonance imaging (fMRI) paired with electromyography (EMG) (Burciu et al., 2018). The motor symptoms include tremor, rigidity, slowness and difficulties with balance and gait. The later stages of Parkinson's disease are characterized by frank dementia which is a strong cognitive dysfunction (Dickson, 2012).

Dementia with Lewy bodies is the second most common type of neurodegenerative disease. Up to 2% of elderly above 65 years are diagnosed worldwide with DLB (Jellinger & Korczyn, 2018). Delusions and visual hallucinations occur frequently in the early stage of the disease but might be equally common in all stages of the disease (Hashimoto et al., 2015). Patients experience impairments in visual recognition, attention and construction at higher degree compared to AD patients (McKeith et al., 2003).

Dementia with Lewy bodies shares many features with Parkinson's disease dementia (PDD). These include cognitive impairment and fluctuations, memory disorder and parkinsonian motor signs. Parkinsonism develops over years in many DLB patients. Akinesia, which is characterised by an inability to move own's muscles voluntarily is observed in both diseases (Jellinger & Korczyn, 2018). Nevertheless, we can observe different symptoms in patients with dementia that are not linked to Alzheimer's disease. These include euphoria, agitation, irritability, disinhibition and eating abnormalities. Some conditions like apathy are the most prevalent in Vascular dementia, Frontotemporal lobar degeneration and Alzheimer's disease (Kazui et al., 2016). The mechanisms of apathy include impaired cognitive processing of planning, impaired emotional-affective processing (motivation) and initiation (Massimo et al., 2018). On the other hand, vivid hallucinations are very common in patients with Dementia with Lewy bodies (Kazui et al., 2016).

The severity of some BPSDs increases as the dementia progresses. Sleep disturbances and apathy become more severe with progression of VD, DLB and AD. Agitation, irritability and euphoria increases in DLB with progression of the disease. Anxiety and depression increase in VD patients (Kazui et al., 2016). Indeed, higher prevalence ratio was found for diagnoses of multiple dementias like AD and dementia with Lewy bodies at once compared to single dementia pathology (James et al., 2012). But the relationship between the development of BPSDs and the dementia stage is not clear. According to other studies, the psychiatric symptoms in patients with Alzheimer's disease are correlated with the dementia stage, increasing with the progression. However, no correlation was found in patients with Lewy bodies (Hashimoto et al., 2015).

2.3 Dementia and age

The strongest risk factor for dementia is age. The prevalence of dementia among older age groups (85 years or older) is approximately 40%. However, some studies suggest that there is a stronger relationship between neurofibrillary tangles (NFTs) and diagnosis of AD in lower age group between 70-74 years (Middleton et al., 2011). The neurofibrillary tangles are composed of abnormally processed microtubule - associated protein tau that participates in a transport of vesicles in the neurons. These pathological alterations in tau are observed in AD and PD pathology (Means et al., 2016).

On the other hand, some studies report that dementia can be present in patients before 65 years of age. It used to be described as "presenile dementia" but it is common to be called "young-onset dementia" in the current published literature. The prevalence of young-onset dementia is 54 per 100 000 between the ages of 30 and 65 years. There are less comorbidities in younger patients that can worsen the cognitive impairment (Rossor et al., 2010).

2.4 Mild cognitive impairment

Mild cognitive impairment (MCI) is considered to be a precursor of dementia in Alzheimer's disease. It represents an early stage of cognitive decline that lasts minimum of six months before the development of dementia. The estimated duration of MCI ranges from one up to ten years. However, it is difficult to set a cut point when the MCI becomes dementia (Wilson et al., 2011).

The hippocampus and entorhinal cortex are the main brain regions affected in MCI and AD. The atrophy in those brain regions and reduction of neurons is associated with aggregates of amyloid beta oligomers and neurofibrillary tangles (Giau et al., 2019). Therefore, mild cognitive impairment affects semantic, working as well as episodic memory. The attention, speed and executive functioning is also disrupted. However, the level of reduction in cognitive functions might be close to performance patterns similar to AD

patients as well as close to performance of healthy individuals. It is difficult to distinguish MCI from normal aging (Demetriou & Holtzer 2017).

Patients with amnestic MCI had a higher risk of developing AD compared to non-amnestic type MCI or dementias not linked with AD (Schneider et al., 2010). The non-amnestic MCI patients have higher risk of developing other neurodegenerative diseases such as Parkinson's disease dementia, dementia with Lewy bodies or frontotemporal dementia (Giau et al., 2019). Recent studies show that mild cognitive impairment can be a risk factor and an early stage of cognitive decline in Parkinson's disease (Goldman et al., 2015).

2.5 Neuropathology of Alzheimer's disease

Clinical diagnosis of dementia in terms of neuropathologic findings is difficult due to overlapping symptoms and often multifactorial causes. There is a huge variety of degenerative pathologies causing the diagnosis to be inconsistent. Indeed, pathophysiology does not have to reflect clinical symptoms. The progression of dementia develops over years changing the cognition, function and behaviour of an individual (Raz et al., 2016).

There are three components essential for the diagnosis of Alzheimer's disease. These include presence of neuritic amyloid plaques at autopsy and neocortical neurofibrillary tangles (NFTs) at high levels. The third element includes clinical dementia with cognitive impairment affecting life on daily basis. The AD neuropathology correlates with the cognitive impairment, but the relationship remains complicated (Nelson et al., 2011). There is a positive correlation between the pathologic markers and cognitive decline, neuroinflammation and neuronal degeneration (Raz et al., 2016). The impairment of functional connectivity is a result of the degeneration of large cortical pyramidal neurons related to AD pathology (Julkunen et al., 2011).

A loss of synapses is part of a normal aging process. However, studies found distinctive synapse elimination in neocortex and hippocampus in AD patients (Scheff & Price, 2006). Further, GABAergic interneurons in hippocampus are lost decreasing the inhibitory synaptic contact (Rozycka & Liguz-Lecznar, 2017).

To be able to diagnose or predict dementia, we need to be able to identify markers before the actual onset of the disease before a progressive loss of cognitive function in patients is detected. Some studies indicate changes in speed of walking, hearing and olfaction up to 15 years before AD dementia develops (Albers et al., 2016).

Clinical research found some changes in motor and sensory systems at early stages of AD. These changes may be caused by neurological impairment or might be independent of cognitive symptoms of AD. The specific markers of dementia in the “preclinical stage” have yet to be defined (Albers et al., 2016).

3. Measurements of changes related to dementia

3.1 Introduction of TMS-EEG methodology

Transcranial magnetic stimulation (TMS) combined with electroencephalography (EEG) is a non-invasive type of technology for investigating the connectivity and cortical reactivity in physiological and pathological conditions like dementia (Julkunen et al., 2011). This multimodal imaging approach contributes to the understanding of connectivity between different brain regions (Bortoletto et al., 2015). TMS-EEG directly stimulates and records from the cerebral cortex and can assess changes in the connectivity and cortical reactivity in healthy or in pathological states (Chang et al., 2019).

Transcranial magnetic stimulation induces action potentials in neurons using time-varying magnetic field and then the electrical brain activity is captured using electroencephalography (Conde et al., 2019). Electroencephalography is highly available and cheap method, which allows to detect changes in the activity of neurons in the human brain. An advantage is the high temporal resolution allowing a precise description of brain activity patterns. However, the spatial resolution is limited compared to other neuroimaging techniques (Al-Qazzaz et al., 2014).

The induced activation by TMS at the specific area of the brain propagates to brain regions that are functionally and anatomically connected. EEG can measure the electrical signal created by the excitatory and inhibitory neuronal activity (Bortoletto et al., 2015). This response induced by the TMS can help us to define the relationship between different brain areas. When area A is active first, then it can increase or decrease activity in the second area B (Bortoletto et al., 2015).

EEG can be used as a physiological biomarker identifying dementia at certain stage using signal processing and analysis. Some studies suggest that dementia can be described on a spectrum that starts with brain being at risk, continues to be mild cognitive impairment and ends with dementia of increasing severinity. (Al-Qazzaz et al., 2014)

3.2 Transcranial Magnetic Stimulation mechanism

Transcranial magnetic stimulation (TMS) is a neuromodulatory technique that is safe and useful for neurophysiological applications. It allows manipulating the human behaviour in a controlled manner by modulating the brain activity in a specific cortical network (Rossi et al., 2009). The neurophysiological method was introduced in 1985 and is used to study the corticospinal pathways in the human brain (Farzan et al., 2016).

TMS works on the basis of Faraday's law of induction where induction coil placed tangential on a specific hotspot and generates time-varying currents. The resulting magnetic field generates a second electric current. The current induced by TMS causes direct depolarization of neurons creating action potentials (Farzan et al., 2016).

Single TMS pulse is often applied to the primary motor cortex activating the upper motor neurons in the specific area of the brain. The application of TMS pulse generates peripheral action potentials in muscles that are easily detectable. These responses are called motor-evoked potentials (MEPs) and we can measure them using electromyography (EMG) (Goetz et al., 2014). The safe dosage for TMS is almost always based on stimulation of the motor cortex. Some possible side effects include induction of seizures, headache, toothache, local pain, some hearing changes or transient acute hypomania (Rossi et al., 2009).

Transcranial magnetic stimulation of the motor cortex can generate two types of waves. First, descending direct wave (D-wave) results from direct activation of corticospinal neurons. Second indirect wave (I-wave) reflects the stimulation of corticospinal neurons via depolarized interneurons (Cirillo & Perez, 2015). The current in the motor cortex can predominantly induce D- or I-waves depending on the orientation and magnitude. There are different TMS protocols to investigate the neural processes like plasticity, excitation, inhibition or connectivity. We can apply one or more pulses of specific frequency and intensity in sensory-motor and non-motor brain regions to address the neural processes (Farzan et al., 2016)

3.3 Electroencephalography mechanism

Electroencephalography is an inexpensive and non-invasive diagnostic tool, which is of great use in dementia pathologies. According to previous studies, changes in the EEG synchrony and reduction in the complexity of EEG signals can be observed in patients with Alzheimer's disease. The EEG signals show lower amplitudes compared to signals from healthy control subjects (Houmani et al., 2018).

The electric field changes propagate to the surface of the scalp but has to pass through many layers including cerebro-spinal fluid, dura, skull and skin. Tightly packed neurons are aligned perpendicular to the surface and their potential propagates at a speed up to 9m/s (Farzan et al., 2016). The most commonly used layout of the electrodes is the 10-20 system that consists of 21 electrodes. An advantage of EEG is that it is not expensive, non-invasive and has a better temporal resolution compared to other techniques like neuroimaging. However, this type of technology is sensitive to artifacts like eye movements and blinks, muscle activity or interference of computers (Cassani et al., 2018).

The electrodes are fitted with a cap according to the International 10-20 system. Electrodes are coated with silver and frequency bands are determined for the data analysis from delta (0.5-3.5 Hz) up to beta (>= 14 Hz) (Salem et al., 2015). Frequency bands recorded by EEG describe different activity of the brain. We can detect unusual frequency patterns from those EEG signals that reflect abnormalities. These can be used to predict stages of dementia which makes EEG a suitable technique for the detection of Alzheimer's disease (Fiscon et al., 2018).

The summation of excitatory and inhibitory postsynaptic potentials is recorded at the scalp. Some studies report an increase in bands with low frequency, but others report decrease in fast-frequency power and amplitude in patients with AD of different severity. The EEG changes with memory, attention, an ability to perform everyday activities or neuropsychological performance in individuals with impaired cognition (Smailovic & Jelic, 2019).

3.4 Motor-Evoked Potentials (MEPs) and TMS-Evoked Potentials (TEPs)

When TMS is applied to the motor cortex it causes a discharge in the spinal motor neurons creating activity in the corticospinal tract. This application directly induces Motor-evoked potentials (MEPs) in muscles. They can vary remarkably in amplitude when the TMS stimulus is applied at different locations and intensities. Therefore, most studies have used sub-threshold or supra-threshold stimulation (Petrichella et al., 2017).

A combination of transcranial magnetic stimulation (TMS) with simultaneous electroencephalography (EEG) can be used to stimulate and record responses from different brain areas that are not limited only to motor areas (Du et al., 2017). The TMS-evoked potential (TEP) is a complex waveform composed of peaks at different latencies lasting 300ms or even more (Hill et al., 2016). It is suitable to use subthreshold intensity around 60% of the MEP treshold to measure TEP when studying the cortical excitability (Komssi & Kähkönen, 2004). TEPs are sensitive to the intensity of a stimulation and orientation of the coil that gives direction of the induced current (Tremblay et al., 2019).

Some studies report that MEPs remain constant during the day (Ter Braack et al., 2019). In contrast, MEPs can be highly variable according to other studies when same stimulation intensity is applied to an area of motor cortex creating fluctuations in the excitability (Darling et al., 2006). When the stimulus intensity and muscle activation increases, the relative variability of amplitudes of MEP decreases (Darling et al., 2006).

The TMS-evoked potential is considered to be a more direct measure of cortical excitability than MEP. The TEP remains constant when measured at different times of the day too (Ter Braack et al., 2019). TEPs have increased power in frequency bands and they are not confounded by muscle artifacts or any other sensory activation that is found in MEP measurements. Stimulation of M1 region generally elicits larger TEPs in comparison with other stimulated locations in the brain. Possible reasons are that M1 is more excitable than other cortical areas (Fecchio et al., 2017).

3.5 TMS protocols to study cortical excitation and inhibition

Several TMS-EEG techniques are used to explore the excitatory and inhibitory processes in the cortex. At first, they were used as TMS-EMG methods to study the activity of the motor cortex. Nowadays we can see both intracortical processes as changes in the amplitude of MEPs as well as in the TEPs. The five commonly used protocols include cortical silent period (CSP), long-interval intracortical inhibition (LICI), short-interval intracortical inhibition (SICI), short-latency afferent inhibition (SAI) and intracortical facilitation (ICF) (Tremblay et al., 2019).

Cortical silent period (CSP) is a silence or a section of reduced electrical activity after an excitatory response known as Motor-evoked potential (Özyurt et al., 2019). The participant has to contract the muscle voluntarily to observe the silent period. The CSP can last up to 300 ms and is dependent on the intensity of the stimulus (Wu et al., 2002). However, the relationship between CSP and intensity of the stimulus remains unclear. When muscle contraction increases, the MEP amplitude also increases but the CSP stays the same (Kojima et al., 2013). The duration also reflects a strength of an inhibition in the motor cortex mediated by the $GABA_B$ receptors. Both MEP and CSP are indicators for plasticity and several neurodegenerative diseases like Parkinson's disease (Özyurt et al., 2019).

Long-interval intracortical inhibition (LICI) is a paired pulse protocol for inhibition in which a suprathreshold conditioning stimulus followed by a second suprathreshold test stimulus. The interval between both stimuli is 50-200ms (Salavati et al., 2018). We can measure LICI from motor-evoked potentials in muscles or we can use EEG from the motor cortex. There is a TEP inhibition peak around 150ms following TMS but the sensitivity to changes in parameters of the stimulation are unclear (Rogasch et al., 2013). Other sites of stimulation can be used for example prefrontal regions. Although the neuronal mechanisms of inhibition are not yet understood, we can still use TMS for the diagnosis neurological disorders. The LICI paradigm also reflects $GABA_B$ inhibition of γ-aminobutyric acid (GABA) release mediated by receptors in the human cortex (Werhahn et al., 1999).

In short, in intracortical inhibition (SICI) the interval between the two subthreshold stimuli is much shorter compared to LICI. This interstimulus interval of 1-6ms inhibits the response in the motor cortex. SICI predominantly affects the I-waves and has been used to study healthy subjects as well as patients with neurological disorders (Wessel et al., 2019). It also increases the neurotransmission through receptors $GABA_A$ causing auto-inhibition of interneurons. SICI reduces short-latency afferent inhibition (SAI) and both are considered neurophysiological markers for neurological disorders (Alle et al., 2009). Some studies observe an increase in SICI as an age-related effect, other studies report decrease in SICI in older individuals (McGinley et al., 2011).

Short-latency afferent inhibition (SAI) in an inhibitory cortical circuit applied to motor cortex in which the TMS test pulse comes 20-25 ms after the first stimulus. This type of stimulation leads to a suppression of the MEP and modulation of N100 component of TEP after median nerve stimulation (Noda et al., 2016). SAI is mediated by $GABA_A$ and cholinergic neurotransmission. Neurons with $GABA_A$ receptors are projecting to the cortex and the antagonist enhances a release of the neurotransmitter acetylcholine. Cholinergic dysfunction as a result of reduced SAI can be significant for neurological disorders like Alzheimer's or Parkinson's disease (Di Lazzaro et al., 2005).

Intracortical facilitation (ICF) results from a paired-pulse TMS over the motor cortex. We can facilitate the MEPs when we apply the subthreshold stimulus at an interval 10-15 ms in advance. Voluntary contraction reduces ICF compared to muscle contraction with fatigue or at rest (Hunter et al., 2016). During ICF, cortical pyramidal cells are activated even though the mechanisms are not clear (Chen et al., 1998). ICF is mediated by N-methyl-D-aspartate (NMDA) receptors and glutamatergic interneurons that are excitatory. The mediation takes place in motor cortex (M1) but might be also influenced by spinal mechanisms (McGinley et al., 2011).

4. TMS-EEG Diagnosis of neurological disorders

4.1 Findings in young healthy subjects

We can assess the cortical connectivity and reactivity by stimulating a specific brain region with TMS and evaluating the propagation of the activity using EEG in young healthy subjects (Petrichella et al., 2017). We can expect some variability when TMS is applied to the cortex probably due to individual differences. TMS will affect some circuits and not others because it triggers polysynaptic circuits with variable delays affecting several synapses. When we stimulate the motor cortex, the TMS-evoked activity spreads to pre-motor, contralateral motor, frontal and even sensory motor areas of the cortex over time (Huber et al., 2008). However, the cortical origin and the functional meaning of TEP peaks are not well understood (Yamanaka et al., 2013).

Applying a single TMS pulse to both right and left motor cortex (M1) creates an activity lasting up to 300 ms that can be recorded with EEG (IImoniemi et al., 2010). A Stimulation of M1 activates the motor network but activation spreads to other areas including cingulate gyrus and temporo-parietal junction. The TMS-EEG is a potential neurophysiological marker for diagnosis of AD because it is useful for detecting interactions of brain areas during motor control which is significantly decreased in AD patients (Hallett et al., 2017). Several TEP components can be identified in the response structure that are in agreement with previous findings. The first one is a negative deflection in EEG that peaks around 15 ms after the stimulus called N15. The second component is the positive P30 followed by N45, P55, N100, and P180. However, the components can be different between individuals (IImoniemi et al., 2010). A close series of positive peaks at 30, 60 and 170 ms and negative peaks at 46, 100 and 279 ms in TEPs can be equally observed. For trials with MEP the latencies are 30, 44, 54, 100, 164 and 270 ms (Petrichella et al., 2017).

The intensity of the TMS stimulus can affect the amplitude of TEP components. Supra-threshold stimulation evokes larger (more negative) N100 component compared to sub-threshold TMS stimulation. A decrease in GABA

and increase in glutamate neurotransmitter levels predicts larger N100 component in pre-frontal cortex but no correlation was found when TMS was applied to M1. The N100 component is linked to cognitive performance (Du et al., 2018). Motor-evoked potentials can be a measurement of upper-motor function in healthy individuals. We can measure the amplitude and latency of MEPs that provides information about the function of the motor cortex. When TMS is applied to the primary motor cortex, the descending corticospinal volleys activate the spinal motor neuron that generates the MEPs (van den Bos et al., 2017).

Voluntary contraction changes the shape of MEPs in many ways. Mainly it causes facilitation of MEPs, i.e. the latency gets shorter, the duration is wider, and the amplitude is increased. A possible explanation is that more motor neurons are put near the firing threshold (Brum et al., 2016). Indeed, the corticospinal excitability is modulated by voluntary movement, but the ability differs based on the muscle type being contracted. On the other hand, the stimulation intensity has a major effect on MEPs (Saito et al., 2014)

The orientation of the coil has an effect on the MEPs. Anterior-posterior (AP) currents induced by the coil have higher thresholds and often evoke longer MEPs. A posterior-anterior (PA) current flow that is induced by placing the coil at an angle of 45° evokes MEPs that have lower intensity and shorter-latency responses (Adank et al., 2018) After close observation, the posterior-anterior (PA) currents recruit the indirect waves (I - wave) and the anterior-posterior (AP) currents recruit the late I - waves suggesting an activity of different excitatory inputs (Day et al., 1989).

Frequency of pulses might affect the amplitude of MEPs. Low frequency pulses (around 1 Hz) reduce the MEP amplitude by 10 - 25%. High frequency pulses (5 - 20 Hz) increase the MEP amplitude by around 35% measured for 60 seconds. These observations are related to brain plasticity mechanisms (Fried et al., 2017). Most studies with TMS tend to focus on certain stimulus strengths usually evoking EMG response of 50 microvolts (Goetz et al., 2014).

4.2 Findings in old healthy subjects

The age-related decline in motor and cognitive performance can be probed by TMS. A decline in sensorimotor and cognitive functions is part of normal aging. The TMS measurements are different in older adults compared to young healthy subjects. However, there is a huge heterogenity in elderly population partly explaining diverse TMS results (Houde et al., 2018).

The sensorimotor deficits in older adults are correlated with altered excitability specifically different excitatory and inhibitory mechanisms in the motor cortex (Levin et al., 2014). A decrease in cortical excitability is part of normal aging. This is demonstrated in reduced magnitude of paired pulse inhibition in elderly when the interstimulus interval is 1-5 ms. However, no effect of age is registered for paired pulse facilitation with interstimulus interval of 11-15 ms (Peinemann et al., 2001).

The amplitude of MEPs changes with aging. Some studies show that the amplitude of MEPs are significantly smaller in older subjects compared to young controls suggesting impaired efficiency in intracortical circuits of cerebral cortex (Oliviero et al., 2006). Rossini et al. (1992) also revealed lower MEP amplitudes and higher motor thresholds when comparing these two groups. The negative correlation between age and the amplitude of MEP at most stimulus intensities is in agreement with previous findings. The amplitude of MEPs was also more reduced during isometric contraction (Talelli et al., 2008).

On the other hand, other studies report no significant change in MEP amplitude between young and older subjects. Elderly have increased SICI and LICI and decreased ICF compared with young subjects (McGinley et al., 2011). LICI of P180 and N100 was increased in older group when 100 ms and 150 ms interstimulus intervals were used. The findings suggest that aging is associated with potentiation of inhibition in $GABA_B$ receptors (Opie et al., 2018). But contradictory results like a decrease in SICI related to aging are also reported (Marneweck et al., 2011). The cortical silent period (CSP) after a single TMS pulse is longer than in young adults (McGinley et al., 2011).

Higher stimulus intensities are needed in older subjects to evoke the same amplitude of MEP as reached in young subjects. In other words, the rate of increase in MEP amplitude relative to increasing intensity of stimulus is slower in elderly. These results point to lower corticospinal and M1 excitability in older adults (Pitcher et al., 2003).

Another reason for changes in the cortical excitability is the problem with the definition of resting motor threshold. The resting motor treshold (rMT) is the minimum intensity of stimulation needed to elicit a response of 50 microvolts. Usually me measure 10 trials and find the lowest intensity in at least half of the trials (Cosentino et al., 2018). The resting motor treshold strongly modulates the values of MEP. Lower rMT caused larger MEP values. However, no age-related changes were found for the stimulus and response (Smith et al, 2011).

When elderly participants were divided into "young" old aged 55 - 65 years and "old" old above 65 years old, no differences between rMT were found between both groups (Smith et al., 2011). On the other hand, the motor thresholds are not always modulating MEP values. Some studies found the MEP values were not affected by motor thresholds (Talelli et al 2008).

The TEP components also change with physiological aging. A single pulse stimulation applied to the motor cortex in elderly causes shorter latency of P30 but the amplitude of this component is not affected by age. The latency of P180 is longer in elderly and also shows altered spatial distribution. The amplitude of N45 is increased in older adults (Opie et al., 2018). The increase in N45 and N100 amplitudes was demonstrated in one study but no significant effect was observed in a second experiment (Premoli et al., 2014).

Other studies found decreased amplitude of N45 in elderly and increased amplitude of P30 after stimulating the primary motor cortex (Ferreri et al., 2017). Reduced inhibition on N100 and reduced amplitude of this component was demonstrated with SICI paradigm. The ICF induced facilitation and reduction in amplitude of component N45 in elderly and N45 was inhibited in young adults (Noda et al., 2017).

4.3 Findings in patients with Mild Cognitive Impairment

The prodromal state of Alzheimer's disease is impaired episodic memory or other cognitive loss called mild cognitive impairment (MCI). Subjects with MCI have a higher risk of developing AD and early detection of changes would be desirable in the diagnosis of both MCI and AD (Julkunen et al., 2011). The degree of cognitive impairment correlates with the progression to greater severity of dementia in individuals with MCI representing an early stage of AD (Morris et al., 2001).

No significant changes were observed in P30 peak amplitude between the MCI and AD group or when compared to the healthy controls. The latencies of P30 components also remained similar (Julkunen et al., 2011). The amplitude of N100 component is significantly lower in MCI subjects that the amplitude in control subjects (Julkunen et al., 2008).

Different protocols were used to assess the intacortical connectivity in patients with MCI. The SAI seems to be unimpaired and ICF together with SICI is probably impaired (Padovani et al., 2018). The reduced SAI in MCI patients was also recorded where the healthy control subjects matched in age with the patients. ICF and SICI were not different for these two groups (Tsutsumi et al., 2012). The SAI was not impaired in other studies suggesting a possible normal cholinergic activity in patients with MCI even when the regulation that keeps the levels normal remains unclear (Sakuma et al., 2007). More studies found lack of impairment in SAI in MCI patients that were classified as non-AD and they also had impaired SICI and ICF (Padovani et al., 2018).

There are contradictory findings about the motor threshold in MCI subjects. The motor threshold is significantly higher in the left hemisphere in MCI subjects compared to AD patients. Indeed, the motor threshold for healthy controls is much lower (Julkunen et al., 2008). However, no significant changes in the motor threshold were observed between the controls, MCI patients and AD patients (Julkunen et al., 2011).

4.4 Findings in Alzheimer's disease patients

A substantial effort is made to develop an accurate diagnostic tool using the preclinical biomarkers to diagnose Alzheimer's disease (AD) and discriminate the disease from others like frontotemporal dementia (FTD). The accuracy of identifying AD with TMS is very high reaching 90% at an early stage of the disease (Benussi et al., 2018). A number of clinical studies conclude that EEG is a suitable technology for AD detection at early stages. EEG predicts the stages of dementia because it generally correlates with the severity of cognitive impairment (Fiscon et al., 2018).

The primary motor cortex experiences change with the development of Alzheimer's disease (Chen et al., 1991). The motor function is intact in early stages of AD therefore the structural changes in M1 are very moderate compared to other brain areas. The functional connectivity alterations possibly precede the structural changes therefore we could distinguish MCI and diagnose AD (Julkunen et al., 2011).

In Alzheimer's disease, the findings on MEP amplitude are very heterogeneous. For example, it has been found that the MEP amplitude can be increased, or it can remain at normal levels (Vucic & Kiernan, 2017). The MEP amplitude reflects the function of motor cortex neurons with higher-threshold (Vucic & Kiernan, 2017). The MEP amplitude remains normal at early stages of Alzheimer's disease but the levels can increase with disease progression (Ni & Chen, 2015). An increased amplitude of MEP evoked by paired TMS was found in AD patients compared to young and old healthy participants (Pepin et al., 1999). However, there were also normal levels of MEP amplitude that did not differ between AD patients and age-matched healthy controls have been observed (Di Lorenzo et al., 2013). The MEP latency is usually shorter in AD patients (Khedr et al., 2011).

The TMS-evoked P30 component is significantly reduced in early stages of AD when compared to healthy controls and MCI patients indicating changes in the cortical connectivity. The location of the reduction is the sensorimotor network and temporo-parietal area both interconnected with the motor cortex being stimulated (Julkunen et al., 2008). But when P30 amplitude was related

to the clinical dementia rating scale, different results were found. Lower amplitude of P30 peak in AD patients was observed in comparison with healthy controls and the cognitive decline correlates with the P30 amplitude as a response. The latencies of this component were similar (Julkunen et al., 2011). However, AD patients exhibited significantly delayed latency in P30 component compared to frontotemporal dementia patients (Wang et al., 2016). The P30 latency was significantly different with a delay not only compared to a FTD group but also to the control group (Jiménez-Escrig et al., 2002). Higher amplitudes of P30 in superior parietal cortex in AD patients predict worse memory and cognitive performance (Bagattini et al., 2019). The amplitude as well as latency of N20 TMS component had normal values in AD patients and age-matched healthy controls (Di Lorenzo et al., 2013).

Short-latency afferent inhibition (SAI) is specifically impaired in AD patients compared to patients with FTD. According to these findings, the sensitivity of distinguishing these two conditions from another is 92% (Benussi et al., 2017). Reduced SAI in AD patients is also observed in comparison with age-matched healthy controls (Di Lazzaro et al., 2002). These findings in AD may point to the dysfunction of cholinergic circuits (Di Lazzaro et al., 2006). Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) are not impaired in AD suggesting normal glutamatergic neurotransmission (Benussi et al., 2018). Other studies found no effects for SICI and ICF in AD patients and age-matched healthy controls (Di Lorenzo et al., 2013).

The resting motor treshold (rMT) is reduced when compared to most of the groups. RMT for AD group is significantly lower compared to MCI subjects (Julkunen et al., 2011). In comparison with frontotemporal dementia patients, the RMT values are reduced (Wang et al., 2016). When compared with healthy controls, the resting motor threshold decreased in AD patients (Di Lazzaro et al., 2002). It is also reduced in AD when we compared to age-matched healthy subjects (Di Lazzaro et al., 2004). Insterestingly, early stages of AD and MCI patients have preserved normal levels of rest motor threshold (Ni & Chen, 2015).

4.5 Findings in other dementia patients

Even though the diagnostic criteria exist, it remains poorly diagnosed and it is difficult to distinguish frontotemporal dementia from other dementias (Nardone et al., 2018). The MEP amplitude is reduced, and the latency is prolonged in FTD indicating a possible dysfunction in motor circuits (Vucic & Kiernan, 2017).

The latency of P30 component is higher in a group of FTD patients compared to AD patients but the amplitude is similar for both groups. No correlation was found between P30 amplitude and cognitive scores evaluated with Montreal Cognitive Assessment (MoCA) scores and Mini-Mental State Examination (MMSE) (Wang et al., 2016). A longer latency of the P30 component was observed when FTD patients were compared with healthy controls. Indeed, the results show smaller amplitude of P30 in FTD patients. The amplitudes and latencies of N200 TMS component had no significant differences between groups (Chen et al., 2015).

Short-latency afferent inhibition (SAI) is normal in frontotemporal dementia patients suggesting optimal function of cholinergic circuits (Cantone et al., 2014). A notable dysfunction of short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) circuits was found in frontotemporal dementia patients with mild symptoms of the disease (Benussi et al., 2017). The SICI impairment is a marker for abnormal $GABA_A$ neurotransmission and ICF impairment is a marker for glutamatergic neurotransmission (Benussi et al., 2018). The functional decline, i.e., specifically the disease severity correlates with the SICI, ICF and LICI measures in FTD patients. In particular, there was a reduction in all three protocols in FTD group (Benussi et al., 2020).

On the other hand, other studies found no significant changes in ICF values in FTD patients, AD patients and controls when paired pulse TMS was applied. Results suggest that the motor cortex is probably not involved in this type of dementia (Pierantozzi et al., 2004).

Patients with Parkinson's disease dementia have a motor and mood symptoms (Brys et al., 2016). The MEP amplitude is significantly increased in PD patients (Chen et al., 2001). More studies also found increased MEP amplitude that might be related to the changes in the motor pathway (Cantello et al., 1991).

There are conflicting results on short-latency afferent inhibition (SAI). The levels can be normal, reduced or even enhanced in PD patients (Dubbioso et al., 2019). Some studies show significantly reduced SAI compared with control subjects. The gait speed is correlated with SAI values in participants with PD (Rochester et al., 2012).

The cognitive impairment is related to the cholinergic dysfunction in PD patients that will develop dementia as a sign of severe cognitive decline. SAI was reduced in PD patients that experience visual hallucinations, but their cognitive impairment was only mild (Manganelli et al., 2009). Other studies report significantly enhanced SAI levels in hemiparkinsonian patients in their affected side when compared to age-matched controls (Di Lazzaro et al., 2004a). The results on SICI and LICI in PD patients are controversial, because the levels can remain normal or can be decreased (Ni & Chen, 2015).

Dementia with Lewy bodies (DLB) share many features with Parkinson's disease dementia like cognitive fluctuations and motor impairments. The P30 TMS component has a lower amplitude in DLB compared to AD patients but the latency is delayed. The delayed response of this component correlates with the severity of mentioned cognitive fluctuations (Cromarty et al., 2016).

SICI was measured in DLB patients and compared with age-matched controls and AD patients. SICI was significantly reduced in DLB and AD patients, both are cholinergic forms of dementia (Di Lazzaro et al., 2007). But other studies report no significant difference in SICI between DLB patients and controls (Nardone et al., 2006).

5. Discussion

5.1 Continuum model and MEP amplitude

Transcranial magnetic stimulation with electroencephalography is a powerful and useful non-invasive tool to study the cortical excitability of the human cortex. The findings are abnormal for the patients with neurodegenerative diseases and these clinical biomarkers could aid and potentially confirm an early diagnosis of dementia (Ni & Chen, 2015).

It is beneficial to think about dementia as a pathological and clinical continuum slowly progressing in time with a decrease in cognitive function. According to the model of clinical trajectory, the preclinical stage precedes the mild cognitive impairment (MCI). The MCI patients with positive biomarkers will necessarily develop clinical AD dementia (Sperling et al., 2012).

The amplitude of MEP is reduced in older subjects compared to controls which might be a sign of impaired intracortical circuits thus a prediction of dementia in the future (Oliviero et al., 2006). The same reduction of MEP amplitude is found in patient with frontotemporal dementia suggesting impaired motor circuits (Vucic & Kiernan, 2017). But we can also argue that reduced MEP amplitude is a measurement of normal aging process because there is a huge heterogeity in elderly (Houde et al., 2018).

Opposite findings were observed in patients with Alzheimer's disease. Their MEP amplitude remains at normal level or is enhanced when compared to both old and young subjects (Pepin et al., 1999). Increased MEP amplitudes were found in PD patients too (Chen et al., 2001). An increase in MEP amplitude in AD patients is probably because some subjects in the group might have worse stage of Alzheimer's disease and progressive dementia (Ni & Chen, 2015). Not all AD patients have exactly the same symptoms resulting in high intersubject variability in MEP levels (Vucic & Kiernan, 2017).

5.2 P30 component and TMS protocols

The P30 component might be a biomarker of dementia helping to distinguish different neurodegenerative diseases. The amplitude of P30 is normal in healthy controls compared to elderly and it is not affected by age reducing the potential factor (Opie et al., 2018). In contrast, the amplitude of P30 in AD patients is decreased compared to healthy controls (Julkunen et al., 2011). The reduction is located in fronto-central cortex corresponding to the sensorimotor area. The activity is mediated by $GABA_A$ neurotransmission located with the motor cortex (Julkunen et al., 2008). The latency of P30 is delayed compared to patients with FTD distinguishing these two dementia conditions. Indeed, longer latency was found in FTD patients too (Wang et al., 2006).

The TMS protocols to study excitatory and inhibitory processes and connectivity provide us with promising results (Farzan et al., 2016). Patients with mild cognitive impairment have the same overall results as patients with frontotemporal dementia which might be just a more severe form of dementia on the continuum scale. Both groups of patients have normal levels of short-latency afferent inhibition (SAI) that is unimpaired (Padovani et al., 2018; Cantone et al., 2014). Normal SAI suggests an optimal function of cholinergic activity in both groups (Sakuma et al., 2007).

On the other hand, short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) are impaired in MCI and FTD groups where FTD patients had a mild form of the disease (Padovani et al., 2018; Benussi et al., 2017). The SICI is a reflection of changes in the $GABA_A$ neurotransmission (Benussi et al., 2018). Impaired glutamatergic and NMDA receptor neurotransmission is a result of disturbed ICF levels (McGinley et al., 2011).

An exactly opposite findings in patients with Alzheimer's disease can be used as a biomarker for diagnosis of this type of dementia. SAI is impaired in AD patients when compared to FTD patients (Benussi et al., 2017). This impairment points out to the dysfunction of cholinergic circuits in AD dementia (Di Lazzaro et al., 2006). In contrast, SICI and ICF are not impaired in AD

patients indicating a normal glutamatergic neurotransmission (Benussi et al., 2018).

We have not identified any specific biomarkers on the diagnosis of Parkinson's disease dementia and dementia with lewy bodies. Findings on SAI for PD patients are not clear, because SAI can be normal, decreased or increased (Dubbioso et al., 2019). SICI and LICI can be normal or decreased (Ni & Chen, 2015). Indeed, findings on SICI in DLB patients were also not distinct (Di Lazzaro et al., 2007; Nardone et al., 2006).

5.3 Limitations

Many questions remain after the discussion opening the possibility for deeper research in the topic. Currently, there is no single biomarker that could be used to confirm any of the neurodegenerative diseases. However, our findings could be translated into clinical applications that could be used for diagnosis (Ni & Chen, 2015).

Small sample size is very common in studies with TMS-EEG methodology. In some studies, only five patients with MCI and five patients with AD were compared with four healthy controls (Julkunen et al., 2008). Other studies included only nine subjects in their experiment (Julkunen et al., 2011). Small sample size causes low statistical power that negatively affects the opportunity to find a true effect. Therefore, studies have a higher chance to produce a false negative results. If the true effect is found, it is still likely that the magnitude of the effect will be exaggerated (Button et al., 2013).

The subjects in the studies are not always representative of the whole population. The limitation comes from the TMS measurements that have a very high variability not only between subjects, but also within-subjects (Ni & Chen, 2015). For example, findings on SAI for PD patients are very inconsistent telling us a huge diversity of measurements (Dubbioso et al., 2019). The results have a low reproducibility due to high variability among patients. Replication studies usually does not reach previous nominal statistical significance and only achieve around 50 % power of the original study (Button et al., 2013).

5.4 Conclusion

The aim of this review is to investigate the usage of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) for the possible diagnosis of dementia. Answers to the three questions that we have asked at the beginning are found below.

1. What are the differences in TMS evoked potentials (TEPs) between healthy controls and patients with dementia as part of some neurodegenerative disease?

Based on our research presented in the review, one of the promising components of TMS-evoked potentials is the P30 component that could be a potential biomarker of dementia. The amplitude of P30 is not be affected by age (Opie et al., 2018). In Alzheimer's disease patients, the amplitude of P30 is reduced compared to healthy controls (Julkunen et al., 2011). Patients with FTD had smaller P30 amplitude compared to healthy subjects too (Wang et al., 2016). The latency of P30 in patients with frontotemporal dementia is longer and delayed as compared to AD. This distinguished these two types of dementia (Wang et al., 2006). Other TMS induced components like N200 did not show any significant differences between healthy young controls and patients with dementia like frontotemporal dementia (Chen at al., 2015). Even though more research is needed, we can assume that reduction in P30 component is linked to dementia.

2. How does the motor evoked potentials (MEPs) differ between healthy participants and people with dementia?

Findings on motor-evoked potentials focus mainly on the differences in MEP amplitude. The MEP amplitude is decreased in healthy elderly suggesting that the reduction can be a sign of normal process of aging (Houde et al., 2018). In some dementia patients like patients with FTD, the MEP amplitude is reduced probably due to impaired motor circuits (Vucic & Kiernan, 2017). On the other hand, Alzheimer's disease patients and patients with Parkinson's disease dementia have increased MEP amplitude or even enhanced levels (Pepin et al., 2001; Chen et al., 2001). Therefore, we can conclude that MEP amplitudes help us to distinguish dementia from normal aging. More research is needed to identify possible factors that influence the motor evoked potentials (MEPs).

3. What are differences in measurements using TMS protocols in people with dementia compared to healthy controls?

Findings on TMS protocols to investigate excitation and inhibition show us a clear pattern between dementia patients and healthy controls (Farzan et al., 2016). Short-latency afferent inhibition (SAI) is unimpaired in patients with MCI and FTD (Padovani et al., 2018; Cantone et al., 2014). Normal SAI levels probably point to an optimal cholinergic activity in both groups (Sakuma et al., 2007). Their short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) are impaired in FTD and MCI patients (Padovani et al., 2018; Benussi et al., 2017). The SICI is a result of changes in the $GABA_A$ neurotransmission (Benussi et al., 2018). Disturbed ICF levels are linked to glutamatergic and NMDA receptor neurotransmission (McGinley et al., 2011).

However, findings on Alzheimer's disease dementia patients are contrasting these two groups. SAI is impaired in Alzheimer's disease patients compared to FTD patients (Benussi et al., 2017). SICI and ICF are not impaired in AD patients that indicates normal glutamatergic neurotransmission (Benussi et al., 2018).

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