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Cognitive workload across the spectrum of cognitive impairments: A systematic review of physiological measures

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ABSTRACT

Our objective was to identify the physiological measures that are sensitive to assessing cognitive workload across the spectrum of cognitive impairments. Three database searches were conducted: PubMed, PsychINFO, and Web of Science. Studies from the last decade that used physiological measures of cognitive workload in older adults (mean age >65 years-old) were reviewed. The cognitive workload of healthy older individuals was compared with the cognitive workload of younger adults, patients with mild cognitive impairment (MCI), and patients with Alzheimer's diseases (AD). The most common measures of cognitive workload included: electroencephalography, magnetoencephalography, functional magnetic resonance imaging, pupillometry, and heart rate variability. These physiological measures consistently showed greater cognitive workload in healthy older adults compared to younger adults when performing the same task. The same was observed in patients with MCI compared to healthy older adults. Behavioral performance declined when the available cognitive resources became insufficient to cope with the cognitive demands of a task, such as in AD. These findings may have implications for clinical practice and future cognitive interventions.

1. Introduction

Cognitive workload is defined as the mental effort or the amount of attention allocated to perform a task (Kahneman, 1973). The concept of cognitive workload may be explained by a large number of theories including working memory, cognitive, or attentional theories (Baddeley, 1996; Kahneman, 1973; Sweller, 1994; Treisman, 1964). Central to these theories is the notion of limited resources. Based on the concept that our attentional capacity is limited, performance decreases when the task demands exceed the available capacity or when the available cognitive resources are allocated to other mental activities (Kahneman, 1973). In other words, when the cognitive workload required by the task is lower than the available cognitive resources, the task will be executed accurately. However, when the cognitive workload exceeds the available cognitive resources, the task performance will decrease. These cognitive resources may decrease due to physiological changes in cognitive functions as a result of healthy aging or dementia.

With fewer cognitive resources available to allocate to a task, older adults may show greater cognitive workload to perform equally well on a task as younger adults. This increased cognitive workload may be a predictor of future cognitive decline (Ahmadlou, Adeli, Bajo, & Adeli, 2014; Aurtenetxe et al., 2013; F. C. Maestu, 2008). An anticipated silver tsunami, with older adults becoming the fastest growing segment of the population, will lead to an exponentially increasing number of individuals with cognitive impairments (Reitz, Brayne, & Mayeux, 2011). Cognitive decline is believed to progress from a preclinical state to mild cognitive impairment (MCI) and later to Alzheimer's disease (AD), which is the most common type of dementia (Reitz et al., 2011). It is therefore paramount to find measures that could detect early cognitive decline in older adults, even before their manifestation in everyday behavior. Early detection of cognitive deficits may have implications for early clinical diagnosis, timely medical intervention, and early implementation of an effective rehabilitation protocol to stem the cognitive deterioration before cognitive symptoms emerge. Since cognitive deficits are associated with decreased quality of life (Lawson et al., 2014), early identification and management of cognitive deficits could lead to better quality of life for older adults.

Different measures including subjective, behavioral, and physiological measures are available to assess cognitive workload. Subjective measures such as self-report ratings (e.g., NASA-Task Load Index) can be collected immediately after each task (Hart & Staveland, 1988). However, this method of assessment may be problematic in terms of reliability since it depends on the perception of the individuals. Even when subjective rating scales are applied repeatedly within a task, it is unclear if the subjective methods provide a continuous measure of fluctuations in cognitive workload during task performance (Antonenko, Paas, Grabner, & Gog, 2010). Behavioral measures such as performance from neuropsychological tests may be indirect measures of cognitive workload amount. Yet, similar to subjective measures, behavioral measures are not continuous. Physiological measures have the advantage to assess cognitive workload in-real time and can provide a continuous recording of data over time. Physiological measures may reflect early cognitive change which may appear before manifestation of symptoms in behavioral performances (Ahmadlou et al., 2014; Aurtenetxe et al., 2013; Bajo et al., 2010; Bokde et al., 2006; Chapman et al., 2007; Kochan et al., 2010; Leyhe et al., 2009; F. C. Maestu, 2008; Vannini et al., 2008).

Cognitive workload has been associated with a range of physiological measures. The most common physiological measures include electroencephalography (EEG) or magneto-encephalography (MEG), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), measures from eye tracking or/and pupillometry (e.g. pupil size), cardiovascular measures (e.g. blood pressure), and electrodermal measures.

In this literature review, we will provide an overview of studies that used the most common physiological measures to assess cognitive workload across the spectrum of cognitive impairments, including normal healthy aging, MCI, and AD. We restricted our search to the last decade because the literature during this period in comparison to other decades showed increased use of technologies such as high resolution fMRI. In this review, we will therefore address 2 main questions: 1) What are the physiological measures sensitive to assessing cognitive workload in healthy aging? 2) What are the physiological measures sensitive to assessing cognitive workload in

mild cognitive impairment and Alzheimer's disease?

Finally, we will address a number of remaining problems and point out directions for future research in this field.

2. Methods

2.1 Data sources and searches

This systematic review adhered to the PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). The four authors developed the search strategies with the assistance of an academic librarian. The literature search was performed using a combination of the keywords: cognitive workload, physiology, neurophysiology, cognitive science, electroencephalography, magnetoencephalography, functional magnetic resonance imagery, positron emission tomography, eye tracking, pupillometry, blood pressure, electrodermal measures, and their related search terms. The full list of search items can be found in our predefined protocol (available on request). Only articles written in English and published from January 1, 2006 to June 7, 2017, were included. Articles were searched in the following databases: PubMed, PsychINFO, and Web of Science. A hand search of the reference list of candidate articles was also performed.

2.2 Study selection

For the purpose of this review, all prospective or retrospective case series, comparative, case-control, cohort studies, and RCT's were selected on a number of eligibility criteria: (i) studies including at least one age group with an average age of 65 years old or older with or without MCI or Alzheimer's disease; (ii) studies including physiological measures in resting-state conditions associated with cognitive tests; (iii) studies including physiological measures in real-time while participants performed a cognitive task. Case reports ($n < 10$), editorials, guidelines, letters, and reviews were excluded.

2.3 Study and data extraction

Titles and abstracts were scanned for relevance by M.R. The full texts of candidate

articles were then appraised independently by H.D. and M.R. to confirm the eligibility. The two reviewers were not blinded to authors and study outcomes, because blinding has little effect on the outcome of systematic reviews. In case of disagreement, a third reviewer (J.C.M) made the final determination regarding eligibility. Data extractors collected information about population characteristics (number of adults, age, Mini Mental State Examination (MMSE) scores or Montreal Cognitive Assessment (MOCA) scores when available, task paradigm (type of task, number of conditions), main outcomes, and main results.

3. Results

The search process produced a total of 244 articles (electronically = 220; hand search = 24) out of which only 40 were eligible for final inclusion in the review (Fig. 1). Tables 1 and 2 summarize the studies in healthy aging (n = 13) and studies in MCI and/or AD (n = 28). The 13 studies on healthy aging included 12 studies that used a cross-sectional design, and one study that used a cohort design. Of the 28 studies on MCI and/or AD, 26 used a cross-sectional design and two studies used a cohort design.

Studies included in the literature review will be discussed in two sections. The first section will identify the physiological measures sensitive to healthy aging. The second section will characterize the physiological measures sensitive to MCI and/or AD.

3.1. What are the physiological measures sensitive to assessing cognitive workload in healthy aging?

3.1.1. Study that used physiological measures during resting state conditions

a. EEG

EEG provides a direct measure of electrical activity produced by the brain via electrodes that are placed on the scalp. This technique, which measures changes in cognitive activity over time produces outputs with high temporal resolution. The rhythmic activity is divided into slow rhythm frequency bands (delta, theta, and alpha bands) and fast rhythms frequency bands (beta and gamma bands) (Volf & Gluhih,

2011). Based on the literature search, one study identified age-related changes in the resting state EEG power of the slow and fast rhythms recorded at different sites of the brain (Volf & Gluhik, 2011). The objective of the study was to investigate whether the observed age-related changes reflected progressive compensatory rearrangements of cerebral activity during healthy aging. Their results showed that the fast rhythms (beta or gamma) increased when subjects' eyes were open in healthy older adults compared to younger adults. An increase in the power fast rhythms, specifically in beta bands, may reflect mobilization of larger resources. According to authors, this result supports the notion that a reorganization of cortical networks occurs due to age related physiological changes. This reorganization of cortical networks is essential for the involvement of compensatory mechanisms.

3.1.2 Studies that used physiological measures while performing a cognitive task

a. EEG

Older adults showed an increase in frontal midline theta power while performing a working memory task (face task) compared to younger adults based on EEG results (Gazzaley et al., 2008). The frontal midline theta power is localized at the medial prefrontal cortex. These findings suggest that older adults invested more overall effort in performing the task. Furthermore, the authors did not find significant differences in frontal midline theta power between relevant face stimuli and irrelevant scene stimuli in older adults, contrary to what they observed in younger adults. This result suggests that older adults exhibited difficulties with inhibition of irrelevant stimuli.

b. fMRI

Another technology that measures brain activity is fMRI. It detects changes in blood flow related to neural activity. This technique measures blood oxygenation level dependent (BOLD) signal and has the advantage to monitor brain activity with high spatial resolution.

Regardless of task difficulty, fMRI studies showed that older adults over-activated specific brain regions to achieve the same performance as younger adults while

performing a working memory task (Cappell, Gmeindl, & Reuter-Lorenz, 2010; Fischer et al., 2010). Compared to young adults, older adults showed an increase in brain activity in the right dorsolateral prefrontal cortex (especially the middle frontal gyrus sub-region) while performing a working memory task (Cappell et al., 2010). Similarly, older adults showed an increase in brain activity in the left temporo-parietal junction and left posterior cingulate gyrus compared to the younger group (under placebo conditions) while performing a spatial working memory task during an fMRI examination (Fischer et al., 2010). The dorsolateral prefrontal cortex, temporo-parietal junction, and posterior cingulate gyrus have all been associated with working memory. The discrepancies in activation of different brain regions between the two studies might be explained by differences in task design (n-back task for Cappell et al., 2010; spatial delayed-matching task for Fischer et al., 2010). The over-activation of these brain regions might reflect the involvement of compensatory mechanisms due to age-related cognitive decline (Cappell et al., 2010; Fischer et al., 2010). Another fMRI study showed that older adults used a different pattern of brain activation compared to young adults while performing a cognitive interference task (Zhu, Zacks, & Slade, 2010). Although both groups recruited functionally similar regions while performing the task, older adults had an activation pattern confined to smaller regions compared to younger adults with longer responses times to complete the task. Interestingly, older adults activated additional regions in the left frontal hemisphere (the left superior and medial frontal gyri) while performing the task (Zhu et al., 2010).

fMRI measures are not only sensitive to cognitive workload but also to task difficulty. With increasing task difficulty, fMRI studies also suggested that older adults had insufficient cognitive workload capacities and consequently showed decreased performances (Cappell et al., 2010; Fischer et al., 2010; Ginestet & Simmons, 2011). Cappell et al. (2010) also showed that decreased performance of the working memory task was accompanied by decreased activation in regions of right dorsolateral prefrontal cortex in older adults compared to younger adults. Similarly, older adults showed an under-recruitment of fronto-parietal regions, especially in the

left inferior frontal gyrus (Brodmann Area (BA) 9) and left inferior parietal lobule (BA 40) (Fischer et al., 2010). Furthermore, older adults had a decrease of connectivity strength as the task difficulty increased (Ginestet & Simmons, 2011).

c. Functional near-infrared spectroscopy (*fNIRS*)

The fNIRS technique is a type of functional neuroimaging technology that may be used to measure the occurrence of spontaneous slow oscillations of cerebral hemodynamics (Vermeij et al., 2014). The authors investigated the influence of age and cognitive workload on slow oscillations, using the n-back task. Results showed that healthy older adults exhibited decreased very-low-frequency oscillations in oxygenated and total haemoglobin compared to younger adults while performing a task that requires no working memory demand (control condition: 0-back) (Vermeij, Meel-van den Abeelen, Kessels, van Beek, & Claassen, 2014). In the task that requires working memory demand (2-back condition), no significant differences between the two groups were observed. Contrary to younger adults, very-low-frequency oscillations in healthy older adults did not reduce with increased cognitive workload. These findings suggest that very-low-frequency oscillations in oxygenated and total haemoglobin were not influenced by the cognitive workload in healthy older adults (Vermeij et al., 2014).

d. *PET*

One of the first imaging studies to investigate individual differences in cognitive workload used PET (Haier, 1993). This measure observes metabolic processes in the brain. Karlsson et al. (2009) investigated dopamine D1 receptor binding at rest and while performing a cognitive task in both younger and older adults. Whereas younger adults showed a reduction in binding receptor in three striatal compartments during the inhibition task compared to rest, no significant reduction in binding receptors was found in older adults. Findings provided evidence that the D1 system in older adults was less responsive to the cognitive workload required by the task when compared to younger adults (Karlsson et al., 2009).

e. *Pupillometry*

Task-evoked pupillary responses (TEPR) are successfully used to provide an estimate of the cognitive workload required to perform a task (Kahneman, 1973; Kahneman & Beatty, 1966). Changes in pupil dilation, measured by an eye tracker were assessed as a direct measure of cognitive workload in two studies (Allard, Wadlinger, & Isaacowitz, 2010; Piquado, Isaacowitz, & Wingfield, 2010). Allard et al. (2010) used changes in pupil dilation to assess the level of cognitive workload required in older adults and younger adults while they viewed facial stimuli of varying emotions. Older adults had smaller changes in pupil dilation toward emotional-neutral face pairs than younger adults while performing the task. The authors argued that older adults possess a lower physiological sensitivity of the pupil to small changes in cognitive workload, when compared to younger adults. Similarly, another eye tracking study found that unadjusted pupil sizes of older adults were smaller than younger adults while listening and recalling digits or sentences (Piquado et al., 2010). However, when normalized for their more limited range, older adults had larger normalized pupil sizes compared to the younger adults during list acquisition and during the retention interval before recalling the list. This result suggests that older adults needed a greater effort than younger adults to reach their level of success. Dragan et al. (2017) examined the relationship between memory-guided visual search and pupillary responses in different groups of adults including one group of younger adults and one group of healthy older adults. Two memory tasks were administered in which participants had to detect the target in a visual scene. The authors analyzed visual search and pupillary responses, expressed as the change in pupil size, which is independent of absolute pupil size. Findings showed that older adults had worse memory-guided search and poorer pupillary responses than younger adults.

Like fMRI measures, TEPR are not only sensitive to cognitive workload of individuals but also to task difficulty in working memory. In this study, both younger and older adults' pupil size increased when the number of items to be remembered increased (Piquado et al., 2010). Although TEPR in younger and older adults were sensitive to an increase in digit lists in working memory, pupillary responses were not sensitive to

the complexity of sentences in older adults (Piquado et al., 2010). This measure may be useful to determine the degree of difficulty required by the task but also to detect subtle cognitive deficits in healthy aging.

f. *Cardiovascular measures*

Cardiovascular measures such as heart rate, systolic blood pressure and diastolic blood pressure were found sensitive to cognitive effort (for review, see Gendolla & Wright (2005)). Heart rate variability measured by an electrocardiogram is the analysis of beat-to-beat intervals. Blood pressure is usually measured by a finger blood pressure cuff. Among standard cardiovascular measures, systolic blood pressure was found to be the more reliable measure of cognitive workload (Gendolla & Wright, 2005). Hess and Ennis (2012) used cardiovascular measures (heart rate, systolic blood pressure and diastolic blood pressure) as an indicator of cognitive workload and fatigue to assess the impact of aging on cognitive performance. Participants completed tasks with low (addition task) or high cognitive demands (subtraction task). Older adults showed greater changes in systolic blood pressure than younger adults at all levels of task difficulty (Hess & Ennis, 2012).

These findings are in line with results from the same authors using changes in systolic and diastolic blood pressure to investigate differences in cognitive workload during a visual memory task (Ennis, Hess, & Smith, 2013). These two last studies also revealed that changes in systolic blood pressure were sensitive to task difficulty. Older adults exhibited smaller changes in systolic blood pressure as difficulty increased, which was not the case for the younger adults (Ennis et al., 2013; Hess & Ennis, 2012). These findings suggest that older adults had greater level of disengagement from the task than younger adults at higher levels of task difficulty (Ennis et al., 2013; Hess & Ennis, 2012).

Using a blood pressure measure, older adults had higher levels of very-low-frequency oscillations in blood pressure when the load level increased (2-back condition), compared to younger adults (Vermeij et al., 2014). However, these measures were not influenced by task difficulty in older adults, contrary to what the

authors observed in younger adults. Older adults also showed a decrease in heart rate variability measures in the high-difficulty condition (hard trial) compared to the low-difficulty condition (easy trial), using an electrocardiograph (Mukherjee, 2011). Heart rate and certain heart rate variability measures were found to be reliable and sensitive tools in the evaluation of cognitive workload in older adults. In this study, there was no comparison group.

In general, older adults usually invested more overall effort than younger adults in performing an identical cognitive task.

3.2 What are the physiological measures sensitive to assessing cognitive workload in MCI and AD?

3.2.1 Studies that used physiological measures during resting state conditions

a. EEG/MEG

Alterations in the EEG/MEG rhythms in resting state conditions were associated with cognitive decline in patients with MCI and AD (Babiloni et al., 2015; Babiloni et al., 2006; Stam et al., 2006). Babiloni et al. (2006; 2015) investigated EEG measures during resting-state conditions in healthy older adults, patients with MCI and patients with AD. Findings showed that occipital delta sources and theta relative power increased and alpha 1 sources in the parietal, occipital temporal, and limbic cortices decreased with greater cognitive decline (Babiloni et al., 2006; Babiloni et al., 2015). Patients with AD also showed reduced functional connectivity in delta and theta bands compared to healthy older adults although no significant between-group differences in source density in any of the frequency bands were found (Hata et al., 2016). Discrepancies between studies may be due to differences in the severity of cognitive decline. Correlation analyses showed that higher functional connectivity in the delta band reflected better performance in a test assessing global cognitive function (MMSE test).

In contrast to EEG, MEG is hardly affected by the skull, and does not require a reference electrode. A MEG study investigated the synchronization of brain regions, by measuring the functional connectivity in patients with AD compared to healthy

older adults (Stam et al., 2006). Findings showed that functional connectivity was increased in patients with AD compared to healthy older adults locally in the theta (centro-parietal regions) as well as the beta and gamma bands (occipito-parietal regions) (Stam et al., 2006). The synchronization in alpha 1 and beta bands, especially involving interhemispheric temporal connections, were positively correlated to global cognition. The authors supported the relevance of using a simple resting-state condition for cognitive workload.

b. fMRI

The EEG/MEG results corroborate fMRI findings that showed distributed changes in brain connectivity in patients with AD compared to healthy older adults, using the eigenvector centrality (EC) method (Binnewijzend et al., 2014). This analysis considered the brain as one large network rather than dividing it into several subnetworks. Patients with AD had greater changes in brain connectivity bilaterally in the medial frontal cortex, particularly the anterior cingulate and paracingulate gyrus compared to healthy older adults. These two regions are related to executive functions (Binnewijzend et al., 2014). These results indicated that frontal areas had a major role in the functional brain network in patients with AD. The authors discussed the possibility of a functional compensatory mechanism. However, contrary to healthy older adults, no significant correlations were found between changes in brain connectivity and MMSE scores in patients with AD (Binnewijzend et al., 2014).

c. Pupillometry

Using repetitive stimulation of the pupil light reflex, patients with AD and patients with MCI showed less pronounced pupil size decrease and amplitude increase over time than controls (Bittner, Wieseler, Wilhelm, Riepe, & Müller, 2014). Moreover, higher MMSE was associated with a higher increase of relative amplitude and greater decrease of latency in AD and MCI, and absolute amplitude increase in AD alone. In other words, changes in pupil dynamics over time were less pronounced in AD and MCI and might reflect cognitive deficits. These authors showed that the use of repetitive stimulation of the pupil light reflex is better than initial pupil measurement

(e.g pupil size) because it is independent of age-related physiological differences in pupil size.

3.2.2 *Studies that used physiological measures while performing a cognitive task*

a. *EEG/MEG*

Patients with MCI usually invested more overall effort than healthy older adults in performing an identical cognitive task. These results were found in EEG studies (Cummins et al., 2008) and MEG studies (Ahmadlou et al., 2014; Aurtenetxe et al., 2013; Bajo et al., 2010; Lopez et al., 2014; Maestu et al., 2008). Similarly, patients with AD in the early stages needed greater effort than patients with MCI and healthy older adults to execute the task (Hidasi, Czigler, Salacz, Csibri, & Molnár, 2007; van der Hiele et al., 2007; van Deursen, Vuurman, van Kranen-Mastenbroek, Verhey, & Riedel, 2011; van Deursen, Vuurman, Verhey, van kranen-Mastenbroek, & Riedel, 2008). Changes in physiological measures and decreased task performances were observed as AD severity increased (Garn et al., 2015).

Using EEG measures, patients with amnesic MCI demonstrated lower EEG theta power around the frontal midline electrode compared to healthy older adults during a working memory task, which was associated with poorer performances in neuropsychological tests (Cummins, Broughton, & Finnigan, 2008). The authors suggested that the reduced theta power observed around the frontal midline electrode reflected cognitive deficits in patients with MCI. Using MEG measures, patients with MCI also showed bilateral higher activity in the ventral pathway (ventral prefrontal, middle temporal gyrus, medial temporal lobe) than healthy older adults during performance in a working memory task (Maestu et al., 2008). Similarly, Bajo et al. (2010) demonstrated an increase in posterior interhemispheric connectivity in the gamma band while patients with MCI performed a working memory task. To some extent, patients with MCI also showed an increase in functional connectivity in most of bands while performing a mental calculation task (Lopez et al., 2014). These changes were also associated with lower cognitive performance, which suggests that the increase in functional connectivity in most of bands was considered a compensatory mechanism for their cognitive decline. To be able to match the task

performance of healthy older adults, patients with MCI showed modulated theta band power in frontal regions early and after stimulus onset (Aurtenetxe et al., 2013). The importance of theta band while performing a cognitive task was also highlighted in another MEG study (Ahmadlou et al., 2014). Indeed, the complexity of functional connectivity networks involved in the working memory task in patients with MCI was markedly reduced in the theta band of the whole brain and intra left hemisphere (Ahmadlou et al., 2014).

Studies showed that some EEG/MEG measures were not only sensitive to patients with MCI but also to the task difficulty (Cummins et al., 2008; Lopez et al., 2014). Only patients with MCI demonstrated significantly lower EEG theta power under high demand condition compared to low demand condition (Cummins et al., 2008). A similar pattern was observed in a MEG study (Lopez et al., 2014). When the task difficulty increased (e.g subtraction task), a decline in synchronization changes was noted only in patients with MCI (Lopez et al., 2014). These two last studies showed that patients with MCI have fewer cognitive resources available to meet the processing requirements of more demanding tasks (Cummins et al., 2008; Lopez et al., 2014).

Consistent with EEG/MEG findings in patients with MCI, patients with AD in the early stages needed more effort to perform the cognitive task compared to healthy older adults (Beuzeron-Mangina & Mangina, 2009; Hidasi et al., 2007; van der Hiele et al., 2007; van Deursen et al., 2011, 2008). Event-related potential components (ERPs) are measured by EEG. By using averaging techniques, ERPs extract specific sensory, cognitive or motor events. ERPs during a number-letter task were especially useful to detect patients with probable AD at an early stage (Chapman et al., 2007). Patients in very early stages of AD displayed abnormally high P450 amplitudes over parietal and occipital sites as opposed to healthy older individuals that may be explained by compensatory recruitment in parieto-occipital areas (Beuzeron-Mangina & Mangina, 2009). Another EEG study analyzed the brain activity before and after the execution of a cognitive task (Hidasi et al., 2007). Following the completion of the cognitive task, the authors showed that the effect of

the task on delta, alpha 2 and beta 1 frequencies was the opposite in patients with AD compared to healthy older individuals (Hidasi et al., 2007). The relative alpha 2 band power and alpha1 coherence differentiated AD patients from healthy older adults following completion of a cognitive task (Hidasi et al., 2007). The higher amount of relative alpha 2 band in patients with AD may correspond to a long-lasting effect of the increased effort invested in the execution of the task in patients with AD or to a compensatory mechanism for their cognitive decline (Hidasi et al., 2007). Alpha 1 coherence was defined as the covariance of alpha activity at two electrode sites that can be used as an indicator of effective cortical connectivity (Hidasi et al., 2007). Unchanged alpha 1 coherence was also observed in the AD group, which may correspond to decrease in the level of functional connectivity of cortical areas recruited during the participation of the cognitive task. Alpha reactivity during memory tasks was decreased in patients with AD compared to healthy older adults and related to performance on cognitive tests (van der Hiele et al., 2007).

Patients with AD also had an increase of the local gamma band power and higher early gamma band responses such as 40-Hz steady state response power compared to patients with MCI and healthy older adults (van Deursen et al., 2011, 2008). Fast neural oscillations such as gamma bands were found to be an important mechanism for perceptual and cognitive processes (van Deursen et al., 2011; van Deursen et al., 2008). Increased local gamma band power in patients with AD could reflect a compensatory mechanism for alteration of long distance connectivity (van Deursen et al., 2008). Similarly, early gamma band responses might reflect a compensatory mechanism for their cognitive decline. These EEG measures, recorded during ongoing activity have been shown reproducible and able to differentiate patients with AD from patients with MCI and healthy older adults. A cohort study of qEEG measures found that theta power measured during face-naming encoding was closely related to AD severity (Garn et al., 2015).

b. *fMRI*

Consistent with EEG and MEG findings in patients with MCI, an fMRI study showed changes in functional connectivity in patients with MCI while they engaged in a

cognitive task with the same level of performance as healthy older adults (Bokde et al., 2006). These authors investigated changes in functional connectivity that may precede changes in brain activation in patients with MCI compared to healthy older adults (Bokde et al., 2006). Although no differences in task performances or brain activity were found between the two groups, results showed stronger correlation between the right middle fusiform gyrus and the left cuneus (parietal lobe) in patients with MCI compared to healthy older adults (Bokde et al., 2006). The authors suggested that the increase in functional connectivity could be the initial steps of a compensatory mechanism in patients with MCI.

Another fMRI study showed that patients with MCI needed to activate additional regions while performing a spatial mental imagery task (e.g clock-specific tasks) to maintain the same level of performance as the healthy older adults (Leyhe et al., 2009). Patients with MCI also showed an over-activation in the right anterior cingulate and right precuneus compared to controls while performing a working memory task (Kochan et al., 2010). A longitudinal fMRI study (6 years of follow-up) showed that greater hippocampal activation during a memory task predicted a greater degree and rate of subsequent decline in patients with MCI (Miller et al., 2008). Consistent with these findings, patients with MCI with a MMSE score between 24 and 25 had stronger activity in specific regions (lingual gyrus, cuneus, and precuneus) than healthy older adults, despite similar performance in the spatial control task (Saur et al., 2010).

While previous studies showed similar behavioral performances while performing the task (Kochan et al., 2010; Leyhe et al., 2009; Saur et al., 2010), other studies revealed poorer behavioral performances between patients with MCI and healthy older adults using fMRI measures (Sole-Padulles et al., 2009), and PET measures (Gronholm, Rinne, Vorobyev, & Laine, 2007). Discrepancies between the studies might be explained by differences in task design and patient characteristics. Higher cognitive reserve was associated with increased brain function in patients with MCI and AD, indicating that active compensatory mechanisms were still at work in patients with higher cognitive reserve (Sole-Padulles et al., 2009).

fMRI measures were found to be also sensitive to task difficulty. Kochan et al. (2010) showed the effects of increments in working memory load on whole-brain patterns of activation and deactivation in patients with MCI compared to healthy older adults. Patients with MCI showed an under-activation (reduced activity) in the right anterior cingulate and right precuneus when the task increased in difficulty. In order to perform the high demand condition of the task, patients required more general cognitive resources leading to greater deactivation of default network in the posterior cingulate-medial precuneus compared to healthy older adults (Kochan et al., 2010). The authors suggested that the deactivation of specific regions could be a compensatory mechanism to overcome deficient functioning in other task-related regions. As observed in patients with MCI, fMRI studies showed that patients with AD in the mild stages had a higher activation in specific regions while performing a visuospatial task (Leyhe et al., 2009; Vannini et al., 2008). Compared with controls, patients with mild AD showed an increase of activation in the right middle temporal gyrus while performing the task. This may indicate an attempt to compensate for dysfunctional areas in the dorsal visual pathway (Vannini et al., 2008). Similarly, the higher activation of the left precuneus in patients with mild AD during retrieval of clock time representations could reflect a compensatory mechanism of neurodegenerative processes (Leyhe et al., 2009). The authors argued that patients with AD needed greater effort to complete the cognitive task than controls.

Similar to what we observed in patients with MCI, patients with early AD who scored between 24 and 25 on the MMSE had higher activity in specific regions while performing a cognitive task (Saur et al., 2010). This result is consistent with another fMRI study that showed positive correlation between cognitive reserve and brain activity in patients with AD whereas negative correlation between cognitive reserve and brain activity was observed in healthy older adults. In other words, patients with mild AD recruited additional regions to support performance in the cognitive task. Findings suggested that active compensatory mechanisms were still at work among patients with mild AD (Sole-Padulles et al., 2009). Similar to EEG/MEG findings in patients with AD regarding task difficulty, fMRI results of Vannini et al. (2008) found

that patients with mild AD showed weaker or no BOLD signal in several areas of the dorsal visual pathway including bilateral precuneus, inferior parietal lobe and middle occipital gyrus, compared with controls (Vannini et al., 2008). This deactivation in several network regions could demonstrate the failure to modulate the neural response to increased task demand (Vannini et al., 2008).

c. *PET*

Consistent with EEG and fMRI findings, patients with MCI showed an increased activation in the anterior cingulate compared with the controls when naming newly learned objects, using PET measurements. This greater activation in the anterior cingulate was accompanied with poorer performances in learning the names of unfamiliar objects (Gronholm et al., 2007).

d. *Pupillometry*

Dragan et al. (2017) examined the relationship between memory-guided visual search and pupillary responses in patients with MCI, patients with AD, and healthy older adults, using two memory tasks. Findings showed that patients with probable early AD had worse memory-guided search than healthy older adults. Patients with AD exhibited decreased pupillary response compared to all other groups, with no difference between the response to novel and repeated trials in either task. These results suggest that the changes in pupil size might also reflect a deficit in memory in patients with AD.

4. **Discussion**

The objective of this review was to determine the physiological measures sensitive to assessing cognitive workload in healthy aging and age-related neurodegenerative diseases.

We identified six physiological measures of cognitive workload in this review: (1) EEG; (2) MEG; (3) fMRI; (4) PET; (5) pupillometry; and (6) cardiovascular measures. Any of the six physiological measures identified in our systematic review showed to be accurate in assessing cognitive workload in older adults and individuals with neurodegenerative diseases. Overall, studies showed that specific regions could

serve as compensatory mechanisms that allow healthy older adults or patients with MCI or mild AD to achieve similar behavioral performances. However, when cognitive resources available were insufficient, (e.g. patients with severe stages of AD), there is a threshold where the brain can no longer compensate, which leads to a decline in behavioral performances.

These physiological measures consistently showed greater cognitive workload in healthy older adults compared to younger adults regardless of task difficulty. Increased theta power, over-activation of specific brain regions, increased functional connectivity, larger normalized pupil sizes, and greater changes in systolic blood pressure were indices of compensatory mechanisms in healthy age-related cognitive decline (Allard et al., 2010; Cappell et al., 2010; Ennis et al., 2013; Fischer et al., 2010; Gazzaley et al., 2008; Hess & Ennis, 2012; Piquado et al., 2010). While healthy aging did not affect performance in the cognitive tasks in some studies (Cappell et al., 2010; Karlsson et al., 2009), others showed a decline in behavioral performances (Fischer et al., 2010; Piquado et al., 2010; Zhu et al., 2010), especially in situations of insufficient cognitive resources. This finding supports the notion of limited resources as a result of aging indicated by previous theories (Baddeley, 1996; Kahneman, 1973; Sweller, 1994; Treisman, 1964). Discrepancies between the results might be due to the nature of the task and the level of cognitive workload required by the task (Cappell et al., 2010). The pattern of these physiological measures was also modulated by task difficulty (Cappell et al., 2010; Ennis et al., 2013; Fischer et al., 2010; Hess & Ennis, 2012; Piquado et al., 2010).

Abnormalities in physiological measures also occurred in older adults with MCI and AD even in resting state conditions (Babiloni et al., 2015, 2006; Bittner et al., 2014; Stam et al., 2006). MCI is recognized as a transitional state between healthy aging and dementia (Ahmadlou et al., 2014; Aurtinetxe et al., 2013; Bajo et al., 2010; Bittner et al., 2014; Bokde et al., 2006; Kochan et al., 2010; Leyhe et al., 2009; F. Maestu et al., 2008). Compared with healthy older adults, greater cognitive workload appeared in patients with MCI, prior the manifestation of cognitive deficits in behavioral performances (Ahmadlou et al., 2014; Aurtinetxe et al., 2013; Bajo et al.,

2010; Bokde et al., 2006; Kochan et al., 2010; Leyhe et al., 2009; Maestu et al., 2008). These findings suggest that patients with MCI exhibited sufficient cognitive resources to compensate for their cognitive decline. Using EEG, MEG, or fMRI techniques, over-activation of specific brain regions and increased functional connectivity between different brain regions were used as compensatory mechanisms for the cognitive decline of patients with MCI (Bajo et al., 2010; Bokde et al., 2006; Gronholm et al., 2007; Kochan et al., 2010; Leyhe et al., 2009; Lopez et al., 2014; Maestu et al., 2008; Saur et al., 2010). When cognitive resources were insufficient, some studies showed that patients with MCI performed worse on behavioral tasks compared to healthy older adults (Sole-Padulles et al., 2009).

Although patients with AD allocated a high amount of cognitive resources to the cognitive task, these resources were insufficient to successfully execute the task. This may be reflected by reduced functional connectivity (Hata et al., 2016), decreased pupillary responses (Dragan et al., 2017) or alterations of pupil's light reflex (Bittner et al., 2014). Patients with AD showed greater cognitive workload accompanied with decreased behavioral performances during the cognitive task compared to older adults with MCI or healthy older adults (Leyhe et al., 2009; Saur et al., 2010; Sole-Padulles et al., 2009; van der Hiele et al., 2007; van Deursen et al., 2011; van Deursen et al., 2008). The higher amount of alpha 2 band after the task, the increased local gamma band power and early gamma band power, the higher P450 amplitudes over parietal and occipital sites, the over-activation or additional activation of specific regions in patients with AD were used as compensatory mechanisms for their cognitive decline (Beuzeron-Mangina & Mangina, 2009; Hidasi et al., 2007; Leyhe et al., 2009; Saur et al., 2010; Sole-Padulles et al., 2009; van Deursen et al., 2011, 2008).

Each physiological measure has strengths and weaknesses. In this review, a large number of studies (n = 23) used EEG or MEG to measure cognitive workload in healthy older adults, patients with MCI or AD. These techniques may be used in resting state conditions and during cognitive tasks (Babiloni et al., 2015, 2006; Binnewijzend et al., 2014; Stam et al., 2006; Volf & Gluhik, 2011). However, EEG

has low spatial resolution and it is difficult to draw precise inference on the activated brain areas. EEG is also susceptible to motion artefacts, such as noise, blinking and movement. A variety of studies in older adults also used neuroimaging techniques such as fMRI. While this technique provides a good spatial resolution, fMRI studies are often too intrusive and difficult to apply in real-world activities that require high cognitive demand, such as driving. Only two studies explored PET measures (Gronholm et al., 2007; Karlsson et al., 2009). This could be explained by the fact that this technique is invasive and difficult to apply. Few studies were performed with cardiovascular measures or pupillometry. One of the reasons could be due to medication intake or physiological changes related to aging that limit the sensitivity of these techniques (Allard et al., 2010; Bittner et al., 2014; Dragan et al., 2017; Ennis et al., 2013; Hess & Ennis, 2012). Contrary to fMRI or PET measures, cardiovascular and pupillary measures provide no clues about the locations of the underlying controlling neural systems. However, the limited intrusiveness of these measures allows for monitoring of cognitive workload during complex activities of daily life such as driving. Pupillary measures, such as TEPR, were found to be less intrusive than cardiovascular measures (Mukherjee, 2011).

This review has some limitations. It is possible that this review does not provide an exhaustive list of neurophysiological measures due to the focus on cognitive workload in aging and early dementia. However, this review emphasizes the need of future studies that compare the sensitivity of non-invasive neurophysiological measures of cognitive workload as early markers of cognitive decline. The fact that we only included group(s) of patients with a mean age above 65 years-old might explain the relatively few number of studies in MCI in our literature review. Most of the reviewed studies in patients with MCI or AD examined physiological measures while they are on medication. There was no information about the effect of medication and other comorbidities on these measures, which remains to be elucidated. In the reviewed studies, most of the tasks used while recording physiological measures showed a lack of extensive norms among younger and older adults, which makes difficult to generalize the results. In this review, we found a

large heterogeneity in participant characteristics and task design. Indeed, age, number of participants, stage of severity, MOCA or MMSE scores varied between the studies as well as the nature of task and task difficulty. This could partly explain discrepancies between the results.

4.1 Future research directions

There are several important future areas of research made salient by the present review.

The literature demonstrated that physiological measures could detect early cognitive symptoms in older adults, even prior to the presence of cognitive deficits in behavioral performances. These findings have clinical implications in early and accurate diagnosis of dementia. The early detection of cognitive symptoms may also lead to the adequate monitoring of the disease progression and early intervention. Future research on the use of physiological measures in detecting and monitoring cognitive deficits should be considered.

One study in our literature review used a longitudinal approach (Miller et al., 2008). Longitudinal studies may be helpful in detecting intra-individual changes in brain activity, as inter-individual variation can have a masking effect (Mak et al., 2015). Contrary to performances in cognitive tasks, physiological measures are less affected by practice effects and are therefore helpful to detect discrete cognitive changes over time. The incorporation of physiological measures in longitudinal studies should be encouraged.

As discussed earlier, aging is associated with physiological measures that may limit the sensitivity of these measures. For these reasons, we recommend the use of measures that take into account physiological changes due to aging (e.g small pupil diameter in older adults). Future research should also continue the development of new indicators to accurately assess the cognitive workload.

4.2 Implications

The early detection of cognitive deficits may have implications in pharmaceutical and

rehabilitation interventions. To date, pharmaceutical and rehabilitation interventions are initiated after significant changes in cognitive functions are observed (Connolly & Lang, 2014; Van Vleet et al., 2016). Previous studies showed that cognitive function could be improved through cognitive rehabilitation interventions (Van Vleet et al., 2016). Although the benefits of these interventions have been proven in older adults (Van Vleet et al., 2016), their effectiveness may vary among individuals depending on their mental state at the moment of the training. The use of objective markers such as physiological measures for cognitive training could be a useful approach to monitor the participant's mental effort and engagement in the training. More research on cognitive training interventions should incorporate physiological markers. This would particularly be useful in a population of older adults in general, where a greater heterogeneity is observed.

5. Conclusion

We conclude that a great variety of physiological measures is available to detect cognitive workload in healthy aging, MCI, and AD. All physiological measures showed sensitivity in detecting changes in cognitive workload across the spectrum of cognitive impairment. Most of studies included in this review used techniques like EEG or MEG to measure cognitive workload. Future research should focus on a comparative analysis of the accuracy of physiological measures to detect and monitor early cognitive deficits in older adults. These findings may have implications for clinical practice and future cognitive interventions.

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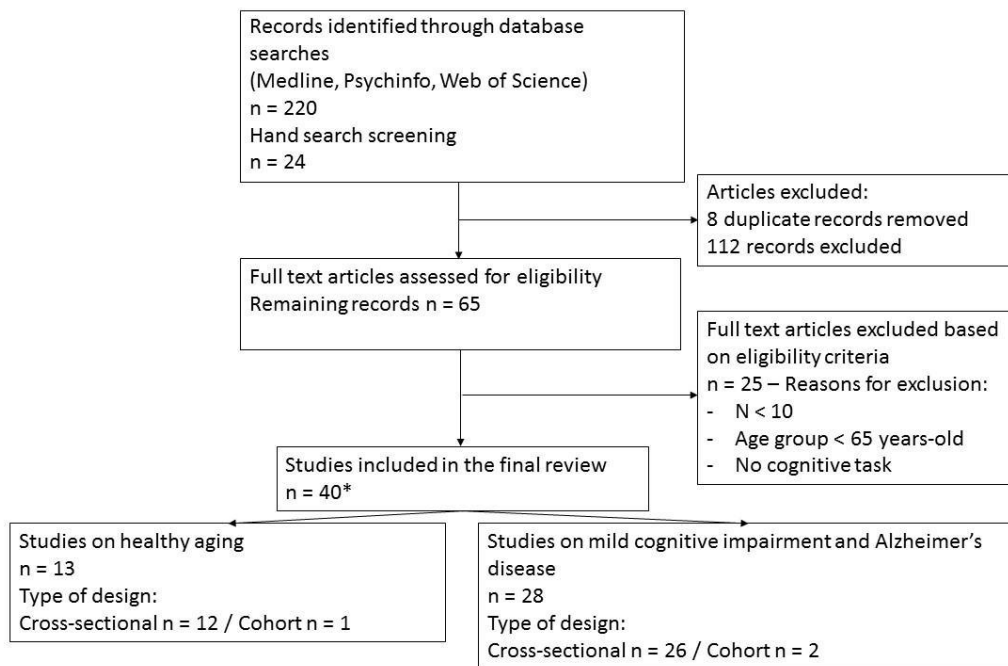


Fig.1. Flow diagram of the screening process of the included articles

*Among 40 studies, one study (Dragan et al., 2017) has been described in the two sections

Table 1. Studies that used physiological measures in healthy aging

References	Population characteristics	Task paradigm	Main outcomes	Main results	Between-group or within group comparisons ¹
In resting state conditions					
EEG measures					
Volf et al. (2011)	32 older adults, age \pm SD: 65.1 \pm 1.2; 33 younger adults, age \pm SD: 22.1 \pm 0.4	2 conditions: eyes closed or open	Behavioral data: IQ, originality of drawings in the Torrance test; EEG data: EEG power of the bands delta, theta 1, theta 2, alpha 1, alpha 2, beta 1, beta 2, gamma 1, and gamma 2 bands	Behavioral data: IQ Originality of drawings in the Torrance test EEG data: The mean power of the slow rhythms (delta, theta, and alpha 2) in the eyes-closed condition: The mean power of the fast beta and gamma rhythms in eyes-open condition	Y > O Y = O Y > O Y < O
While performing a cognitive task					
EEG measures					
Gazzaley et al. (2008)	26 older adults, age (range): 65.7 (60-72); 20 younger adults, age (range): 23.1 (19-30)	Working memory task with 3 conditions: 1. face task: remember faces and ignore scenes 2. scene task: remember scenes and ignore	Behavioral data: recognition accuracy, RT for face and scene WM tasks; Frontal EEG measures: frontal midline theta	Behavioral data for both face and scene tasks: Accuracy RT EEG data: Theta power for face stimuli Theta power in younger participants: relevant stimuli > irrelevant stimuli; in older	Y > O Y = O Y < O

		faces 3. Passive task: passively view faces and scenes		adults: relevant stimuli = irrelevant stimuli	Y < O Y = O
fMRI measures					
Cappell et al. (2010)	23 older adults, age ± SD: 68.4 ± 6.5; 21 younger adults, age ± SD: 20.8 ± 1.7	Verbal working memory task with 3 different memory loads (low memory load: 4, medium memory load: 5, high memory load: 7 letters)	Behavioral data: accuracy and RT; fMRI data: brain activity, especially in the prefrontal regions	Behavioral data: Accuracy for loads 4 and 5: Accuracy for load 7 RT for loads 4,5, and 7 fMRI data: activation in right BA 46 with - low memory load - medium memory load - high memory load Task difficulty in both groups: Activation in BA 46, BA 49, BA 45 in both groups	Y = O Y > O Y < O Y = O Y < O Y > O Low < medium < high
Fischer et al. (2010)	20 older adults, age (range): 70 (65-75); 20 younger adults, age (range): 25.2 (22-30)	Spatial delayed-matching task with 2 working memory load (low and high)	Behavioral data: accuracy; fMRI data: load-dependent WM-related brain activity	Behavioral data: Accuracy RT Working memory load for accuracy and RT fMRI data: brain activity in the left temporo-parietal junction and left posterior cingulate gyrus Brain activity in the frontal area and parietal area Task difficulty:	Y > O Y < O Low = high Y < O Y ≠ O

				fMRI data: brain activity in the fronto-parietal regions in:	
				- younger adults (under placebo)	Low < high
				- older adults	Low > high
Zhu et al. (2010)	26 older adults, age \pm SD: 74 \pm 6; 23 younger adults, age \pm SD: 20 \pm 3	Flanker task with 3 conditions (incongruent, congruent, neutral)	Behavioral data: accuracy, RT; fMRI data: differential brain activity (Incongruent versus Congruent stimulus conditions) flanker activation (for successful trials and/or error trials)	Behavioral data: accuracy RT fMRI data: regions of activation in the inferior and middle frontal gyri In the frontal regions, cluster in the inferior and middle frontal gyri In older adults, the centroid location was shifted by 19.7mm. The left superior and medial frontal gyri were specifically recruited, partially driven by errors. Bilateral activation was also observed during error processing	Y > O* Y < O Y > O Y > O
Ginestet et al. (2011)	43 older adults, age \pm SD: 68.2 \pm 13.2	N-back task with 3 levels of difficulty (0 -1 - 2 - 3)	Behavioral data: RT. fMRI data: connectivity strength = weighted cost, cost-integrated global and local efficiencies, ranking of cortical areas	Task difficulty: Weighted cost: 1 < 2 < 3 cost-integrated global and local efficiencies, ranking of cortical areas: 1 = 2 = 3	
PET measures					
Karlsson et al. (2009)	20 older adults, age (range): 70.3 (65-75); 20 younger adults,	Condition 1: resting state task; Condition 2: multi-source	Behavioral data: accuracy, latencies. fMRI and PET measurements: D1-	Behavioral data: accuracy Latencies PET measurements: D1 binding potential in sensorimotor, limbic and associative striatum:	Y = O Y < O

	age (range): 25.2 (22-30)	interference task	receptor binding potential calculated for sensorimotor, limbic and associative striatum	- in younger adults - in older adults	rest > task rest = task
Pupil measures					
Allard et al. (2010)	106 older adults, age \pm SD: 72.4 \pm 7.2; 85 younger adults, age \pm SD: 19.7 \pm 1.8	Viewing facial stimuli of varying emotions (emotional images and neutral images)	Pupil data: direct measure of change in pupil dilation of the left eye toward emotional-neutral face pairs	Pupil data: Changes in pupil dilation: For emotional and neutral images - Mood and emotion in older groups: positive or negative < neutral	Y > O
Piquado et al. (2010)	15 older adults, age (range): 74.1 (67-83); 15 younger adults, age (range): 22.6 (19-27)	Condition 1: Listening to spoken digit lists that varied in length (4, 6, or 8 digits) and retaining them briefly for recall. Condition 2: Listening to sentence types that varied in length (9 or 12 words) and syntax and retaining them briefly for	Behavioral data: recall accuracy for lists or sentences correctly reported; Pupil data: Pupil size of the left eye only for lists or sentences correctly reported	Condition 1 – Behavioral data: recall accuracy Pupil data: pupil size at each point Normalized pupil size measures - during the condition - as task difficulty increased in both groups Condition 2 – Behavioral data: recall accuracy Pupil data: normalized pupil sizes measures Sentences that varied - In length during retention interval - In syntax Normalized pupil size in older adults during	Y > O* Y > O Y < O 4 digit list < 6 digit list < 8 digit list; Y = O Y < O 9 words < 12 words object-relative sentences =

		recall.		retention interval	subject-relative sentences
Dragan et al. (2017) ^a	10 older adults, age: 66.4, MOCA: 28.1, 17 younger adults, age \pm SD: 22.8 \pm 3.1	Condition 1: Flicker change detection task Condition 2: Target detection task	Eye data: Visual search: Average repeated entropy, fixation times and location, number of fixations, scene old/new judgments search times Pupil data: Peak velocity; response velocity : change in pupil size due to stimulus onset	Condition 1 Visual search: Entropy from center of movement Fixation durations in repeated trials Number of fixations Search times in repeated trials Pupil data: Peak velocity Only in younger adults, faster velocities in repeated trials than did novel trails Condition 2 Visual search: Search times in repeated trials Pupil data: Change in pupil size For young and old groups, faster velocities in repeated trials than did novel trails	Y < O Y < O Y < O Y < O Y > O Y < O Y > O
Cardiovascular measures					
Hess and Ennis (2012)	51 older adults, age (range): 70.9 (62-84); 52 younger adults, age (range): 31.6	Condition 1: Addition task (low demand) - subtraction task (high demand).	Cardiovascular data for each phase: single changes in systolic and diastolic blood pressure and heart rate	Cardiovascular data: Change in systolic blood pressure Heart rate: younger adults > older adults Change in systolic and diastolic blood pressure in	Y < O Y < O

	(19-45)	Condition 2: multiplication problems	responses	older adults	Low > high
Ennis et al. (2013)	57 older adults, age \pm SD: 73.0 \pm 4.6; 59 younger adults, age \pm SD: 32.3 \pm 5.5	Memory search task with different levels of difficulty (size of the memory set from 2 to 10 consonants)	Cardiovascular data: Changes in systolic blood pressure	Cardiovascular data: Changes in systolic blood pressure at all levels of the task Task difficulty: - in older adults - in younger adults	Y < O level 8 > level 10 level 8 = level 10
Vermeij et al. (2014)	14 older adults, age \pm SD: 70.3 \pm 4.7; 14 younger adults, age \pm SD: 26.4 \pm 3	N-back task with two levels (0 - 2)	fNIRS data and photoplethysmography : frequency oscillations of cerebral hemodynamics and blood pressure	VLFO of O2Hb during the 0-back condition (control condition) Blood pressure Cerebral oscillations (O2Hb and tHb): - in young group: - in older group Blood pressure in both groups	Y > O Y < O 0-back > 2-back 0-back = 2-back 0 back < 2-back

Abbreviations: BA: Brodmann Area; COWAT: Controlled Oral Word Association Test; CVLT: California Verbal Learning Test; EEG: electroencephalography; fMRI: functional magnetic resonance imaging; IQ: Intellectual Quotient; NS: non significant; SD: Standard Deviation; PET: positron emission tomography; WAIS: Wechsler Adult Intelligence Scale; WM: Working Memory; WCST: Wisconsin Card Sorting Test

^a only data regarding younger adults and healthy older adults are displayed in this table

¹ Y = O: no significant differences between younger adults and healthy older adults

Y > O: significant decrease in behavioral or physiological measures in healthy older adults compared to younger adults

Y < O: significant increase in behavioral or physiological measures in healthy older adults compared to younger adults

² low = high: no significant differences in behavioral or physiological measures between the high and low demand conditions

low > high: significant decrease in behavioral or physiological measures in the high demand condition compared to low demand condition

low < high: significant increase in behavioral or physiological measures in the high demand condition compared to low demand condition

* tendency to be significant

Table 2. Studies that used physiological measures in MCI and AD

References	Population characteristics	Task paradigm	Outcomes	Main results	Between-group or within group comparisons ¹
Resting state conditions					
EEG / MEG measures					
Babiloni et al. (2006)	193 patients with mild AD age \pm SE: 76.2 \pm 0.6, MMSE score \pm SE: 20.7 \pm 0.2 ; 155 patients with MCI, age \pm SE: 72.1 \pm 0.7, MMSE score \pm SE: 25.9 \pm 0.2; 126 healthy older adults, age \pm SE: 65.4 \pm 0.9, MMSE score \pm SE: 28.3 \pm 0.1	Resting-state eyes-closed condition	EEG data: cortical sources of EEG rhythms (delta, theta, alpha 1, alpha 2, beta 1, and beta 2)	EEG data: Parietal, occipital, temporal, and limbic alpha 1 sources Occipital delta sources These 5 EEG sources were correlated with MMSE score in all subjects	O > MCI > AD O < MCI < AD
Stam et al. (2006)	18 patients with AD, age \pm SD: 72.1 \pm 5.6, MMSE score (range): 19.2 (13-25); 18 healthy older adults, age \pm SD: 69.1 \pm 6.8, MMSE score (range): 29 (27-30)	eyes-closed no task state	MEG data: Functional connectivity = synchronization likelihood and coherence (delta, theta, alpha 1, alpha 2, beta and gamma bands)	Alpha 1 et beta band for long distance intrahemispheric interactions Functional connectivity locally in the theta (centro-parietal regions), beta and	O > AD O < AD

				<p>gamma bands (occipito-parietal regions)</p> <p>In patients with AD, significant correlations between alpha 1, alpha 2 and beta band synchronization likelihood and MMSE scores</p>	
Babiloni et al. (2015)	<p>90 patients with AD age \pm SE: 72.3 ± 0.8, MMSE score \pm SE: 19 ± 0.4; 100 patients with MCI, age \pm SE: 70.7 ± 0.8, MMSE score \pm SE: 27.4 ± 0.1; 45 healthy older adults: age \pm SE: 70.1 ± 1.1, MMSE score \pm SE: 29.1 ± 0.2</p>	<p>Resting-state eyes-closed EEG rhythms: alpha 1 and 2 Structural MRIs</p>	<p>EEG data: cortical alpha rhythms Structural MRIs: grey matter density EEG recordings were available in 2 subgroups on 19 healthy older adults and 14 AD subjects.</p>	<p>Significant correlation between amplitude of occipital sources of alpha 1 rhythms and MMSE score in healthy older adults, patients with MCI and patients with AD</p> <p>Correlation between the amplitude of occipital alpha 1 sources and MMSE score across all subjects</p> <p>Structural MRIs:</p>	<p>O > MCI and AD</p>

					Occipital grey matter density
Hata et al. (2016)	28 patients with probable AD age \pm SE: 74.2 ± 8.9 , MMSE score \pm SE: 18.7 ± 4.5 ; 30 healthy older adults: age \pm SE: 70.1 ± 1.1 , MMSE score \pm SE: 29.2 ± 1.0	Resting-state during eyes open and closed state	EEG data: Artifact-free EEG (delta, theta, alpha1, alpha2, beta1, beta2) functional connectivity = lagged phase synchronisation	EEG data: Delta lagged phase synchronization over most cortical regions Theta lagged phase synchronization between the right DLPFC and right posterior IPL Positive correlation between 4 of the delta band connections and MMSE score The four functional connections included: (1) the left and right middle temporal area (MT), (2) the right frontal eye field (FEF) and left posterior inferior parietal lobule (pIPL), (3) the anterior cingulate cortex (aCC) and left	0 = AD 0 > AD 0 > AD

pIPL, and (4) the left anterior inferior parietal lobule (aIPL) and left hippocampal formation (HF).

Negative correlation between delta functional connection between right MT and right Aud and CDR scores

fMRI measures

Binnewijzend et al. (2014)	39 patients with AD, age \pm SD: 67 \pm 8, MMSE \pm SD: 22 \pm 3; 43 healthy older adults, age \pm SD: 69 \pm 7 MMSE \pm SD: 29 \pm 1	fMRI data: brain connectivity = EC mapping	fMRI data: EC values located in the precuneus and the occipital cortex	O > AD
			Mean EC values were more spread across the entire cingulate cortex	O < AD
			EC values in the left and right occipital cortex	O > AD
				O < AD

EC values found bilaterally in the medial frontal cortex

Both lower EC in the occipital regions and higher EC in the medial frontal regions were related to MMSE scores across groups

In AD patients, no relation between EC and MMSE scores was found.

Lower occipital EC values were associated with lower performance on the MMSE in healthy older adults

Pupil measures

Bittner et al. (2014)	66 patients with AD, age \pm SD: 74.4 \pm 7.5, MMSE \pm SD: 20.4 \pm 5.0; 42 patients with MCI,	Pupillary light reflexes of the left eye: Repetitive stimulation	Pupil data: pupil size, latency, amplitude, relative amplitude	Effect of repetitive measurement on pupillary light reflexes: Pupil size decrease	0 < MCI; 0 < AD MCI < AD*
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age \pm SD: 69.8 \pm 8.4,
MMSE \pm SD: 25.7 \pm 2.4,
44 healthy older
adults, age \pm SD: 66.4 \pm
8.3, MMSE \pm SD: 28.8
 \pm 1.2

over time
Pupil diameter
decrease over time
Amplitude increase
over time

O > MCI*; O > AD

After correcting for
age, significant
correlation between
MMSE score and pupil
size, amplitude, and
relative amplitude

In MCI patients,
significant correlation
between MMSE score
and amplitude, relative
amplitude and latency
under repetitive
stimulation

In AD patients,
significant correlation
between MMSE score
and amplitude, relative
amplitude and latency
under repetitive
stimulation

While performing a cognitive task					
EEG / MEG measures					
Cummins et al. (2008)	12 patients with amnesic MCI, age \pm SD: 70.2 ± 8.9 ; 12 healthy older adults, age \pm SD: 67.8 ± 8.3	Modified version of the Sternberg recognition task with low (4 words) or high (8 words) memory load. Recognition and retention phases	EEG data: theta power	EEG data: During recognition interval, theta power around the frontal midline electrode During retention interval, theta power at parietal and temporal electrodes	O > MCI O > MCI low > high ² low = high
Bajo et al. (2010)	22 patients with MCI, age \pm SD: 74.8 ± 3 , MMSE score \pm SD: 27.7 ± 1 ; 19 healthy older adults, age \pm SD: 71.6 ± 8 , MMSE score \pm SD: 29.5 ± 0.7	Modified version of the Sternberg task	Behavioral data: hit responses; MEG data: synchronization likelihood = index of functional connectivity (alpha 1, alpha 2, beta 1, beta 2, gamma)	Behavioral data: hit responses MEG data: Interhemispheric synchronization during the memory task between left and right anterior temporo-frontal regions (in all bands) and in posterior regions in the gamma	O = MCI O < MCI

				band	
Maestu et al. (2008)	15 patients with MCI, age \pm SD: 74.8 ± 3.0 , MMSE score \pm SD: 27.7 ± 1 ; 20 healthy older adults, age \pm SD: 71.6 ± 8 , MMSE score \pm SD: 29.5 ± 0.7	Modified version of the Sternberg letter-probe task	Behavioral data: total number of hits, misses and RT MEG data: brain magnetic profiles	Behavioral data: total number of hits, misses and RT MEG data: bilateral activity in the ventral pathway in both the target and the non-target stimuli	O = MCI O < MCI
Aurtenetxe et al. (2013)	12 patients with aMCI, age \pm SD: 74.8 ± 4.8 , MMSE score \pm SD: 25.3 ± 1.8 ; 13 healthy older adults, age \pm SD: 70.6 ± 6.3 , MMSE score \pm SD: 28.7 ± 1.4	Modified version of the Sternberg task	Behavioral performance: hits, errors and correct rejections; MEG data: spectral power dynamics in source space on the recognition phase of the target stimuli (theta (4-8 Hz), alpha (8-12 Hz), beta (12-30Hz), gamma (30-45H))	Behavioral data: hits, errors and correct rejections MEG data: Differences to target stimuli in spatial-time frequency patterns in theta, alpha, beta and gamma spectral bands. Theta over the right frontal pole at early latencies Beta band in right fronto-parietal regions at late latencies Alpha band in the	O = MCI O \neq MCI O < MCI O < MCI O > MCI

				temporo-occipital region of the right hemisphere between 489 and 528 ms and gamma power over left parietal regions between 372 and 489 ms	
Ahmalidou et al. (2014)	18 patients with MCI, age \pm SD: 74.8 ± 3 ; 19 healthy older adults, age \pm SD: 71.6 ± 8	Sternberg Task	Behavioral data: number of hits; MEG data: networks' complexities were measured by Graph Index Complexity and Efficiency Complexity	Behavioral data MEG data: Complexity of functional networks at both alpha and theta band and more pronounced at the theta band in the whole brain and intra left hemisphere	O = MCI O > MCI
Lopez et al. (2014)	38 patients with MCI, age \pm SD: 72.5 ± 4.5 , MMSE score \pm SD: 27.1 ± 2.2 ; 32 controls, age \pm SD: 71.8 ± 3.8 , MMSE score \pm SD: 29.3 ± 0.9	Condition 1: resting state Condition 2 and 3: 1- and 3- subtraction tasks	MEG data: Functional connectivity assessed with phase locking value in the five frequency bands	MEG data: In resting-state condition: Connectivity values in low frequency-bands (frontal delta and antero-posterior right theta) Connectivity values in the alpha band,	O < MCI O > MCI

especially
 interhemispheric and $O > MCI$
 in central and $O < MCI$
 posterior regions, as
 well as the beta band $O < MCI$
 in frontal regions
 In the subtraction
 task:
 Functional
 connectivity:
 - in the alpha
 band
 - in most $O < MCI$
 frequency
 bands $O > MCI$
 - in anterior
 regions of the
 default mode
 network
 In both groups, delta
 connectivity: resting
 state < mental
 calculation
 Broad
 desynchronisation in
 the beta band in both
 groups in the
 subtraction tasks

				compared to resting state. Similar findings were found in the gama band in both groups. Connectivity changes in theta band between task and resting state Connectivity changes in alpha band between task and resting state	
Chapman et al. (2007)	12 patients with AD, age \pm SD: 75.8 \pm 4.5; 12 healthy older adults, age \pm SD: 74.2 \pm 4.8	The Number-Letter paradigm	Behavioral data: correct trials of the number-letter task; EEG data: ERPs	Behavioral data: correct trials of the number-letter task; EEG data: ERPs (C145, C250, P3) differences between the relevant and irrelevant stimuli	O = AD O > AD
Hidasi et al. (2007)	10 patients with AD, age (range): 67.4 (58-79), MMSE score (range): 29.8 (29-30); 14 healthy older adults, age (range): 67.2 (55-78), MMSE score (range): 20.21 (16-24)	2 conditions: eyes closed (before-task period) and reverse counting task with eyes closed.	EEG data: relative frequency spectra of the 6 frequency bands, coherence for interhemispheric and intrahemispheric short-range and long-range electrode pairs recorded before and after the execution of	EEG data: Before and after task Theta Beta1 After task, alpha 2 band Coherence values in the alpha 1, alpha2 and beta2 bands Beta2 coherence	O < AD O > AD O < AD O \neq AD O < AD

			a cognitive task (delta, theta, alpha1, alpha2, beta1, beta2)	values, irrespective of task performance	
				Increase in fast (alpha 2 and beta 1), and a decrease in slow (delta) frequencies in patients with AD following the completion of the cognitive task	
				Decrease of alpha 2 band after the task in the healthy older adults	
van Der Hiele et al. (2007)	16 patients with AD, age \pm SD: 78 \pm 8, MMSE score \pm SD: 21 \pm 4; 18 patients with MCI, age \pm SD: 74 \pm 5, MMSE score \pm SD: 24 \pm 3; 22 healthy older adults, age \pm SD: 70 \pm 5, MMSE score \pm SD: 28 \pm 1	Condition 1: Resting state Condition 2: picture learning task (memory activation)	EEG data: Theta relative power during eyes closed; alpha reactivity during the task; alpha coherence during eyes closed; alpha coherence during the task	EEG data: Theta relative power during eyes closed Alpha reactivity during the task Alpha coherence Alpha reactivity during task decreased in AD patients only	O and MCI < AD O > AD O = AD
van Deursen et al.	15 patients with AD,	Condition 1: Resting-	EEG data: Local gamma	Gamma band power in	O and MCI < AD

(2008)	age \pm SD: 75.2 \pm 6.9 , MMSE score \pm SD: 20.8 \pm 2.7; 20 patients with MCI, age \pm SD: 70.6 \pm 7.2, MMSE score \pm SD: 26.3 \pm 1.6; 20 healthy older adults, age \pm SD: 69.5 \pm 6.1, MMSE score \pm SD: 29.3 \pm 0.8	state condition (eyes open), Condition 2, 3 and 4: music listening, story listening and movie watching tasks	band power	4 conditions Differences were located in the parietal, occipital and posterior temporal regions
Beuzeron-Mangina et al. (2009) ^a	25 patients with Alzheimer Disease, age: 69.9, MMSE: 26.5 \pm 2.3, 25 healthy older adults, age: 70.4, MMSE: 30.0	Memory Workload Paradigm: indicate whether the stimulus belonged to the memorized set size, by pressing buttons for target words and non- target words	EEG data: Topographic distribution of ERP amplitudes ERP latencies	Topographic distribution of ERP amplitudes: P450 amplitudes over parietal and occipital sites ERP latencies: P450 latencies over anterior regions P450 latencies over posterior regions Delayed P450 latencies over pre-frontal and frontal regions in AD patients as opposed to healthy older adults

van Deursen et al. (2011)	15 patients with AD, age \pm SD: 75.2 ± 6.9 age, MMSE score \pm SD: 20.8 ± 2.7 ; 20 patients with MCI, age \pm SD : 70.6 ± 7.2 , MMSE score \pm SD: 26.3 ± 1.6 ; 20 healthy older adults, age \pm SD: 69.5 ± 6.1 , MMSE score \pm SD: 29.3 ± 0.8	Condition 1: resting state (eyes open) Condition 2: auditory 40-Hz stimulation	EEG data: 40-Hz SSR power	EEG data: 40 Hz SSR power particularly in the auditory cortex Moderate correlation between 40-Hz SSR and ADAS-cog score 40-Hz SSR power : resting state < stimulation	O and MCI < AD
Garn et al. (2015)	118 patients with AD, median age (range): 76 (52-90), median MMSE score (range): 23 (26-15)	Condition 1: resting state with eyes closed Condition 2: face-name encoding task	EEG markers: slowing (relative band powers), synchrony (coherence canonical correlation, Granger causality) and complexity (auto, mutual information, Shannon/Tsalis entropy)	The highest coefficient of determination between QEEG marker and MMSE score was found for the theta (4-8Hz) relative band power Relative theta power increased with decreasing MMSE score MMSE scores explained 33% of the variation in the relative theta power during the face encoding and 31% of auto-mutual	

information in resting state with eyes closed MMSE score explained 25% of the variations in the overall QEEG factor
 In probable AD, QEEG coefficients of determination were also higher than in the whole group, where MMSE scores explained 51% of the variations in relative theta power

fMRI measures

Bokde et al. (2006)	16 patients with MCI, age \pm SD: 69.9 \pm 7.8, MOCA score \pm SD: 27.2 \pm 1.5; 19 healthy older adults, age \pm SD: 66.7 \pm 4.2, MOCA score \pm SD: 29.2 \pm 1.0	Face-matching task	Behavioral data: score and RT; MRI data: brain activity, functional connectivity between the right middle fusiform gyrus and all other voxels in the brain	Behavioral data: score and RT fMRI data: - brain activity - Functional connectivity to visual cortex, parietal lobes and right DLPFC - Functional connectivity to	O = MCI O = MCI O > MCI O < MCI O > MCI
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					the cuneus
					- Functional connectivity to the frontal areas, right superior temporal gyrus and left IPL
Kochan et al. (2006)	35 patients with MCI, age \pm SD: 78.0 ± 3.9 , MMSE \pm SD: 27.9 ± 1.6 ; 22 healthy older adults, age \pm SD: 77.2 ± 3.3 , MMSE \pm SD: 29.3 ± 1.0	Visuospatial associative working memory task with 3 load levels (low, medium, high)	Behavioral data: Accuracy, RT and mean coefficient of variation ; fMRI data: brain activity	Behavioral data: accuracy and RT fMRI data:	O = MCI
				- At lower loads, during the encoding phase: Brain activity in the right anterior cingulate and right precuneus	O < MCI
				- At higher loads, brain activity in the right anterior cingulate and right precuneus	O > MCI
				- deactivation in	O < MCI

the posterior
cingulate-
medial
precuneus

Miller et al. (2008)	25 patients with MCI, age \pm SD: 73.2 \pm 5.3, MMSE score \pm SD: 29.4 \pm 0.71	Visual scene encoding task with 3 conditions: 1. Fixation, 2. Novel, 3. Repeated	fMRI data: brain activity in the hippocampal activation	fMRI data: In patients with MCI, greater activation for novel scenes compared with repeated scenes in the left hippocampal formation Greater hippocampal activation predicted greater degree and rate of subsequent cognitive decline The hippocampal formation was the only brain region that predicted cognitive decline	
Vannini et al. (2008)	13 patients with mild AD, age \pm SD: 68.9 \pm 6.9; 13 healthy older	Angle discrimination task with varying task demand	Behavioral data: RT, percentage of correct responses; fMRI data:	Behavioral data: RT Accuracy fMRI data: brain	O = AD O > AD

	adults, age \pm SD: 68.7 \pm 7.8		brain activity	activity in the right middle temporal gyrus	O < AD O > AD
				Brain activity with increased task demand	
Leyhe et al. (2009)	15 patients with AD, age \pm SD: 71.5 \pm 7.9, MMSE score \pm SD: 22.9 \pm 2.8; 11 patients with MCI, age \pm SD: 75.0 \pm 6.7, MMSE score \pm SD: 27.6 \pm 1.4; 15 healthy older adults, age \pm SD: 70.6 \pm 11.8, MMSE score \pm SD: 29.7 \pm 0.5	Condition 1: an hour hand task; Condition 2: a minute hand task; Condition 3: a semantic control task	Behavioral data: hit rates and reaction times; fMRI data: brain activity	Behavioral data: - for all tasks - for the hour and the minute hand tasks: fMRI data: Additional brain activity in patients with MCI was found in several brain regions compared with controls	O = MCI O \neq AD, MCI \neq AD O > MCI
				Activation during the minute hand task in the right middle temporal gyrus	O and MCI > AD
				Brain activity in the occipital lobes and the left fusiform gyrus Additional activation in	

				the precuneus in patients with AD	
Saur et al. (2010)	12 patients with AD, age \pm SD: 71.0 ± 5.8 , MMSE: 29.6 ± 3.0 ; 10 patients with MCI, age \pm SD: 73.9 ± 5.8 , MMSE: 27.8 ± 1.3 ; 12 healthy older adult, age \pm SD: 70.0 ± 5.5 , MMSE: 29.6 ± 0.5	Clock reading task and a spatial control task	Behavioral data: correct answers and RT; MRI data: parameter estimates of task-related brain activity	Behavioral data for both task Correct answers RT fMRI data: During the spatial control task, brain activity in the left fusiform, the left lingual and right inferior temporal gyrus Correlation between brain activity and cognitive state in several brain regions, including the lingual gyrus, cuneus and precuneus for both experimental tasks	O and MCI > AD O < AD O < MCI and early AD with MMSE score > 23
Sole-Palludes et al. (2009)	16 patients with mild AD, age \pm SD: 76.5 ± 5.8 , MMSE \pm SD: 21.7 ± 4.0 ; 12 patients with aMCI, age \pm SD: $74.3 \pm$	Visual memory encoding task	Behavioral data: score; Brain volume: structural MRI; Brain activity: fMRI	Behavioral data: Score fMRI data: among healthy older adults,	C > MCI; C > AD; MCI > AD

6.2, MMSE \pm SD: 25.8 \pm
2.2; 16 healthy older
adults, age \pm SD: 73.3 \pm
4.9, MMSE \pm SD: 27.8 \pm
0.9

higher cognitive
reserve was related to
larger brain volume
and reduced activity in
several cortical and
subcortical regions
during cognitive
processing.

In patients with MCI
and AD, higher
cognitive reserve was
related to reduced
brain volumes

In patients with MCI,
no significant
correlation between
cognitive reserve and
brain activity

In patients with AD,
higher cognitive
reserve was related to
increased brain
function in the right
anterior cingulate and
lingual gyri

PET measures					
Gronholm et al. (2007)	10 patients with aMCI, age \pm SD: 68.6 ± 8.6 , MMSE score \pm SD: 27.3 ± 1.5 ; 10 healthy older adults, age \pm SD: 65.5 ± 6.9 , MMSE score \pm SD: 29.0 ± 0.7	Naming test	Behavioral data: performance; PET data: relative changes in rCBF between the experimental conditions	Behavioral data: Performance PET data: rCBF in the anterior cingulate	O > MCI O < MCI
Pupil measures					
Dragan et al. (2017) ^a	9 patients with probable early AD, age \pm SD: 69.1 ± 7.8 , MOCA: score < 25; 8 older adults at risk for MCI, age: 69, MOCA: 23.1 ; 10 healthy older adults, age: 66.4, MOCA: 28.1	Condition 1: Flicker change detection task Condition 2: Target detection task	Eye data: Visual search: Average repeated entropy, fixation times and location, number of fixations, scene old/new judgments search times Pupil data: response velocity : change in pupil size due to stimulus onset	Condition 1 Visual search: Entropy from center of movement Fixation durations in repeated trials Number of fixations Search times in repeated trials Pupil data: Change in pupil size Condition 2 Visual search: Search times in repeated trials Pupil data:	O < AD; MCI < AD O < MCI; O < AD O < AD; MCI < AD O < AD. MCI < AD O > AD; MCI > AD O < AD; MCI < AD MCI > AD

Change in pupil size

Abbreviations: ADAS-Cog, the cognitive subscale of the Alzheimer's disease assessment scale; aMCI, amnesic mild cognitive impairment; BRF: Background Rhythm Frequency; DPBRF: Dominant Posterior Background Rhythm Frequency; DLPFC, dorsolateral prefrontal cortex; EC: Eigenvector centrality; ERP, Event Related Potential; IPL, Inferior parietal lobule; SSR, Steady state response; NART: National Adult Reading Test; COWAT, Controlled Oral Word Association Test; D: Dementia; EEG: Electroencephalography; MCI: Mild Cognitive Impairment; NCI: No Cognitive Impairment, MMSE: Mini Mental State Examination; NS: Not significant; PD: Parkinson's Disease; PET: Positron Emission Tomography; rCBF: regional cerebral flow; RT: Response Times, SD: Standard Deviation; SE: Standard Error; WCST, Wisconsin Card Sorting Test

^aonly data regarding patients with AD and healthy older adults are displayed in this table

¹ O = MCI/ AD: no significant differences in behavioral or physiological measures between healthy older adults and patients with mild cognitive impairment/ patients with Alzheimer's disease compared to healthy older adults

O > MCI/ AD: significant decrease in behavioral or physiological measures in patients with mild cognitive impairment/ patients with Alzheimer's disease compared to healthy older adults

O < MCI/ AD: significant increase in behavioral or physiological measures in patients with mild cognitive impairment/ patients with Alzheimer's disease compared to healthy older adults

² low = high: no significant differences in behavioral or physiological measures between the high and low demand conditions

* tendency to be significant