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Eye Blink Rate as a biological marker of Mild Cognitive Impairment ☆

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ABSTRACT

We investigated the relationship between dopamine activity (DA), as measured by Eye Blink Rate (EBR), and cognitive function in old adults with Mild Cognitive Impairment (MCI) and healthy controls. Research has been inconclusive so far about the factors responsible for the transition from MCI to dementia. However, some studies suggest that cortical hyperexcitability in very early stages of pathological aging may progressively lead to cell death, and thus to Alzheimer's disease. Hence, we speculated that a dysfunction of DA activity, as measured by EBR, may characterize people with MCI, and account for their poor cognitive function. Thirty three (33) healthy and thirty six (36) old adults with MCI (Mean age = 67.52 y.o.) participated in this study. The EBR was recorded under resting conditions, using two gold skin electrodes above and below the left eye. Cognitive function was assessed with a battery of neuropsychological tests. Participants with MCI showed significantly higher EBR than the healthy controls. Also, EBR was negatively related to scores on the Montreal Cognitive Assessment test (MoCA) test. We propose that abnormally increased dopamine activity, as indexed by relatively high EBR, may be partially responsible for the neurotransmitter imbalance in the central nervous system of people with MCI, and the overall impaired cognitive performance. In addition, this finding suggests that an abnormally high EBR may be a potential biomarker of the transition from healthy aging to dementia.

1. Introduction

The extension of the life span observed during the last decades has led to a dramatic increase of the number of people suffering from dementia (World Health Organization, WHO, 2003). Currently, there are 5.4 million dementia patients, only in the EU (Ferri et al., 2005). Prognosis of dementia prevalence is even more dramatic, according to international-scale studies (Alzheimer's Disease International, 2010; WHO, 2003), reaching the level of a global epidemic in the upcoming years (Brookmeyer et al., 2007).

As Alzheimer's dementia (AD) still remains untreated, detecting dementia in very early stages, with the goal of preventing or delaying the illness, has now become a public health priority (for reviews see Arnáiz and Almkvist, 2003; Burns and Zaudig, 2002). Efforts to identify individuals who may later develop dementia have focused on the progression from healthy age-related cognitive decline to pathological aging. Mild Cognitive Impairment (MCI) thus is considered an intermediate stage between normal and pathological aging, as a substantial percentage of people diagnosed with MCI converts later to dementia of the Alzheimer's type (Arnáiz and Almkvist, 2003). Consequently, an outstanding issue is to find factors that may predict which MCI patients will later convert to dementia (Rinne and Någren, 2010).

In the past, the belief that amnesic MCI (i.e. MCI with impairments solely in memory and no other cognitive domains) is the pre-stage of AD, used to prevail. However, other evidence now suggests that impairments of processes others than memory, such as learning, attention and executive functions, may also predict progression to AD (for reviews see Arnáiz and Almkvist, 2003; Morris et al., 2001). Early detection (e.g., at the MCI stage) of cognitive impairments in clinical settings is mostly carried out with neuropsychological assessment. Neuropsychological tools may reliably screen for very early dementia symptoms, however only if they are properly interpreted by the clinician (Arnáiz and Almkvist, 2003). This calls for the need to identify other, more objective, markers of central nervous system function, which in combination with the neuropsychological evaluation, could lead to more robust recognition of AD in a prodromal stage. Although functional magnetic resonance imaging (fMRI) (Bäckman et al., 1999; Wagner, 2000) and Transcranial Magnetic Stimulation (TMS) (for a review see Pennisi et al., 2011) have been extensively used for this purpose, they are costly and highly sophisticated technologies. This deters hospitals, let alone AD associations, from utilizing these techniques to detect MCI individuals at-risk for AD. The aim of the present paper is to introduce a cost-effective, simple and reliable marker of CNS function

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which, in combination to neuropsychological assessment, could essentially compose a screening mechanism that may lead to a more valid detection of cognitive impairment prior to Alzheimer's disease (AD), that is MCI.

The suggested herein (bio)marker is the Eye Blink Rate (EBR). EBR is a non-invasive, reliable and easily quantifiable measure of brain central dopamine activity (DA) (Karson, 1983; Mackert et al., 1991; Shukla, 1985; Taylor et al., 1999). How is dopamine related to early dementia symptoms? According to Braak and colleagues, in the very first stages of Alzheimer's disease, neurofibrillary pathology is firstly observed in the entorhinal cortex, and progresses to the hippocampus, which is then spread to the rest of the limbic system and thereafter to other cortical regions (Braak and Braak, 1997; Braak et al., 2005; Delacourt et al., 1999). Given the crucial role of the entorhirnal cortex and the hippocampus in episodic memory (Woodard et al., 2009; Burianova et al., 2010; Coward, 2010), it is not surprising that in the very early stages of AD, such as the preclinical stage of MCI, specifically episodic memory is impaired (Winblad et al., 2004; Dudas et al.2005; Ahmed et al., 2008a, b; Kalpouzos et al., 2009; Leyhe et al., 2009; Fayed et al., 2010). Importantly, dopamine is one of the main neurotransmitters in the hippocampus and the limbic system (e.g. mesolimbic and mesocortical dopamine pathways). Thus, one could expect that individuals with MCI should also show DA deficits, as previously suggested (Albert et al., 2011; Nagaraja and Sivaramakrishnan, 2001).

This argument is supported by recent studies that suggest a DA dysfunction at the core of Alzheimer's dementia. Neurodegeneration, which contributes to the progression from healthy aging to MCI, and then to dementia (Pennisi et al., 2011), has been partly attributed to the anomalous cortical hyperexcitability observed at early stages of pathological aging. Specifically, dopamine seems to modulate cortical cholinergic release, which is typically impaired in AD patients (Martorana et al., 2009). In line with this, administration of L-dopa in AD patients, similar to the effects of acetylcholinesterase inhibitors typically administered in such cases, may reduce this anomalous cortical hyperexcitability, as balance in the function of neurotransmitters seems to be restored after the precursor of dopamine is administered (Martorana et al., 2008; for a review see Martorana, Esposito and Koch, 2010). Cortical hyperexcitability, which eventually leads to cell death (Martorana, Esposito and Koch, 2010) is primarily observed in the primary motor (M1) and premotor cortex, and DA seems to play a key role in this process particularly in M1 (Hosp et al., 2011; for a review see Pennisi et al., 2011).

Dopamine is also directly related to several cognitive functions such as episodic memory, learning and executive functions (for a review see Bäckman et al, 2006), which are considered to be neuropsychological predictors of conversion from MCI to AD (Arnáiz and Almkvist, 2003). Therefore, alterations in the dopaminergic system observed in AD may contribute significantly to the progressive cognitive decline in pathological aging (for a review see Martorana et al., 2010).

In this piece of work, we aimed at investigating DA activity in MCI, and its relationship to cognitive functions, by using a non-invasive marker, EBR. We expect that the group of MCI will have significantly lower EBR than the healthy controls. Also, we expect that EBR will be correlated with general cognitive functions, such as attention, and memory.

2. Method

2.1. Participants

Thirty-six adults (23 females and 13 males) diagnosed with MCI, and 33 healthy controls (23 females and 6 males) participated in the study. Participants in the MCI were assessed according to the Petersen criteria (Petersen and Morris, 2005; for a review see Petersen et al., 2001). The Mini Mental State Examination (MMSE; Folstein, Folstein and McHugh, 1975) was used as a basic screening tool for MCI, but this was complemented with the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) to increase sensitivity of diagnosis and classification (Nazem et al., 2009). Both groups were matched in age and years of education (see Table 1 for demographics and clinical characteristics).

Exclusion criteria for both groups were: i) use of medication that could interfere with the function of the central nervous system and/or eyelid kinetics; ii) a score of 9 or above (for women) and 6 or above (for men) in the Instrumental Activities of Daily Living (IADL; Lawton and Brody, 1969); iii) a history of neurologic and/or psychiatric disorders other than MCI; iv) a score of 5 or above in the Geriatric Depression Scale (GDS short version; Sheikh and Yesavage, 1986); v) a history of substance abuse including alcohol and nicotine; and vi) severe mobility, hearing or vision problems which would impede participation in the study. The exclusion criteria were assessed via a detailed clinical interview of the participant and the caregiver (if applicable). All participants provided a signed informed consent of participation, after being fully informed on the study. The study was approved by the local Bioethics Committee. All participants were recruited from the Greek Association of Alzheimer's Disease and Related Disorders, as well as local day care centers via posters and oral presentations. This study was part of the screening process for the Long Lasting Memories (LLM) Project funded by the European Commission (ICT-CIP-PSP scheme) (see Bamidis et al., 2011; www.longlastingmemories.eu).

2.2. Material

2.2.1. Neuropsychological measures

To assess cognitive status, we employed the MMSE and the MoCA tests. The MMSE, is the most widely used measure of global cognition especially in the geriatric population (Schultz-Larsen et al., 2007). It assesses functions such as orientation to space and time, visuospatial skills, praxis, attention and working memory as well as short-term memory, registration and language (for a review see Brayne, 1998).

Since there is some controversy about the sensitivity of the MMSE to differentiate healthy individuals from individuals with MCI (Nazem et al., 2009; for a review see Tombaugh and McIntyre, 1992; Wind et al., 1997; Yochim et al., 2008), we used this assessment tool in combination with the MoCA. The MoCA was designed as a brief cognitive screening tool that assesses short-term memory, visuospatial abilities, several aspects of executive function, working memory, attention (sustained and executive), language and orientation to time and space. It covers more cognitive domains than the MMSE, and it is thought to be more sensitive to Mild Cognitive Impairment than the MMSE itself (Aggarwal and Kean, 2010).

In addition, the following neuropsychological tests were employed to obtain specific measures of memory and executive attention; the Digit Span Backward task (Wechsler, 1981) and the Trail Making Test (part B) (Reitan and Wolfson, 1995), respectively.

2.2.2. Neurophysiological measure — EOG protocol

Horizontal (electrodes lateral to the external canthi) and vertical (electrodes above and below the left eye) gold skin electrodes were

Table 1
Demographic variables for study participants.

Variables	Healthy	MCI
Age (years)[a]		
Mean	67.48	67.56
SD	6.14	7.28
Range	56–81	57–85
Education (years)[a]		
Mean	9.43	8.23
SD	4.23	5.13
Range	6–16	6–17

SD = standard deviation.
[a] Independent *t*-test: all > 0.05.

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