



Short report

Phasic and tonic alerting in mild cognitive impairment: A preliminary study[☆]Diana Martella^a, Salvadora Manzanares^b, Guillermo Campoy^c, Javier Roca^d, Carmen Antúnez^b, Luis J. Fuentes^{c,*}^a Basque Center on Cognition, Brain and Language, Paseo Miketelegi, 20009 Donostia-San Sebastián, Spain^b Unidad de Demencias, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain^c Departamento de Psicología Básica y Metodología, Facultad de Psicología, Universidad de Murcia, Campus de Espinardo, 30100 Murcia, Spain^d Departamento de Psicología Evolutiva y de la Educación, Facultad de Psicología, Universidad de Valencia, Avenida Blasco Ibáñez, 21, 46101 Valencia, Spain

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ABSTRACT

In this preliminary study we assessed the functioning of the different attentional networks in mild cognitive impairment (MCI) patients, taking as theoretical framework the Posner's cognitive neuroscience approach. Two groups of participants were tested in a single short experiment: 20 MCI patients (6 amnesic, 6 non-amnesic and 8 multiple-domain) and 18 healthy matched controls (HC). For attentional assessment we used a version of the Attention Network Test (the ANTI-V) that provided not only a score of the orienting, the executive, and the alerting networks and their interactions, but also an independent measure of vigilance (tonic alerting). The results showed that all subtypes of MCI patients exhibited a selective impairment in the tonic component of alerting, as indexed by a decrease in the d' sensitivity index, and their performance in executive network increased up to the HC group level when phasic alerting was provided by a warning tone. Our findings suggest that a core attentional deficit, especially the endogenous component of alerting, may significantly contribute to the behavioral and cognitive deficits associated with MCI.

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1. Introduction

It is amply assumed that mild cognitive impairment (MCI) refers to the transitional stage between the cognitive changes of normal aging and mild dementia (Hwang et al., 2012; Petersen et al., 2001), and is characterized by a heterogeneous syndrome that sometimes signals the presence of Alzheimer's disease (AD) (Aretouli et al., 2013). Although the memory deficit is amply accepted as part of the cognitive deterioration exhibited by both MCI and AD patients, impairment of executive functions in general, and attentional functions in particular has also been reported (Aretouli et al., 2013; Fernández et al., 2011; Fuentes et al., 2010; Saunders and Summers, 2011; Tales et al., 2011). Given that attention can affect other cognitive processes, such as memory and language, the identification of different patterns of attentional deficit could be a useful diagnostic marker and promote attention-dependent intervention strategies.

In previous studies, we highlighted the relevance of taking a theoretical background for neuropsychological testing (Fernández et al., 2011;

Fuentes et al., 2010). Regarding attentional deficits we used the cognitive neuroscience approach developed by Posner and his colleagues (Posner and Petersen, 1990) that distinguishes three attention-related neural networks. The *orienting network* serves the functions of endogenous and exogenous selection of information among several sensory inputs. The *executive network* is involved in the ability to control our own behavior in order to achieve intended goals, resolving conflict among alternative responses. And the *alerting network* is involved in achieving (phasic alerting) and maintaining (tonic alerting or vigilance) a general state of activation of the cognitive system.

Importantly, the three networks can be easily assessed in one single experiment through the Attention Network Test (ANT). The original ANT (Fan et al., 2002) and subsequent versions of the test, such as the ANTI (Attention Network Test for Interactions; Callejas et al., 2004), consist in a combination of the Posner's cueing task and the Eriksen's flanker task. The flanker task serves to assess responses to conflict, a function of the executive network. The test shows a central arrow, the target, pointing to the right or to the left. The target is flanked by two arrows on both sides and may be pointing either in the same direction (congruent condition) or the opposite direction (incongruent condition). Participants are told to respond to the direction of central arrow and ignore the distracters. A conflict score can be computed by subtracting reaction times (RTs) in the congruent condition from RTs in the incongruent condition. The cueing task serves to assess attention

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to spatial locations, a function of the orienting network. In the cued trials, the target is presented at the same location of a previous peripheral cue. In the uncued trials, the target is presented at the opposite location of the peripheral cue. An orienting score is computed by subtracting RTs in the cued trials from RTs in the uncued trials. A warning tone presented before the visual cue (the ANTI version) serves to assess the preparedness of the participant for the upcoming target, a function of the alerting network. An alerting score is computed by subtracting RTs in the warning tone trials from RTs in the no tone trials. The ANT has proved its utility to assess the function of the attentional networks not only in behavioral studies (Callejas et al., 2004; Fuentes and Campoy, 2008), but also in neuroimaging studies (Fan et al., 2005), in psychiatric populations (Casagrande et al., 2012), and in patients diagnosed with dementia or previous stages to dementia (Fernández et al., 2011; Fuentes et al., 2010; Van Dam et al., 2013).

By using an ANTI version, Fuentes and Campoy (2008) demonstrated that alerting, implemented phasically by playing a warning tone previous to the visual cue, could improve the functioning of the orienting network, but impaired the functioning of the executive network. Subsequently, by using the Fuentes and Campoy's task, Fernández et al. (2011) demonstrated that all tested MCI participants showed a deficit in the functioning of the executive network (see also Van Dam et al., 2013; Zheng et al., 2012), but the warning tone improved rather than impaired the conflict score. This result suggests that phasic alerting triggered by the warning tone produced a better functioning of the executive network in patients diagnosed with MCI, irrespective of whether they presented vascular damage or not. Alerting deficits were also observed by Saunders and Summers (2011) in both amnesic and non-amnesic MCI patients by using reaction time tasks. Thus, although the aforementioned studies used different attentional tasks, a common observation is that sustained attention seems to be compromised in most MCI patients, irrespective of their etiology or subtype. These results open the question that attention deficits associated with MCI in general might be better characterized as a failure to maintain an appropriate level of tonic alertness or vigilance, fundamental for a correct functioning of the other two networks, and necessary for optimal cognitive performance. The lack of a sufficient tonic alerting state might have been overcome by presenting the warning tone, which might have provided the patients with the necessary alertness to regulate the functioning of the executive network (Fernández et al., 2011).

In the present study we aimed to directly assess the hypothesis that tonic alerting or vigilance is compromised in diverse subtypes of MCI patients. For this purpose we used the ANTI task of Fuentes and Campoy (2008) and the ANTI-V task (Attention Network Test for Interactions and Vigilance) of Roca et al. (2011). The ANTI-V task includes trials in which participants are asked to detect a small and infrequent change in the length of the target arrow (vigilance trials). If MCI patients are characterized by a deficit in the ability to maintain a tonic level of attention over time, then we should find: (1) that the warning tone will regulate the functioning of the executive network (Fernández et al., 2011); and (2) the patients, irrespective of their MCI diagnosis will show a larger proportion of errors in the vigilance trials compared with the control group. Finally, the application of the Signal Detection Theory (SDT) to the vigilance data should provide relevant information about the nature of the expected deficit. That is, whether the deficit might be better characterized by a change in signal-to-noise sensitivity or in response bias.

2. Method

2.1. Participants

The study included 38 participants, 20 MCI patients and 18 healthy controls (HC). MCI patients (6 amnesic, MCI-a; 6 non-amnesic, MCI-na; and 8 multiple-domain, MCI-mul) were recruited from the Dementia Unit at the University Hospital Virgen de la Arrixaca

(Murcia, Spain). The diagnosis of MCI required that patients complained of memory problems corroborated by an informant, judgment of the neurologist of deficits in memory based on objective assessment according to Petersen's criteria (Petersen et al., 2001), and the absence of dementia as determined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for dementia. We further classified the MCI group in three subtypes on the basis of statistical cut-offs used in previous studies (Loewenstein et al., 2006; Migliacci, Scharovsky and Gonorazky, 2009). Thus, the MCI-a subtype scored ≤ 1.5 SD in one or more memory tests, with other cognitive measures not being affected. The MCI-na subtype scored ≤ 1.5 SD in one or more neuropsychological tests but memory was not affected. The MCI-mul subtype scored ≤ 1.5 SD in one or more neuropsychological tests tapping at least one cognitive domain irrespective of whether there was memory or not. Neuroimaging testing (magnetic resonance in 17 patients, computerized axial tomography in 3 patients) revealed that patients did not differ in respect to atrophy or vascular load. The healthy controls were recruited from the community and were free from important medical conditions (i.e., heart disease, cancer, stroke, MCI and drug or alcohol abuse). The two groups of participants were matched as closely as possible for age, education level and gender. Table 1 shows the main neuropsychological tests in which MCI patients in general showed impaired performance compared with the HC group, and those in which impaired performance was observed in a MCI subtype compared with the other subtypes. All participants gave written informed consent for participation in this study, which was approved by the Ethical Committees of both the Virgen de la Arrixaca Hospital and the University of Murcia.

2.2. Stimuli and procedure

A detailed description of the ANTI task can be found in the Fuentes and Campoy (2008) study. The only change respect to our previous study was the inclusion of infrequent target arrows for the vigilance task (the ANTI-V task). Whereas the arrows for frequent targets were 36 pixels in length, the arrow presented in the vigilance task was 33 pixels in length. The experiment consisted of two different blocks of trials. In the ANTI block there were 20 practice trials followed by 48 experimental trials in which the vigilance condition (short target arrows) was not presented. In the ANTI-V block there were 20 practice trials followed by 192 experimental trials in which the vigilance condition was randomly presented. The sequence of events in each trial is illustrated in Fig. 1. The basic display was presented for a variable duration between 1200 and 2600 ms. The warning tone was delivered in half of the trials for 50 ms (warning tone condition), with an equivalent empty audio file being run in the other half of the trials (no tone condition). The orienting visual cue appeared 350 ms after the tone and was presented 50 ms in the central box of either the upper or the lower box row. The cue-target SOA was kept constant at 100 ms. The target and the flankers were presented either in the same row as the cue (50% of trials, the valid condition), or in the other row (50% of trials, the invalid condition). In trials without a visual cue, the basic configuration remained on during the same interval (no-cue condition). The target display was presented until the participants responded. Flanker arrows could point to the same direction of the target (the congruent condition) in half of the trials, or to the opposite direction of the target (the incongruent condition) in the other half. Participants were instructed to respond as fast and accurate as possible. Finally, in the 25% of the trials (only the ANTI-V block), the target central arrow was reduced in length. The participants were encouraged to identify these infrequent stimuli by pressing the spacebar and ignoring the direction of the central arrow in these trials. Participants performed the ANTI block first, followed by a 5-min rest period and then they performed the ANTI-V block without any additional rest.

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