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Short report

Phasic and tonic alerting in mild cognitive impairment: A preliminary study☆

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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 amnestic, 6 non-amnestic 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.

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 amnestic and non-amnestic 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 amnestic, MCI-a; 6 non-amnestic, 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.

Table 1
Sociodemographic information, means of neuropsychological testing results (standard deviations in parentheses) and GDS scores for the two groups of participants (HC and MCI), and the three MCI subtypes.

Sociodemographic data and tests	HC	MCI	MCI-a	MCI-na	MCI-mul
N	18	20	6	6	8
Sex, female/male	11/7	16/4	5/1	4/2	7/1
Age, years	66.6 (7.5)	66.5 (8.3)	62.7 (10.2)	65 (5.9)	69.7 (8.9)
Education					
Elementary/primary	3/8	9/5	1/1	5/1	5/3
High school/university	2/5	2/2	2/2	0/0	0/0
GDS	2	3	3	3	3
MMSE**	28.7 (1.2)	25.8 (3.1)	27.5 (2.2)	26.8 (1.5)	23.8 (3.6)
Word list immediate recall***	7.5 (1.2)	5.6 (1.6)	6.3 (1.5)	4.6 (1.5)	6.2 (1.3)
Word list delayed recall***cc	5.6 (1.1)	2.4 (2.4)	2.3 (2.6)	4.7 (1.9)	0.8 (1.2)
Word list recognition***	18.7 (1.0)	16.30 (2.5)	17 (2.3)	17.3 (1.2)	15 (2.9)
Digit/symbol coding***a,b	46.9 (13.9)	26.6 (15.3)	41.8 (2.4)	22.2 (9.3)	16.7 (10.5)
Clock drawing test*	9.53 (0.63)	8.35 (2.00)	9,17 (0.98)	8.75 (1.25)	7.44 (2.71)
CTT-1 (second)**a	60 (23.4)	138.9 (86.7)	76.7 (33)	136 (51)	190.1 (105.3)
CTT-1 (errors)*a,c	0.13 (0.34)	0.90 (1.45)	0.1 (0.4)	0.2 (0.4)	2 (1.8)
CTT-2 (second)**	116.8 (49.5)	213.2 (96.5)	171 (101.3)	234 (112.6)	239 (66.2)
CTT-2 (errors)	0.25 (0.58)	1.88 (4.11)	3.2 (6.8)	1.2 (0.9)	1.2 (2.2)
Verbal fluency*	18.8 (3.7)	14.9 (5.2)	17.3 (5.9)	14.3 (5.9)	13.5 (4.1)
Boston naming test*	14.3 (1.4)	12.7 (5.2)	13.8 (1.3)	12 (2.7)	12.6 (1.9)
FAB**a	15.6 (2.3)	12.6 (3.6)	15.5 (1.9)	12.5 (4.8)	10.6 (2.2)

*abc $p < 0.05$; **cc $p < 0.01$; *** $p < 0.001$
*Significant difference between HCI and MCI; [a]Significant difference between MCI-a and MCI-mul; [b]Significant difference between MCI-a and MCI-na; [c]Significant difference between MCI-mul and MCI-na.
HC = healthy controls; MCI = patients with mild cognitive impairment; MCI-a = MCI-amnestic; MCI-na = MCI-non-amnestic; MCI-mul = MCI-multiple domain; GDS = Global Deterioration Scale; MMSE = Mini Mental State Examination; CERAD = the Consortium to Establish a Registry for Alzheimer's Disease; CTT = Color Trail Test; FAB = Frontal Assessment Battery.

2.3. Statistical analyses

The first block of trials (the ANTI block) served just to assess the attentional networks functioning and their interactions, whereas the second block of trials (the ANTI-V block) served just to assess tonic alerting or vigilance. For the ANTI block, median RTs of correct trials ranging between 200 and 1700 ms were included in the statistical analyses. A group (patients, control) × warning tone (present, absent) × cueing (valid, invalid, no-cue) × congruency (congruent, incongruent) mixed-design ANOVA was performed on both mean of median RTs and mean percentage of errors. Regarding the vigilance task, the rate of hits (proportion of correct spacebar responses to the infrequent targets) and false alarms (proportion of incorrect non spacebar responses to the infrequent targets) was used to compute the sensitivity (d′) and response bias (β) indexes, following the Signal Detection Theory (SDT) procedure. Vigilance performance indexes were submitted to one-way ANOVA with group as the between-participants factor. Further analyses assessed differences between the three subtypes of MCI in both blocks.

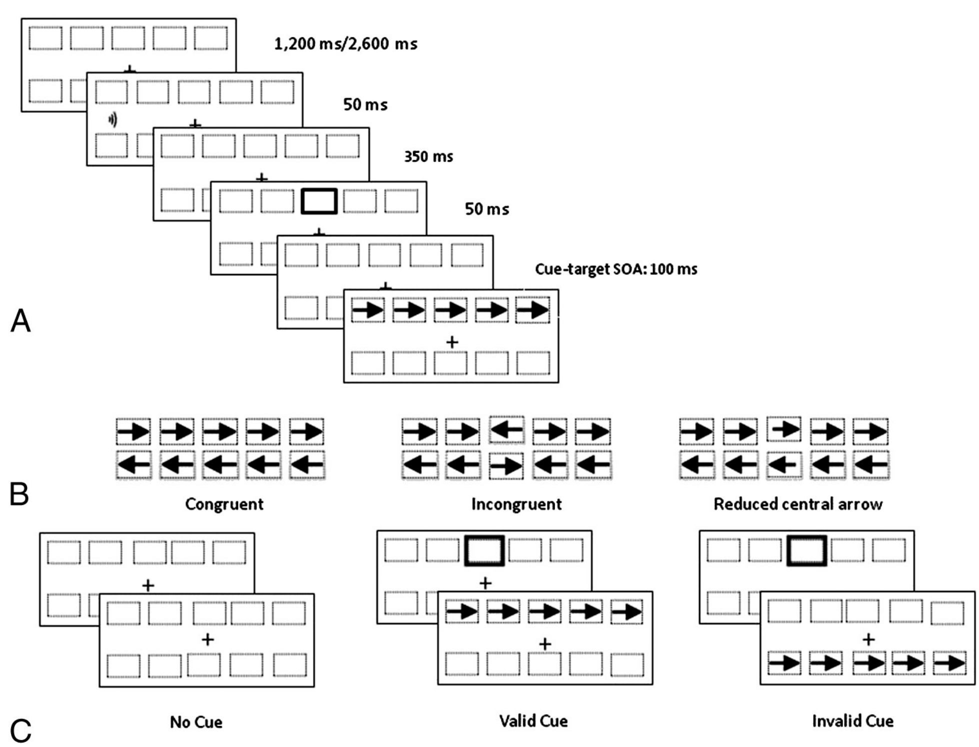

Fig. 1. Procedure and stimuli used in the ANTI-V. (A) Schematic representation of the procedure. (B) The target stimuli. (C) The visual cue conditions.

Table 2
Mean of median correct reaction times, standard deviations (between parentheses), and mean percentage of errors for the two groups of participants as a function of warning tone (tone, no tone), cueing (valid, invalid, no-cue) and congruency (congruent, incongruent).

	Patients		Controls	
	Tone	No tone	Tone	No tone
Reaction time (ms)				
Valid congruent	342 (74.44)	378 (72.30)	336 (104.02)	345 (108.84)
Incongruent	448 (98.48)	447 (127.46)	388 (119.15)	482 (171.80)
Invalid congruent	435(98.54)	457 (136.89)	414 (159.74)	404 (127.60)
Incongruent	507 (110.95)	469 (97.64)	516 (144.32)	498 (130.51)
No-cue congruent	372 (91.21)	489 (117.36)	341 (110.47)	401 (119.10)
Incongruent	472 (147.21)	492 (128.02)	455 (131.53)	492 (169.12)
Percentage of errors				
Valid congruent	12.08 (18.62)	15.83 (19.48)	6.94 (8.21)	4.63 (5.87)
Incongruent	26.25 (25.07)	26.67 (28.56)	5.09 (6.48)	6.02 (8.49)
Invalid congruent	22.08 (19.36)	21.67 (21.19)	12.50 (14.65)	16.20 (21.48)
Incongruent	37.50 (25.43)	39.17 (24.19)	22.69 (21.73)	20.37 (19.00)
No-cue congruent	12.50 (15.88)	20.00(18.22)	6.48 (8.36)	7.41 (10.26)
Incongruent	24.58 (26.28)	34.17 (30.34)	4.63 (5.87)	8.79 (9.25)

3. Results

3.1. RTs analysis (ANTI block trials)

The analysis of RTs (Table 2) showed significant main effects of warning tone ($F(1,36) = 9.43$; $p < .01$; $\eta^2 = .21$), cueing ($F(2,72) = 23.98$; $p < .0000001$; $\eta^2 = .40$) and congruency ($F(1,36) = 111.27$; $p < .0000001$; $\eta^2 = .75$). Similarly to previous studies (Fuentes and Campoy, 2008), the warning (tone, no tone) × cueing (valid, invalid) partial interaction was significant ($F(1,36) = 5.28$; $p < .01$; $\eta^2 = .12$) suggesting that the cueing effect was greater when the warning tone was present (89 ms) than when it was absent (44 ms). The group × congruency interaction was significant ($F(1,36) = 6.28$; $p < .01$; $\eta^2 = .14$). We observed larger congruency effects for the HC group (98 ms) than for the MCI group (50 ms). The group × warning tone × congruency interaction was also statistically significant ($F(1,36) = 8.76$; $p < .01$; $\eta^2 = .20$), indicating that contrary to the HC group, for MCI patients the congruency effect was not observed when the warning tone was absent (congruency effect = 28 ms; $p > .05$), but it was when the warning tone was present (congruency effect = 93 ms; $p < .001$). Importantly, the congruency effect exhibited by the MCI group when the warning tone was present is comparable to that exhibited by the HC group (see Fig. 2). When we compared performance among the three subtypes of MCI, we only observed a significant subtype × warning tone × congruency interaction ($F(2, 28) = 5.37$; $p = .01$; $\eta^2 = .28$). The interaction was due to the alerting tone increasing the congruency effect more in the multi-domain MCI subtype than in the other two subtypes.

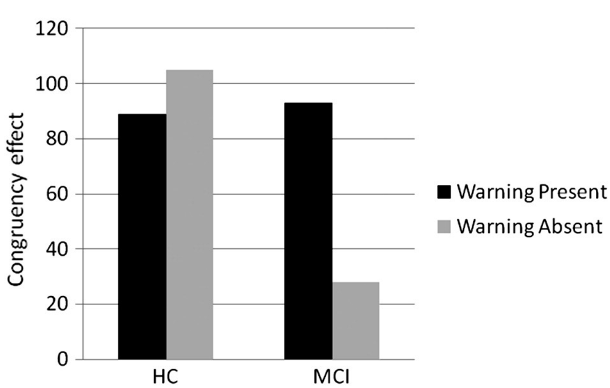

Fig. 2. Congruency effects for each group of participants as a function of warning tone (present, absent). HC = healthy controls; MCI: mild cognitive impairment.

3.2. Accuracy analysis (ANTI block trials)

The error percentage analysis (Table 2) showed significant main effects of group ($F(1,36) = 9.45$; $p < .01$; $\eta^2 = .21$), warning tone ($F(1,36) = 5.05$; $p < .01$; $\eta^2 = .12$), cueing ($F(2,72) = 23.20$; $p < .000001$; $\eta^2 = .39$), and congruency ($F(1,36) = 11.87$; $p < .001$; $\eta^2 = .25$). Patients made more errors (24.37%) than controls (10.15%); there were more errors in the warning tone absent (18.41%) than in the warning tone present (16.11%); performance was better in the valid (12.94%) than in both the invalid and the no-cue conditions (24.02% vs. 14.82%, respectively); and performance was worse in the incongruent (21.33%) than in the congruent condition (13.19%). The group × congruency interaction was significant ($F(1,36) = 6.23$; $p < .01$; $\eta^2 = .15$). The congruency effect was observed only for the MCI group ($p < .001$), but not for the HC group ($p = .36$). That is, errors were sensitive to conflict effects only for patients. Finally, the cueing × congruency interaction was also significant ($F(2,72) = 3.61$; $p < .01$; $\eta^2 = .09$). The congruency effect was observed only with both invalid ($p < .0001$) and no-cue ($p < .0001$) trials. No other interactions reached statistical significance (all $ps > .05$). MCI subtypes did not interact with any other factor in the error percentage analyses.

3.3. Vigilance analysis (ANTI-V block trials)

Groups differed significantly in the hit percentage ($F(1,36) = 17.04$; $p < .001$; $\eta^2 = .32$) (HC = 87%; MCI = 50%), but not in the false alarm percentage ($F < 1$). Regarding the SDT analysis, the d′-sensitivity index was significantly lower for patients (1.73) than for controls (3.11) ($F(1,36) = 16.19$; $p < .001$; $\eta^2 = .31$), but there were no statistical differences in the response β-bias between the two groups ($F < 1$). These results are illustrated in Fig. 3. MCI subtypes did not show any difference in neither the hit nor the false alarm percentages.

4. Discussion

In this study we used a recent version of the Attention Network Test that allowed us to assess not only the functioning of the attentional networks and their interactions, but also the vigilance component of the alerting network in a rather direct way. Two groups of participants, a group of patients with a mild cognitive impairment diagnosis and a group of matched healthy controls, performed a combination of the Fuentes and Campoy (2008) ANTI task and the Roca et al. (2011) ANTI-V task. The more relevant findings from the present study concern the modulation of congruency effects by phasic alertness, and the deficit in vigilance observed in MCI patients, irrespective of their subtype. In our previous research, we found that phasic alertness triggered by the warning tone regulated the functioning of the orienting and executive networks in patients diagnosed with dementia with Lewy bodies (Fuentes et al., 2010), and the functioning of the executive network in MCI patients, irrespective of whether they presented subcortical vascular damage or not (Fernández et al., 2011). These results suggest that patients in very early stage of dementia might manifest a deficit in reaching and keeping an appropriate level of alerting, a function that might depend on the LC providing noradrenaline to the fronto-parietal circuitry involved in both phasic and tonic alerting (Sturm and Willmes, 2001).

On the basis of these previous findings we hypothesized that our patients, irrespective of their MCI subtype, would exhibit a similar deficit in executive control, signaled by the congruency effect, under no warning conditions. Importantly, the executive control score would

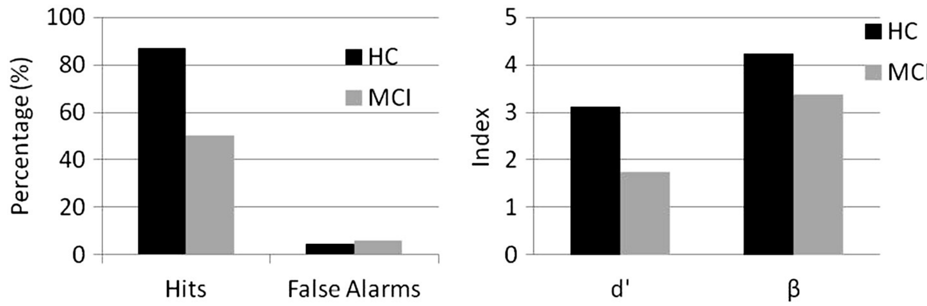

Fig. 3. Percentage of hits and false alarms (FA) (left) and sensitivity and response bias (right).

normalize under the warning tone condition. We replicated this pattern of phasic alerting effects with our group of MCI patients. Under the no tone condition we observed an altered pattern of congruency effect, but the executive network score regulated in the warning tone condition, showing a similar size to that observed in the HC group. This pattern of results has two important implications. First, it indirectly reveals a deficit in reaching and keeping an appropriate level of sustain alertness or vigilance to appropriately deal with target processing and responses, so that patients needed the exogenous alertness provided by warning tone for normal executive network performance. Second, the inclusion of the vigilance trials provided a direct measure of such tonic alertness deficit. As predicted, the MCI patients were less able to distinguish between a standard target arrow and a shorter target arrow that required a different response. It produced a higher percentage of errors in the MCI group than in the HC group, and this pattern occurred for the three MCI subtypes. In line with a deficit in vigilance, the group differences were observed in d′ rather than in response bias (β).

In summary, our vigilance ANT task seems to be useful to measure an ample range of attentional components and their interactions in a rather short testing time. In addition, both indirect (phasic) and direct (tonic) measures of alertness can be obtained, so that the test allows for a more complete assessment of such a basic attentional function that has been thought to be at the core of more complex cognitive deficits associated with early dementia. By using experimental tasks such as those described here, we were able to dissociate the particular cognitive deficits associated with different diagnoses. Whereas cholinergic dysfunction affecting the orienting network might be differentially observed in MCI patients with subcortical vascular damage (Fernández et al., 2011), executive control dysfunction might be a more general symptom affected in most patients diagnosed with MCI (Aretouli et al., 2013; Van Dam et al., 2013). However, the present results suggest that a deficit in tonic alertness might be on the basis of those attention deficits which can be observed not only in people diagnosed with dementia (Fuentes et al., 2010), but also in several subtypes of mild cognitive impairment (the present study, see also Saunders and Summers, 2011). Therefore, these patients might clearly benefit from an appropriate intervention program that promotes endogenous alerting.

Conflict of interest

No conflicts of interests.

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