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Is There a Specific Pattern of Attention Deficit in Mild Cognitive Impairment with Subcortical Vascular Features? Evidence from the Attention Network Test

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Key Words
Attention network test · Vascular mild cognitive impairment · Cholinergic system

Abstract
Background: Mild cognitive impairment (MCI) is an intermediate state between normal aging and early dementia. Some MCI patients show white matter hyperintensities in magnetic resonance imaging, revealing subcortical vascular damage (SVD). This study aimed to evaluate potential attention deficits not previously described in these patients. Specifically, we evaluated attention network functioning in MCI on the basis of Posner's cognitive neuroscience model, which considers attention as a set of networks: alerting, orienting and executive control. ***Methods:*** Three groups of participants were tested: 19 MCI patients with SVD (svMCI), 15 MCI patients free from SVD (nvMCI) and 19 healthy controls (HC). We used a task in which the three attention networks and their interactions can be assessed simultaneously, the Attention Network Test (ANT). ***Results:*** The svMCI group showed smaller orienting effect compared with the nvMCI and HC groups. In contrast to the HC and nvMCI groups, svMCI patients did not show improvement in the executive network from the valid visual cue. ***Conclusions:*** svMCI patients show a deficit in orienting attention networks. This deficit could be related to an effect of SVD on the cholinergic system because acetylcholine is implicated in the modulation of covert orienting responses of attention.

Introduction

Mild cognitive impairment (MCI) is a transitional stage between normal aging and early dementia [1]. Frisoni et al. [2] suggested the term mild cognitive impairment with subcortical vascular features (svMCI) as a possible preliminary stage of subcortical vascular dementia (SVaD). The main criteria for svMCI are: (1) the presence of periventricular and deep white matter lesions observed with neuroimaging techniques such as magnetic resonance imaging (MRI), revealing subcortical vascular damage; (2) neurological signs such as lower facial weakness or gait disorders that constitute evidence of cerebrovascular disease, and (3) deficits in executive and memory functioning [2]. Because attention is an important component of executive control mechanisms, assessment of attention functioning in svMCI patients is crucial.

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Previous studies that assessed attention in MCI patients produced inconclusive results. Whereas Nordlund et al.'s [3] svMCI patients showed impaired performance in the Trail Making Test compared with controls and with nonvascular MCI patients, Frisoni et al. [2] found no difference in attention performance between persons with svMCI and those with nonvascular MCI. Given that attention is a domain general process that can affect the performance of many other processes including language, memory and executive control, the establishment of a differential pattern of attention deficits in svMCI could improve its clinical diagnosis as well as help define appropriate therapeutic approaches to this disease. To our knowledge, no theory-based attention assessment has thus far been carried out with svMCI patients, despite the fact that some researchers have shown differences between Alzheimer's disease (AD) and SVaD patients in attention performance [4, 5]. The lack of a theoretical framework in neuropsychological studies may make the process of evaluation and data interpretation in this field difficult.

The aim of this study is to examine whether the functioning of the different components of attention are affected in a selective way in svMCI. We worked under Posner's cognitive neuroscience theory of attention [6], which considers attention as a set of networks that may work independently and/or in an interactive manner. Posner's theoretical framework divides attention into three networks, each of which is associated with different functions, neurotransmitters and brain areas. The *alerting network* is involved in preparing and sustaining alertness and in processing high priority signals. This network is related to the right frontal and parietal areas [7] and is modulated by norepinephrine [8]. The *orienting network* is required in the selection of information from among several sensory inputs. The parietal and frontal lobes, the temporo-parietal junction, the pulvinar, and the superior colliculus seem to be related to covert orienting shifts. The cholinergic system modulates these areas [8]. The *executive network* is involved in cognitive control and self-regulation, as in conflict resolution tasks, planning or error detection, and emotion. The anterior cingulate cortex (ACC) and the lateral prefrontal cortical areas are associated with the executive network; dopamine, which is generated in the basal ganglia, modulates these brain regions [9].

The Attention Network Test (ANT) was designed to evaluate the functioning of the three attention networks and their interactions in a single task [10–13]. The executive network is assessed by means of a response to conflict consisting of a flanker task. In this paradigm, a central arrow (the target) points to the left or the right. The target is flanked by four distracting arrows that can be either congruent (pointing in the same direction as the target) or incongruent (pointing in the opposite direction to the target). Subjects are told to respond to the direction of the target arrow and to ignore the distracters. The orienting network is assessed by using peripheral cues to summon attention to a location. In valid-cue trials, the target is presented at the location of the previous peripheral cue, while in invalid-cue trials, it is presented at a location opposite that of the peripheral cue. The alerting network is assessed by observing the effects of playing a tone prior to the cue presentation.

In this study, we tested attention deficits in persons diagnosed with either svMCI or nonvascular MCI (nvMCI) and compared their performance with that of a group of healthy matched controls (HC). The ANT version used in this study [11, 12] has proven useful not only for assessing the functioning of the attention networks but also for studying their interactions [11, 12, 14, 15].

Methods

Participants

The study included 53 participants, 34 MCI patients and 19 HC. MCI patients were recruited from the Unit of Dementia at the University Hospital Virgen de la Arrixaca (Murcia, Spain), where they had been diagnosed as suffering from MCI according to Petersen's criteria [1]. Each MCI patient underwent a structural MRI. Nineteen MCI patients, all of whom met the criteria suggested by Frisoni et al. [2], were included in the svMCI group. The remaining 15 participants were found to be free of vascular brain damage and constituted the nvMCI group, in which cortical atrophy was the unique MRI finding. This classification was based on imaging data obtained from MRI flair T_2-weighted images or from fast-spin echo T_2-weighted images in the few exams in which a Flair sequence was not acquired. Hyperintense foci were considered pathologic only when they were larger than 3 mm in maximum diameter in the white matter of the semioval centers or larger than 5 mm in the deep gray nuclei. The imaging exams were reviewed by an expert radiologist (J.M.G.S.) [16]. Based on these results, we classified MCI patients as svMCI when they met the criteria of Frisoni et al. [2] and as nvMCI when they were free from vascular brain damage. Of the svMCI patients, 79% showed periventricular subcortical vascular damage, 21% in the basal ganglia and 16% in the thalamus. The more frequent neurological signs of subcortical vascular damage in svMCI patients were abnormal corticobulbar reflexes (37% of patients), gait disorders (21%), lower facial weakness (21%), bradykinesia (21%), and action tremor (16%). HC 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 three groups of participants (HC, nvMCI, and svMCI) were matched as closely as possible for

Table 1. Demographic information, means of neuropsychological testing, GDS scores and HIS (standard deviation in parentheses) for each group

Sociodemographic data and tests	Maximum score	HC	nvMCI	svMCI
n		19	15	19
Sex, female/male		9/10	7/8	13/6
Age, years		70.3 (8.1)	66.7 (8.1)	72.2 (7.6)
Education, years		5.6 (2.6)	4.8 (3.1)	3.58 (3.5)
MMSE[a, b]	30	29.3 (1.2)	25.9 (2.7)	24.6 (3.3)
GDS[a, b]	7	1 (0)	3 (0)	3 (0)
Blessed-Dementia Scale	28	–	4.4 (3.4)	5.6 (2.6)
Hachinski Ischemic Scale[b, c]	16	1.4 (1.0)	1.7 (1.8)	5.8 (3.4)
Cerad battery				
Semantic fluency[a, b]		16.1 (2.2)	13.4 (2.8)	12.1 (2.8)
Boston Naming test	15	12.9 (1.1)	12.7 (1.8)	12.3 (1.7)
Word List Memory[a, b]	10	7.3 (1.1)	5.7 (1.7)	5.7 (1.6)
Word List Recall[a, b]	10	5.1 (1.6)	3.1 (1.4)	3.1 (1.8)
Word List Recognition[a]	20	18.7 (1.2)	16.0 (5.0)	17.0 (2.8)
Constructional praxis	11	9.9 (1.2)	9.5 (2.1)	9.0 (1.9)
Recall of constructional praxis[a]	11	8.2 (2.0)	5.5 (3.3)	6.4 (3.2)
TMTA[b, *]		80.6 (30.2)	129.3 (59.3)	164.8 (77.2)
TMTA (errors)		0.6 (1.6)	1.6 (2.7)	1.7 (2.7)
Barcelona Test				
Forward Digit Span	9	4.4 (0.6)	4.5 (0.6)	4.0 (0.7)
Backward Digit Span	8	3.1 (0.5)	3.1 (0.7)	3.1 (0.7)
Abstraction[a, b]	12	6.5 (2.0)	4.7 (2.2)	5.1 (1.5)
Phonological fluency (P)		8.1 (3.7)	8.3 (4.9)	5.5 (3.8)

HC = Healthy controls; nvMCI = MCI patients free from brain vascular damage; svMCI = MCI patients with subcortical vascular features; MMSE = mini mental state examination; GDS = Global Deterioration Scale; HIS = Hachinski Ischemic Scale; CERAD = the Consortium to Establish a Registry for Alzheimer's Disease.

[a] Significant difference between HC and nvMCI. [b] Significant difference between HC and svMCI. [c] Significant difference between nvMCI and svMCI. * TMT B was not included due to the small number of records in this condition as a consequence of the low academic level of the patients and controls.

age, education level and gender (table 1). All participants gave written informed consent for participation in the study, which was approved by the Ethical Committees of both the Virgen de la Arrixaca Hospital and the University of Murcia.

Attention Network Test

The ANT is a computerized test that provides measures for the three attention networks defined by Posner and Petersen [6]: alerting, orienting and executive control. A description of the original test can be found in Fan et al. [10]. In the present study, we used a modified version, the ANT-I, introduced by Callejas et al. [11], which makes possible a better evaluation of the interactions between the networks. The specific implementation of the test has been described in detail by Fuentes et al. [14].

The basic display, which was visible throughout the test, consisted of a black fixation cross between two rows of five rectangular boxes arranged horizontally (fig. 1). Each trial began with presentation of the basic configuration for a variable interval lasting between 1,200 and 2,600 ms. The precise duration was determined at random, with the constraint that the entire range was homogeneously represented within each block of trials. After this interval, an alerting tone (2,000 Hz, 50 ms) was presented (tone condition) or an equivalent empty audio file was run (no-tone condition). Then, after an interval of 350 ms, a visual cue was presented in two-thirds of the trials. The visual cue was located on the central box of either the upper or the lower row and consisted of an increase in the outline of the box from 1 to 4 pixels in width. The cue lasted 50 ms and could appear in the same box as the upcoming target (valid-cue condition) or in the other row (invalid-cue condition). In trials without a visual cue, the basic configuration remained on during the same interval (no-cue condition). Finally, after an interval of 50 ms (stimulus onset asynchrony, SOA 100) or 450 ms (SOA 500), five black arrows were presented inside each of the five boxes of either the upper or the lower row. The arrow presented in the central box was the target, whereas the arrows presented in the other four boxes were the flankers. Flanker arrows could point in the same direction as the target (congruent condition) or in the opposite direction (incongruent condi-

tion). The target and flankers were presented until the participant responded, indicating the direction of the target arrow by pressing the right or left key of a response box. Participants were instructed to respond as quickly and as accurately as possible.

The experiment comprised 288 trials divided into 3 blocks of 96 trials. The 96 trials of a block represented all the combinations of alerting (tone, no tone), validity (valid-cue, invalid-cue, no-cue), cue-target SOA (100 ms, 500 ms), flanker congruency (congruent, incongruent), target locus (upper row, lower row), and target orientation (right, left). Target locus and orientation were not experimental factors and were not considered in statistical analyses. Before the experimental phase, participants ran 10 practice trials, with additional blocks of 10 new trials until there were at least nine correct responses with no reaction times longer than 2.5 s in the last practice block. During the experiment, resting periods were established every 48 trials.

Statistical Analyses

Sociodemographic data, participants' performance on neuropsychological tests, and the Hachinski Ischemic Scale (HIS; which evaluates the possibility of vascular causes for the cognitive impairment [17]) scores were analyzed by simple analysis of variance (ANOVA) with group (HC, nvMCI, svMCI) as the between-subjects factor. When appropriate, post hoc t tests were performed to compare mean scores across groups (table 1).

For statistical analyses of the subjects' ANT performance, reaction times (RTs) above or below 3 SDs from the participant's mean were excluded. In the first analysis, mean RTs were entered into a mixed ANOVA with alerting (tone, no tone), validity (valid-cue, invalid-cue), cue-target SOA (100, 500 ms), and congruency (congruent, incongruent) as the within-subjects factors and group (HC, nvMCI, svMCI) as the between-subjects factor. To better appreciate the possible interactions between alerting and orienting and between orienting and congruency, no-cue trials were not included in this analysis (no-cued trials were irrelevant for those purposes). In the second analysis, a mixed ANOVA was performed for no-cue trials only in order to study the potential interaction between alerting and congruency without the additional alerting effect generated by the visual cue [7, 15]. We further calculated the effects of alerting, validity and congruency in terms of percentage (e.g. congruency effect = [incongruent RTs – congruent RTs] × 100/congruent RTs) and performed three simple ANOVAs on these effects with group as the between-subjects factor. This approach aimed to evaluate the interaction between groups and the three attention networks without the contribution of group differences in overall speed.

Equivalent analyses were performed in terms of percentage of errors. They revealed no additional effects and are not reported.

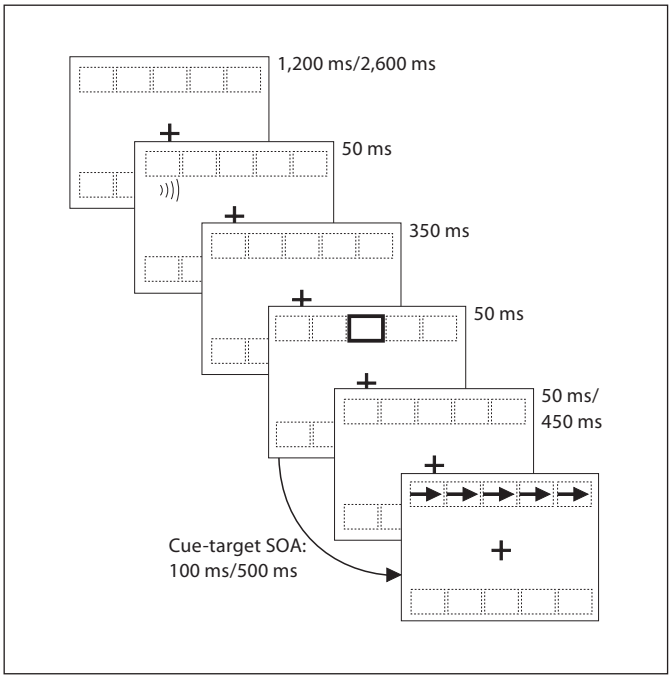

Fig. 1. Outlined representation of the experimental procedure.

Results

Demographic information, neuropsychological assessment, HIS scores, and statistical differences among groups are presented in table 1. Mean RT and accuracy data for each condition are reported in table 2. The first analysis on untransformed ANT data showed significant main effects of group, alerting, validity, and congruency (all $p < 0.01$). Correct responses were faster for HC (732 ms) and nvMCI (848 ms) than for svMCI (1,063 ms), for alerting-tone than for no-tone trials (alerting effect: no-tone trials RTs minus tone trials RTs = 38 ms), for valid-cued than for invalid-cued trials (validity effect: invalid-cued trials RTs minus valid-cued trials RTs = 119 ms), and for congruent than for incongruent trials (953 ms) (congruency effect: incongruent trials RTs minus congruent trials RTs = 144 ms). These three effects illustrate the functioning of the alerting, orienting and executive control networks, respectively. The main effect of SOA was also significant ($p < 0.01$). Responses were faster at the long-SOA condition (SOA effect: short-SOA RTs minus long SOA RTs = 26 ms).

There was an interaction between validity and group ($p < 0.05$). Further analyses showed that there were no significant differences in the validity effect between nvMCI (144 ms) and HC (128 ms) participants ($p = 0.76$). However, the validity effect in svMCI (86 ms) was smaller than in nvMCI and HC participants ($p < 0.05$). Additional analyses showed that contrary to the other two groups, svMCI patients did not show any significant benefit effect of the valid-cue compared with the no-cue condition (1,020 vs. 1,032 ms; $p = 0.58$).

Table 2. Mean RT (ms) and percentage of errors for each experimental condition

Group	SOA	Congruency	Alerting tone			No alerting tone		
			cued	uncued	no cue	cued	uncued	no cue
HC	100	congruent	614 (0.4%)	737 (3.5%)	654 (1.3%)	657 (0.8%)	744 (3.5%)	712 (1.8%)
		incongruent	699 (3.1%)	866 (3.5%)	752 (2.6%)	729 (0.4%)	861 (4.8%)	775 (2.6%)
	500	congruent	612 (0.4%)	738 (3.5%)	662 (1.3%)	680 (0.4%)	754 (0.4%)	716 (2.2%)
		incongruent	677 (0.4%)	838 (0.4%)	743 (2.2%)	684 (1.8%)	829 (4.4%)	779 (3.1%)
nvMCI	100	congruent	716 (3.3%)	804 (3.3%)	812 (1.7%)	759 (0.0%)	850 (0.6%)	825 (2.8%)
		incongruent	827 (5.0%)	1,024 (6.7%)	868 (2.8%)	869 (2.2%)	1,066 (6.1%)	989 (5.0%)
	500	congruent	697 (1.7%)	795 (2.8%)	768 (2.8%)	739 (2.8%)	867 (2.2%)	787 (3.3%)
		incongruent	792 (5.0%)	964 (6.1%)	860 (8.3%)	811 (6.1%)	991 (5.6%)	928 (4.4%)
svMCI	100	congruent	898 (1.3%)	955 (3.9%)	912 (2.2%)	980 (1.3%)	1,012 (2.2%)	1,005 (2.2%)
		incongruent	1,125 (5.6%)	1,161 (7.0%)	1,025 (9.6%)	1,242 (7.3%)	1,267 (10.5%)	1,207 (11.0%)
	500	congruent	833 (2.6%)	1,046 (4.4%)	872 (1.3%)	926 (1.3%)	1,015 (4.4%)	925 (3.1%)
		incongruent	1,108 (8.3%)	1,179 (8.8%)	1,091 (10.1%)	1,050 (7.5%)	1,212 (11.8%)	1,219 (8.8%)

The interaction between group and congruency was also significant ($p < 0.05$). This interaction was due to a higher congruency effect in svMCI (184 ms) than in HC (74 ms) participants ($p < 0.05$). There was also a validity × congruency interaction ($p < 0.05$), which was qualified by the three-way interaction involving group, validity and congruency ($p < 0.05$). Further analyses showed a significant validity × congruency interaction for HC and nvMCI ($p < 0.001$) but not for svMCI ($p = 0.598$). The interaction in the HC and nvMCI groups was due to a smaller congruency effect in the valid-cued condition than in the invalid-cued condition. Although there were no interactions involving alerting, an independent ANOVA for the HC group revealed a significant interaction between alerting and validity ($p < 0.05$), showing a higher validity effect in the alerting tone condition.

The second ANOVA, performed on no-cue trials only, showed an alerting × congruency interaction ($p < 0.05$); however, it was qualified by the three-way group × alerting × congruency interaction ($p < 0.05$). Further analyses showed a significant alerting × congruency interaction in both the HC and the nvMCI group ($p < 0.05$) and a marginally significant interaction in the svMCI group ($p = 0.083$). The alerting × congruency interaction in the HC group indicated a higher congruency effect with an alerting tone than without a tone. Both nvMCI and svMCI patients, however, showed a reduction of congruency effect with the alerting tone.

Finally, three simple ANOVAs were performed to determine the effects of alerting, validity and congruency (in terms of percentage) with group as the between-subjects factor. Group was found to modulate the validity effect ($p < 0.001$), with the svMCI group showing a smaller validity effect than both the nvMCI and the HC groups ($p < 0.01$). The results, therefore, were in agreement with the previous analyses carried out using untransformed RTs (see above). On the other hand, there was no effect of group on alerting or congruency ($p = 0.110$ and 0.196, respectively). The fact that there was no effect of group on the congruency effect when general speed was controlled suggests that the effect found with untransformed RTs was a consequence of long RTs in MCI patients. For that reason, we will not comment on this interaction any further.

Although the three groups were matched as much as possible for demographics, there was, unfortunately, a larger percentage of female participants in the svMCI group than in the other two groups. In order to rule out the possibility that the interaction between validity and group was a consequence of this imbalance, we conducted a new mixed ANOVA with cueing (valid-cue, invalid-cue) as the within-subjects factors and group (HC, nvMCI, svMCI) and gender (male, female) as the between-subjects factors. This new ANOVA revealed no main effects or interactions involving the gender factor. A further ANOVA on the validity effect in terms of percentage of change scores with group and gender as between-subjects factors also showed no effects involving gender.

Discussion

In this research, we assessed the functioning of the attention network in three different groups of participants, HC, nvMCI and svMCI, taking as theoretical framework the cognitive neuroscience model of attention by Posner and Petersen [6]. In this study, we replicated previous findings regarding the functioning of attention networks and their interactions in people without cognitive impairment [11–15]. Our results showed that, in HC participants, the orienting network improved the subjects' focusing of attention on the target location, fostering conflict resolution by incongruent distracters, a role attributed to the executive network. Unlike orienting, the phasic alerting state that was achieved by the alerting tone made the executive network in HC subjects less effective by increasing the flanker effect. Finally, the alerting tone increased the effectiveness of the orienting network in HC participants. Thus, the results obtained with the HC group using the ANT version employed here constitute an appropriate baseline for testing MCI-related alterations in attention networks.

Some relevant attention deficits were found in our patients. Contrary to the results obtained with the HC group, the phasic alerting state did not increase the flanker effect in nvMCI patients; in the latter group, the flanker effect was reduced by the alerting tone. Although in svMCI the interaction was only marginally significant, the pattern of results was similar to that obtained with the nvMCI group. These results suggest that MCI patients might not manifest a particular tonic alerting state that is needed for appropriate cognitive performance. However, the alerting tone helped the patients regulate the level of alertness needed for conflict resolution. MCI patients might then benefit from alerting training programs, as suggested for other neurological patients [14].

A main finding of this study is that the svMCI patients showed a smaller validity effect than did the nvMCI patients and the HC subjects. The reduced validity effect observed in svMCI patients was mainly due to a failure of the cue to summon attention to the cued location. These results suggest a severe orienting network dysfunction in svMCI that could be related to the vascular damage present in these patients. Further evidence for a relationship between vascular effects and the orienting network emerged from a correlation analysis between HIS scores and validity effects (controlled for general slowing) in which the size of the validity effect was inversely related to HIS scores ($r = -0.408$; $p < 0.01$).

How might subcortical vascular damage affect the function of the orienting network in svMCI patients? It is likely that the subcortical vascular damage in these patients impaired the cholinergic system and thereby affected covert orienting responses of attention, which are modulated by acetylcholine (Ach) [8]. The vascular determinants of cholinergic deficits in vascular dementia (VaD) patients have been widely investigated and discussed in the literature [18, 19]. Animal models attempting to reproduce VaD consistently reveal decreases in cholinergic markers [18, 19]. Postmortem studies in animals have also shown significant reductions in choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) activity following chronic (rather than acute) vascular damage [20, 21]. In humans, Wallin et al. [22] found reduced AChE activity in the cerebrospinal fluid of patients suffering SVaD, but no such reduction in patients with AD or frontotemporal dementia. Moreover, several clinical trials involving pharmacological treatment of VaD or SVaD have demonstrated that cholinesterase inhibitors improve cognition in VaD [18, 19, 23]. Immunohistochemical tracing of cholinergic pathways from the nucleus basalis of Meynert (nbM) has shown that, although cholinergic projections from this structure extend to all cortical areas and are considered as diffuse, projections from the nbM areas are organized into discrete bundles that are susceptible to damage by focal strategic subcortical ischemic lesions and diffuse white matter disease [24–26]. On the other hand, the lack of observed effects of disease on the functioning of the orienting network in the nvMCI group could be related to the well-established cholinergic plasticity response, which may represent a compensatory mechanism that occurs concomitantly with progression of AD pathological changes [27–31].

Basal forebrain cholinergic system lesions in monkeys [32] and rodents [33] are related to selective deficits in shifting visuospatial attention but not to tasks involving learning or memory. Neurophysiological studies have also shown an association between acetylcholine and attentional task performance [34]. Collectively, those data suggest that acetylcholine may be mainly involved in attention, with secondary impact on learning and memory functions [35].

The lack of interaction between alerting and orienting networks that was observed in both MCI groups and differed from the results obtained with the HC group might have a number of causes. Given the aforementioned cholinergic deficit in svMCI patients, the phasic alerting state produced by the alerting tone may have no effect on the

orienting network of these patients. The basal forebrain cholinergic neurons that project to the cortex are a target of the ascending noradrenergic system, which modulates the alerting network [8], and the integrity of this connection appears essential for the signal-driven modulation of stimulus processing [36]. The absence of any alerting effect on the orienting network in nvMCI patients could be due to the possible noradrenergic deficit caused by the locus coeruleus neurofibrillary degeneration found in MCI with neuropathology type AD [37]. The nonaffectation of the main effect of alerting in the nvMCI group may possibly be related to a top-down modulation of the noradrenergic alerting system arising from the frontal cortex [38].

Overall, the data presented here show that the ANT provides a useful tool for obtaining effective clinical and research trials in MCI patients. We have shown that a reduced orienting effect in the ANT may be a relevant cognitive marker of cholinergic deficit and a feature of svMCI and, more importantly, that it may help identify patients affected by SVaD. The results presented here provide information that is useful in the identification and understanding of preliminary stages of dementia. These results also suggest possible advances in therapeutic approaches to this disease that involve neuropsychological rehabilitation [14, 39], pharmacological agents [23] or a possible combination of both methods.

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