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RESEARCH ARTICLE

Assessment of the Autonomic Response in Alzheimer's Patients During the Execution of Memory Tasks: A Functional Thermal Imaging Study

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Abstract: ***Background:*** Alzheimer's disease (AD) is a form of dementia characterized by failure of memory that becomes more severe with the progression of the disease. The Free and Cued Selective Reminding Test (FCSRT) is a clinical test used to evaluate such a deficit. However, since the cognitive performances could depend also on the psychophysiological state of the individual, it is important to monitor that state through the peripheral autonomic activity during the execution of the test. Thermal infrared imaging has been used for this kind of assessment in order to preserve the free and unbiased interaction between doctor and patient, thanks to the contactless features of the technique.

Objective: To investigate whether the variation of facial temperature parameters during the FCSRT is indicative of different autonomic states in the early AD with respect to healthy controls (HC).

Results: At a group level, a greater sympathetic activity for the HC with respect to AD during the execution of the test was found, indicative of a suppression of anxiety associated with the performances of the FCSRT in AD patients.

Conclusion: These results indicate that AD and HC may present different autonomic activity associated with the execution of a cognitive task, thus suggesting a different modulation of high-cognition and emotion network.

Keywords: Alzheimer's disease, FCSRT, thermal imaging, memory deficit, visuospatial deficit, autonomic response.

1. INTRODUCTION

Alzheimer's disease (AD) is a form of dementia characterized by failure of memory that becomes more acute with the progression of the disease [1]. In fact, according to the International Working Group on Alzheimer's [2], the core diagnostic criterion is the progressive memory deficit. In order to assess this kind of impairment, many tests and batteries have been proposed.

These tests could be a cause of anxiety and stress for the participants, both for AD and healthy controls (HC) as anxiety and stress may be associated with the execution of learning and cognitive tasks [3]. Furthermore, it is known that the emotional state could affect efficient functioning of the attentional system and the performance of tasks, especially under test conditions [3-6].

The aim of this study is to investigate whether the execution of cognitive/mnemonic tasks elicits a different arousal involvement in AD patients with respect to HC, as revealed by autonomic modulation, and if this may impact the performances in the execution of the tests. In fact, currently, the clinical diagnosis of AD is carried out by interviews and administration of tests. It is therefore relevant to investigate the effect of the autonomic system on the performance.

One of the most effective tests for discriminating AD patients from HC is the Free and Cued Selective Reminding Test (FCSRT) [7, 8]. This test shows a high sensibility and specificity in distinguishing AD patients from HC [9, 10], from other forms of dementia [11] and from Mild Cognitive Impairment (MCI) patients non-converters [12].

It starts with a phase of encoding, during which the patient is required to remember 12 pictures of everyday life shown four at a time. After that, the Immediate Free Recall (IFR) follows, during which the patient is requested to recall all these figures. If he/she cannot remember independently all the figures, the Immediate Cued Recall (ICR) follows. During this phase, the doctor reminds the semantic fields of the not retrieved pictures. This procedure is repeated for three times. After a period of 30 minutes, the test provides the Delayed Free Recall (DFR) during which the patient has to remind all the pictures shown previously. If he/she forgets some of them, the Delayed Cued Recall (DCR) follows, during which all the semantic fields of the missing pictures are reminded by the doctor.

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In order to fill the time between the Immediate Recall and the Delayed one, some filler tests are used. Usually, these tests are chosen according to their ability to discriminate some particular impairment typical of the investigated dementia. In particular, the visuo-constructive and visuo-spatial impairments are typical of the AD, and, in order to discriminate these deficits, in the present study the Clock Drawing Test (CDT) [13] was used. During this test, the patient is requested to draw a circle, then to insert the numbers like it was a clock and, finally, to set the clock hands at ten past ten.

Then, Digit Span Test (DST) was administrated to evaluate short-term memory and verbal working memory impairments [14]. For this test, the participant is asked to repeat sequences of digits verbally presented with a pace of 1 second. The test started with a series of two digits and every time the series is repeated correctly, a new series with one digit more is presented. If the participant cannot remember a sequence, another one of the same length is proposed. If the participant is not able to repeat two sequences of the same length, the test ends.

To evaluate the visuospatial memory deficit the Corsi Tapping Test (CTT) [15] was proposed. During this test, the experimenter has to tap some cubes starting with a sequence of two cubes and, if the participant can repeat correctly the sequence, the number of cubes is progressively increased with a step of one. If the participant cannot repeat two sequences of the same length the test ends. The cubes are touched with the index finger at a rate of 1 cube per second.

For the evaluation of visuo-spatial impairments, the Benton Visual Retention Test (BVRT) [16] was added. It is composed of three Forms (C, D, and E) and can be administered in four different ways (Administrations A, B, C, and D) [17]. In this study, the administration C (Form D) was used, during which the examinee has to reproduce a design in the presence of stimuli, without limits of exposure time.

Finally, the Trial Making Test, versions A e B (TMT A-B) [18] was proposed. TMT-A requires the participant to draw lines connecting sequentially 25 encircled numbers on a sheet of paper. For TMT-B the subject has to alternate between numbers and letters (*e.g.,* 1, A, 2, B, 3, C, *etc.*) [18].

In order to replicate the ecological conditions under which the tests are administered in the clinical routine (without any associated recording of vital signs and autonomic activity, i.e. by not using any contact sensing probe), functional thermal infrared imaging (fIRI) was used to assess indices of peripheral autonomic activity while performing the test.

fIRI (or thermography) is one of the most suitable techniques to be considered for this purpose: it is a non-invasive technique used to measure the peripheral autonomic activity through the modulation of the cutaneous temperature, which is a known expression of the psychophysiological state of the subject [19]. In fact, stress, anxiety or fatigue can produce changes in skin temperature [20]. fIRI has been widely used to study the effect of workload [21] and learning process [3] on the facial skin temperature. In addition, fIRI is an important tool for the detection of the emotional state through the noninvasive and touchless assessment of the autonomic activity [22, 23].

According to the literature, this is the first time that autonomic activity is monitored through fIRI during the administration of cognitive/mnemonic tasks in AD. Since all the above-mentioned tests request abilities compromised in AD, a different autonomic response for patients with respect to HC is expected.

2. MATERIALS AND METHODS

2.1. Participants

Fourteen healthy people (mean age ± SD: 68.4±6.3 years; M/F: 11/3) and sixteen patients (mean age ± SD: 75.5±5.4 years; M/F: 8/8) with a diagnosis of Mild probable Alzheimer's disease, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) participated in the study. The exclusion criteria were moderate-severe cognitive impairment (MMSE <25/30) [24], vascular dementia, behavioral or psychiatric disorders, hydrocephalus, brain lesions, history of stroke or traumatic brain injury and circulatory diseases that could impact the thermal measurement. The Research Ethics Board of the University of Chieti-Pescara approved this study, conducted according to the Declaration of Helsinki. Before the experiment, every participant signed the informed consent and they could withdraw from it at any time. All sessions were scheduled at the same time of the day to mitigate possible effects due to circadian rhythm variations [25].

2.2. Experimental Design

The FCSRT was proposed by Buschke [26] and it was validated for the AD diagnosis by Grober [11]. It consists of an encoding and a recall phase. The immediate and delayed recall were separated by some filler test (CDT, DST, CTT, TMT A-B, BVRT). If the participant took less than 30 minutes for the execution of the filler tests, TMT A-B was provided. Hence, since it was not administered to all subjects, it was excluded from the analyses.

During the administration of this battery, the patient and the examiner were seated in front of each other and they had to interact. In order to separate the different tests and to have a baseline to compare the signal measured during the tasks, 1 minute of rest was provided to separate one test and the next one. The experimental design is shown in Fig. (**1**).

For the thermal measurements, the guidelines suggested in Merla and Romani (2006) [27] Ring and Ammer (2012) [28], and Diakides, Bronzino and Peterson (2012) [29] were followed.

2.3. Functional Thermal Imaging Measurement

For each subject, the facial temperature was recorded during the administration of the tests, by means of a digital thermal infrared camera FLIR SC660 (640 x 480 bolometer FPA, sensitivity/Noise Equivalent Temperature Difference: < 30 mK @ 30°C, FOV: 24° x 18°). The camera was placed at 60 cm from the participant and pointed toward the face of the subject (Fig. **2**). The sample frequency was 1 Hz. To remove the effects related to the potential drift/shift of the sensor's response and optical artifacts, the camera was black-body-calibrated.

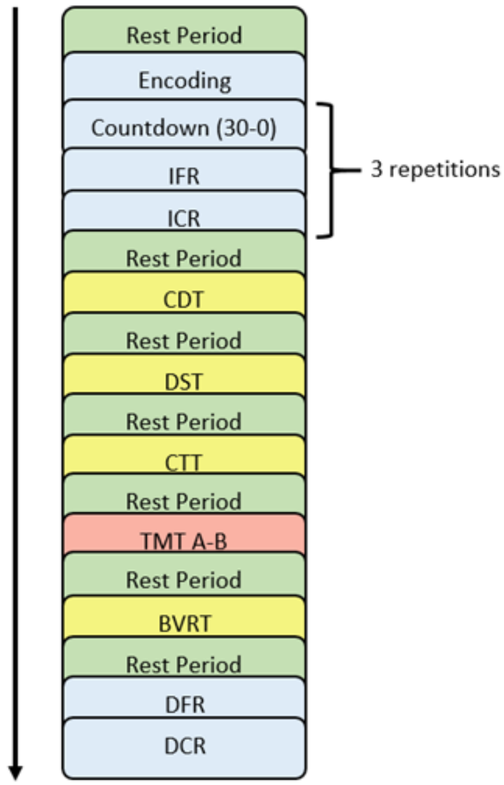

Fig. (1). Experimental paradigm: FCSRT (blue blocks), filler tests (yellow blocks) and rest periods (green blocks) added to separate the different phases.

Fig. (2). Thermogram of a representative participant.

2.4. Thermal Data Processing and Statistical Analysis

Since the participant could freely move during the experiment, the quality of all the recorded thermal videos was preventively checked by visual inspection. No video was rejected.

Seven regions of interest (ROI), reported as indicative for the evaluation of autonomic activity [19], were selected: corrugator, up nose, nose tip, right and left perioral, right and left chin (Fig. **3**).

Fig. (3). ROIs position of a representative participant: corrugator (ROI 1), upper nose (ROI 2), nose tip (ROI 3), right and left perioral (ROIs 4 and 5 respectively), right and left chin (ROIs 6 and 7 respectively)

The time courses of the average temperature were extracted from each ROI. Since the participants could move the head without restriction, a soft-tissue tracking algorithm was used to track each ROIs across all the images of the video, in order to properly consider the temperature from each thermogram. The tracking software has been developed under Matlab environment and validated in Manini et al (2013) [30]. It is based on the 2D cross-correlation between a template region, chosen by the user on the first frame, and a similar ROI in a wider searching region, expected to contain the desired template in each of the following frames.

The thermal signal was further corrected from residual motion artifacts. Motion errors were visually detected and corrected by substituting them with the mean value of the 6 samples before and after the artifact.

For each time series of each ROI, the mean value of the temperature during every experimental condition was evaluated. Then, the difference between the mean value of temperature during each test ($\bar{T}_{task}$) and the mean value of the temperature during the previous baseline ($\bar{T}_{rest}$) was computed (Equation 1). Moreover, the slope of the thermal signal was computed as the ratio between the maximum variation of the signal during the experimental phase and the time taken to get this variation (Equation 2).

$$\Delta T_{avg} = \bar{T}_{task} - \bar{T}_{rest} \tag{1}$$

$$Slope = (T_{\max\_task} - T_{\min\_task})\,/t_{max-min} \tag{2}$$

Furthermore, in order to investigate the different contribution of the sympathetic and parasympathetic system to the thermal fluctuations, the power of the thermal signal in the low frequencies (LF) band (0.03-0.15 Hz) and in the high frequencies (HF) band (0.15-0.35 Hz) has been evaluated. In fact, while the LF band has been assessed to be indicative for the sympathetic system, the HF band is suggestive for both the sympathetic and parasympathetic system, thus the ratio LF/HF is considered an indicator of the balance of the activation of the two systems [31].

Since the minimum duration of each test was greater than the inverse of the lower frequency of the LF band, the LF/HF ratio was evaluated for each task.

For each experimental phase, a Shapiro Wilk Test was performed to assess dataset normality for both time and frequency domain analysis. Since data resulted not normally distributed, Wilcoxon-Mann-Withney test was used to evaluate group differences between AD and HC.

Finally, in order to better investigate the capability to discriminate the two groups by means of the autonomic response during these tests, a Linear Discriminant Analysis was carried out [32].

3. RESULTS

3.1. Behavioural Results

The scores of all the FCSRT and the filler tests discriminate the two groups, except for the DST and CTT. Group differences tested through an independent t-test between HC and AD. are summarized in Table **1**.

Table 1. Behavioural results: t-stat and p-value for the scores of each test between HC and AD.

t test HC vs AD	t stat	p value
IFR	6,9527	$1{,}47*10^{-7}$
ICR	7,4339	$0{,}43*10^{-7}$
CDT	3,2879	0,0027
DST	0,8151	0,4219
CTT	1,2384	0,2258
BVRT	4,9438	$3{,}87*10^{-5}$
DFR	5,4102	$9{,}05*10^{-6}$
DCR	5,8000	$3{,}14*10^{-6}$

3.2. Time Domain Results

Time series of the thermal signals from the considered ROIs are shown in (Fig. **4**) for a representative subject.

The statistically significant differences, during the different experimental phases, for the two groups between the mean values during the test with respect to the previous rest period, are reported in Table **2**.

Table **3** resumes the group differences between the slopes of the temperature during the different experimental phases.

3.3 Frequency Domain

The statistically significant differences between the LF/HF ratio for the two groups during the different experimental phases are summarized in Table **4**.

3.4. Classification

Since the ROI on the Nose Tip resulted to be significant for the CTT for all the three parameters investigated, a discriminant analysis using these variables has been carried out. The results are presented in Table **5**. The original cases are classified properly for the 76,7 %. With the cross validation, the percentage of the cases correctly classified is 73,3%.

4. DISCUSSION

The aim of this study was to assess whether differences in the autonomic system activity during the performance of cognitive/mnemonic tests exist between AD and HC. Since, these tests are created to evaluate some specific impairments, their administration could elicit a state of stress or anxiety that could have, in turn, an effect on the performance. In order to avoid the effect of contact-sensor instrumentation on the performance, it would be advisable to control the psychophysiological state of the participants in a non-invasive way; to this purpose, thermal infrared imaging appears to be one of the most suitable tools. In particular, in this study, the variation of the facial temperature and the LF/HF ratio of the thermal time series have been evaluated, to quantitatively assess the metrics of the autonomic activity of the participants. The main findings are that the temperature variations were lower in the HC group than the AD patients for Nose Tip, Upper Nose, Corrugator, Left and Right Perioral and

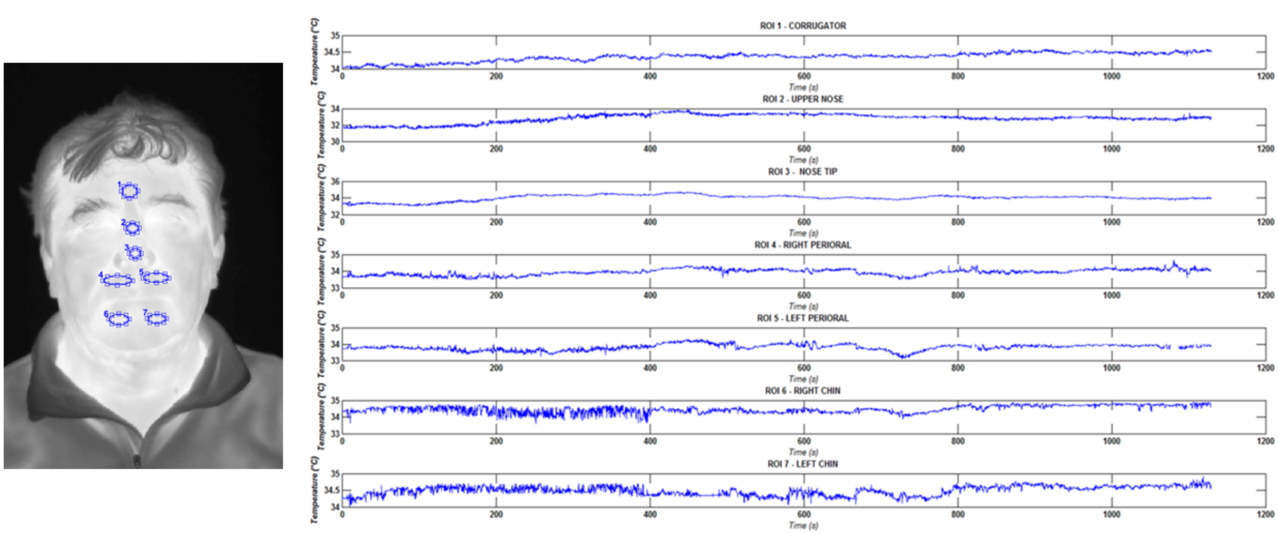

Fig. (4). Thermal signals from the selected ROIs across all the experimental session for a representative subject.

Table 2. Mean values: group differences between HC and AD patients for each ROI during the different experimental phases.

ROI	Experimental Phase	Average temperature - Mean values and standard deviation (HC; AD) °C	z-stat (HC vs AD)	p-value
Corrugator	CTT	(-0.02±0.05; 0.03±0.08)	-1.975	0.048
Upper Nose	CTT	(-0.24±0.19; -0.04±0.13)	-2.902	0.004
Nose Tip	CTT	(-0.19±0.17; 0.03±0.22)	-2.512	0.012
	DST	(-0.05±0.09; 0.06±0.12)	-2.598	0.009
Right Perioral	CTT	(-0.06±0.27; 0.02±0.12)	-2.111	0.035
Left Perioral	CTT	(-0.10±0.26; 0.08±0.12)	-2.307	0.031
Left Chin	CTT	(-0.11±0.30; 0.06±0.08)	-2.217	0.027

Table 3 Slopes. Group differences between HC and AD patients for each ROI during the different experimental phases.

ROI	Experimental Phase	Slope - Mean values and standard deviation (HC; AD) °C	z-stat (HC vs AD)	p-value
Nose Tip	CTT	($2.41{\cdot}10^{-5}\pm 1.02{\cdot}10^{-4}$; $-1.68{\cdot}10^{-4}\pm 3.38{\cdot}10^{-4}$)	2.681	0.007
Upper Nose	DST	(-0.01±0.01; 0.01±0.07)	-2.640	0.008
Right Perioral	DST	(-0.05±0.09; 0.01±0.04)	-2.103	0.036
Left Perioral	DST	(-0.15±0.32; $-1.74{\cdot}10^{-4}$±0.07)	-2.260	0.024

Table 4 LF/HF ratio. Group differences between HC and AD patients for each ROI during the different experimental phases assessed using Wilcoxon-Mann-Whitney test.

ROI	Experimental Phase	LF/HF - Mean values and standard deviation (HC; AD)	z-stat (HC vs AD)	p-value
Corrugator	CTT	19.33±7.80 14.22±6.15	2.029	0.043
Upper Nose	Encoding	14.93±5.96 12.38±1.37	2.684	0.007
	CTT	20.76±9.46 13.82±6.14	2.073	0.038
Nose Tip	CTT	20.78±9.48 14.23±6.15	2.117	0.027
Right Perioral	Encoding	15.90±4.61 12.52±1.14	3.128	0.002
Left Perioral	Encoding	16.66±4.65 12.71±1.17	3.293	$9.92{*}10^{-4}$
Right Chin	CTT	21.29 ±9.97 14.19±6.15	2.203	0.028
	Encoding	14.72±5.90 12.48±1.12	2.802	0.005
Left Chin	Encoding	16.77±4.59 12.68±1.06	3.695	$2.20{*}10^{-4}$

Table 5. Linear Discriminant Analysis for fIRI parameters on the Nose Tip during CTT.

		ID	0	1	Tot
Original	Counts	0	11	0	11
		1	2	9	11
	%	0	71,4	28,6	100,0
		1	18,8	81,3	100,0
Cross Validation	Counts	0	10	1	11
		1	2	9	11
	%	0	71,4	28,6	100,0
		1	25,0	75,0	100,0

Left Chin (Table **2**), while the LF/HF ratio was higher for the HC than the AD for all the considered ROIs, as shown in Table **4**. More precisely, the HC group showed a lower variation of temperature for the CTT and DST. A lower skin temperature variation could be caused by a superficial vasoconstriction that is due to a major activation of the sympathetic system [33], which therefore resulted larger in HC than AD patients. This was confirmed by the LF/HF results; in fact, the HC group showed a higher ratio with respect to AD. This ratio is indicative of the balance between the sympathetic and parasympathetic system, hence the HC group showed a higher sympathetic activation.

Many authors have already investigated autonomic disorders in AD patients [34]. Differences in the heart rate between AD patients and controls were assessed by evaluating the LF/HF ratio and resulting in a hypersympathetic activity for the AD group during 5 minutes of rest in different positions (upright and supine posture) [35]. Conversely, Mellingsæter et al (2015) found a lower LF/HF ratio for the heart rate variability in AD patients with respect to healthy controls during a head-up tilt test [36]. In addition, vasomotor sympathetic functions were investigated, monitoring the reduction of finger pulse amplitude during Valsava manoeuvre, revealing an autonomic dysfunction concerning parasympathetic, as well as vasomotor sympathetic, functions in AD [37]. Since the vasomotor regulation influences the skin temperature, it is valid to suppose an influence of the disease on the thermal signal. In fact, it is known from the literature that AD patients exhibit impaired variations in the circadian temperature [38] and in the thermoregulation [39]. However, the cited studies were carried out during a resting condition and they did not involve any cognitive or mnemonic task, thus the results are clearly related to a functional dysregulation due to the disease. In the present study, whereas, the subjects were requested to perform a battery of cognitive tests, thus the results were dependent mainly on the performance and the possible expectation associated with them. In addition, as no differences were found between the two groups during the resting period, it is possible to suppose that the observed different activation of the autonomic system was mostly related to the test execution rather than to a dysregulation caused by the disease. However, it is worth noticing that the absence of differences between HC and AD during the rest period could have been due to the short length of this phase (1 minute). This is an aspect that needs further studies for being clarified.

The greater sympathetic activity assessed for the HC during both DST and CTT could have been due to a stress condition. In fact, it is known that verbal learning depends on experimental stress [40]. Although differences in the thermal signal were found, the scores of these tests did not show significant differences between the two groups (Table **1**). The CTT and DST are indeed selective for the short term memory deficit, but not very discriminant for AD dementia [41]. The reported results suggested that the performances of the DST and CTT might depend on the psychophysiological state of the participant. However, further studies are necessary to better investigate the relationship between stress and performance and to clarify if this difference in autonomic activation between AD and HC could be indicative of early AD diagnosis.

LF/HF ratio showed significant differences between the two groups also during the encoding phase. During this experimental phase, the participant was asked to memorize the pictures shown by the experimenter. HC participants exhibited higher LF/HF ratio with respect to AD patients, hence a greater activation of the sympathetic system. Deficits in encoding and semantic memory in AD have been investigated so far and it seems that they are related to a lack of attention and decrease of cognitive effort [42]. In addition, it is known that the sympathetic activity during the encoding phase can influence the retrieval [43], thus monitoring the autonomic system during this process could be of great interest, because it influences the recall, from which the AD diagnosis is carried out in the FCSRT.

Concerning the slope of the signal, statistical differences were found for the Nose Tip, Upper Nose, Right and Left Perioral during the CTT and DST. In particular, the HC group exhibited a larger slope for the CTT and a lower slope for the DST with respect to the AD patients (Table **3**). The slope is an indicator of the speed of the changes in the thermal signal. Thus, during the DST the variation of the thermal signal was larger but slower in the HC group than the AD. This test becomes progressively more difficult, starting with a sequence of two digits and adding one more digit every time the participant could properly repeat the sequence. Thus, this result seemed to suggest that healthy people had a sympathetic response delayed towards the end of the test, while the AD exhibited an early response. It was probably caused by a short memory deficit of the AD patients [1]. This effect was not present during the CTT. A possible explanation is that it came soon after the DST and their structure is quite similar. Hence, it is valid to suppose that there was a habituation effect that shifted the response towards the start of the test.

During the other experimental phases, no significant differences were found. This finding suggested the absence of clear differences in autonomic activity between the two groups during these phases.

Furthermore, the possibility to discriminate the two groups by means of the autonomic response during the CTT, considering the Nose Tip, was investigated by means of linear discriminant analysis. An accuracy of 73.3% was obtained. This result, although preliminary, seemed to suggest that autonomic response in AD patients during the execution of cognitive/mnemonic tests could be highly indicative of the disease. However, the limited number of participants did not allow to carry out an accurate and generalizable classification. In fact, the purpose of future studies is to increase the number of participants to improve the discrimination of AD patients from HC. In addition, it could be of great interest to combine thermal infrared imaging with physiological measurements, such as heart rate and galvanic skin response to ground-truth the results here presented, through the integration of different physiological information. In particular, it could be worth focusing on the encoding phase to search a possible precursor of the AD that could be useful to improve the current diagnosis of the pathology.

Moreover, it might be interesting to investigate the DST and CTT randomizing the order of administration to clarify if the effect showed in this study is related to the test itself or to the sequence of administration.

Finally, it could be worth increasing the length of the rest period, in order to assess if the thermal signal could give important information about the autonomic disorders in AD patients, thus providing a useful tool for the AD diagnosis.

CONCLUSION

Referring to the actual state of the art, this study represents the first time that the autonomic activity is recorded by means of thermal response in AD patients during the administration of cognitive/mnemonic tests, in completely ecological conditions.

The results seemed to show a greater activation of the sympathetic system in HC with respect to the AD patients during the CTT, DST and Encoding phase. The findings suggested that the administration of clinical tests could elicit different autonomic responses in AD patients with respect to HC, but further studies are necessary to better investigate the influence of the psychophysiological state to the performance, hence to the AD diagnosis.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Research Ethics Board of the University of Chieti-Pescara.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All humans research procedures followed were in accordance with the standards set forth in the Declaration of Helsinki principles of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONSENT FOR PUBLICATION

All participants gave their informed consent to take part in the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, *et al.* Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 6(8): 734-46 (2007).

[2] Cummings JL, Dubois B, Molinuevo JL, Scheltens P. International Work Group criteria for the diagnosis of Alzheimer disease. Med Clin 97(3): 363-68 (2013).

[3] Eysenck MW, Derakshan N, Santos R, Calvo MG. Anxiety and cognitive performance: attentional control theory. Emotion 7(2): 336 (2007).

[4] Eysenck MW, Calvo MG. Anxiety and performance: the processing efficiency theory. Cogn. Emotion6(6): 409-34 (1992).

[5] Sanders AF. Towards a model of stress and human performance. Acta Psychologica 53(1): 61-97 (1983).

[6] Ashkanasy NM. Emotion and performance. Hum Performan 17(2): 1317-44 (2004).

[7] Lemos R, Simões MR, Santiago B, Santana I. The free and cued selective reminding test: Validation for mild cognitive impairment and Alzheimer's disease. J Neuropsychol 9(2): 242-57 (2015).

[8] Buschke H. Cued recall in amnesia. J Clin Exp Neuropsychol 6(4): 433-40 (1984).

[9] Grober E, Sanders AE, Hall C, Lipton RB. Free and cued selective reminding identifies very mild dementia in primary care. Alzheimer Dis Assoc Disord 24(3): 284 (2010).

[10] Perpetuini D, Bucco R, Zito M, Merla A. Study of memory deficit in Alzheimer's disease by means of complexity analysis of fNIRS signal. Neurophotonics 5(1): 011010 (2017).

[11] Grober E, Hall C, Sanders AE, Lipton RB. Free and cued selective reminding distinguishes Alzheimer's disease from vascular dementia. J Am Geriatr Soc 56(5): 944-46 (2008).

[12] Grober E, Buschke H. Genuine memory deficits in dementia. Develo Neuropsychol 3(1): 13-36 (1987).

[13] Ricci M, Pigliautile M, D'Ambrosio V, Ercolani S, Bianchini C, Ruggiero C, *et al.* The clock drawing test as a screening tool in mild cognitive impairment and very mild dementia: a new brief method of scoring and normative data in the elderly. Neurol Sci 37(6): 867-73 (2016).

[14] Gerton BK, Brown TT, Meyer-Lindenberg A, Kohn P, Holt JL, Olsen RK, *et al.* Shared and distinct neurophysiological compo-

nents of the digits forward and backward tasks as revealed by functional neuroimaging. Neuropsychologia 42(13): 1781-87 (2004).

[15] Binetti, Giuliano, *et al.* Executive dysfunction in early Alzheimer's disease. J Neurol Neurosur Psychiat 60(1): 91-3 (1996).

[16] Sivan, Abigail Benton. Benton visual retention test. San Antonio, TX: Psychological Corporation, 1992.

[17] Benton, Arthur Lester. Contributions to neuropsychological assessment: A clinical manual. Oxford University Press, USA, 1994.

[18] Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. Arch Clin Neuropsychol 19(2): 203-14 (2004).

[19] Cardone D, Merla A. New frontiers for applications of thermal infrared imaging devices: computational psychopshysiology in the neurosciences. Sensors 17(5): 1042 (2017).

[20] Genno H , Ishikawa K , Kanbara O, Kikumoto M, Fujiwara Y, Suzuki R, *et al*. Using facial skin temperature to objectively evaluate sensations. Intern J Indus Erg 19(2): 161-71 (1997).

[21] Veltman JA, Vos WK. Facial temperature as a measure of operator state. (2005).

[22] Salazar-López E, Domínguez E, Juárez Ramos V, de la Fuente J, Meins A, Iborra O, *et al*. The mental and subjective skin: Emotion, empathy, feelings and thermography. Consciousness Cogn 34: 149-62 (2015).

[23] Clay-Warner J, Robinson DT. Infrared thermography as a measure of emotion response. Emo Rev 7(2): 157-162 (2015).

[24] Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res 12: 189-98 (1975).

[25] Marins JCB, Formenti D, Costa CMA, Fernandes AA , Sillero-Quintana M. Circadian and gender differences in skin temperature in militaries by thermography. Infrared Phy Technol 71: 322-28 (2015).

[26] Buschke H. Cued recall in amnesia. J Clin Exp Neuropsychol 6(4): 433-40 (1984).

[27] Merla A, Romani GL. Biomedical applications of functional infrared imaging. Engineering in Medicine and Biology Society, 2005. IEEE-EMBS 2005. 27th Annual International Conference of the. IEEE, 2006.

[28] Diakides M, Bronzino JD, Peterson DR, eds. Medical infrared imaging: principles and practices. CRC press, 2012.

[29] Ring EFJ, Ammer K. Infrared thermal imaging in medicine. Physiol Meas 33: 3 R33 (2012).

[30] Manini B, Cardone D, Ebisch SJH, Bafunno D, Aureli T, Merla A. Mom feels what her child feels: thermal signatures of vicarious autonomic response while watching children in a stressful situation. Front Hum Neurosci 7: 299 (2013).

[31] Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. Brit Heart J 71(1): 1 (1994).

[32] Hair, Joseph F., *et al*. Multivariate data analysis. Vol. 5. No. 3. Upper Saddle River, NJ: Prentice hall, 1998.

[33] Jänig, Wilfrid, and Elspeth M. McLachlan. "Neurobiology of the autonomic nervous system." Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System Oxford (2013): 21-34.

[34] Femminella GD, Rengo G, Komici K, Iacotucci P, Petraglia L, Pagano G, *et al.* Autonomic dysfunction in Alzheimer's disease: tools for assessment and review of the literature. J Alzheimer's Dis 42(2): 369-77 (2014).

[35] Aharon-Peretz J, Harel T, Revach M, Ben-Haim SA. Increased sympathetic and decreased parasympathetic cardiac innervation in patients with Alzheimer's disease. Arch Neurol 49(9): 919-22 (1992).

[36] Mellingsæter MR, Wyller TB, Ranhoff AH, Bogdanovic N, Wyller VB. Reduced sympathetic response to head-up tilt in subjects with mild cognitive impairment or mild Alzheimer's dementia. Demen Geriatr Cogn Disord Extra 5(1): 107-15 (2015).

[37] Algotsson A, Viitanen M, Winblad B, Solders G. Autonomic dysfunction in Alzheimer's disease. Acta Neurologica Scandinavica 91(1): 14-18 (1995).

[38] Prinz PN, Christie C, Smallwood R, Vitaliano P, Bokan J, Vitiello MV, *et al*. Circadian temperature variation in healthy aged and in Alzheimer's disease. J Gerontol 39(1): 30-35 (1984).

[39] Diamond PT, Diamond MT. Thermoregulatory behavior in Alzheimer's disease. J Am Geriatr Soc 39(5): 532-32 (1991).

[40] Spielberger Charles D., and Lou H. Smith. "Anxiety (drive), stress, and serial-position effects in serial-verbal learning." *Journal of Experimental Psychology*72.4 (1966): 589.

[41] Pasquier, Florence. "Early diagnosis of dementia: neuropsychology." Journal of neurology 246.1 (1999): 6-15.

[42] Dick, Malcolm B., Mary-Louise Kean, and Dan Sands. "Memory for internally generated words in Alzheimer-type dementia: Breakdown in encoding and semantic memory." *Brain and Cognition* 9.1 (1989): 88-108.

[43] Smeets, Tom, *et al*. "True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval." *Psychoneuroendocrinology* 33.10 (2008): 1378-1386.

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