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Research Article

Task-Related Temporal Gamma EEG Coherence as a Marker of Alzheimer's disease

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ABSTRACT

Background: Progressive deterioration of synaptic plasticity and synaptic connectivity between neurons is a neurophysiological hallmark of brain ageing and has been linked to the severity of dementia. We hypothesized that electroencephalographic evidence of the disruption of functional connectivity might be used to diagnose Alzheimer's dementia. Improving the accuracy and reducing the time needed to diagnose AD could allow timely interventions, treatments, and care cost reduction. In our previous study, we identified four promising markers. Temporal Gamma EEG coherence marker (TG-marker) was selected for evaluation. This study examined group differences in EEG coherence within global cortical networks at rest and during executive challenges among patients with AD, individuals with mild cognitive impairment, and healthy controls.

Methods: This blinded diagnostic test accuracy study examined diagnostic parameters for TG-marker in individuals with AD, vascular dementia, Parkinson's, depression and healthy controls. The TG-marker sensitivity, specificity, PPV, NPV, and positive and negative likelihood ratio were evaluated.

Results: TG-marker demonstrated high sensitivity (>89%) and specificity (95%) in all neurodegenerative groups with high PPV (>92%) and NPV (>93%).

Conclusions: TG-marker could be a valuable tool in detecting neurodegenerative process in the brain and excluding dementia in TG-marker negative patients. More testing is needed to understand the role of neurodegeneration in pseudo-dementia and age-related brain changes.

Keywords: Alzheimer's Disease (AD); Electroencephalographic; Neurophysiological; Temporal gamma EEG coherence marker; Vascular dementia

INTRODUCTION

Alzheimer's disease (AD) is the most common form of major neurocognitive disorder in older adults. AD is the sixth leading cause of death in the United States, killing more people than breast cancer and prostate cancer combined [1]. Clinicians need to accurately diagnose and manage the early cognitive manifestations of AD; mainly as new therapies are developed.

A definite diagnosis of AD can be established only in the presence of histopathologic evidence [2]. As a probable diagnosis, AD is evaluated by a series of clinical and neurophysiological examinations repeated over a period of time and demonstrating progressive cognitive decline present in at least one area of cognitive domains. Patients and families are often uncertain about the onset of symptoms since the initial manifestations of dementia are discrete and inaccurately ascribed to "ageing." Identifying AD is a time-consuming process, and diagnosis is often missed. One study found that the diagnosis was missed in 21% of demented or delirious patients on a general medical ward, while 20% of non-demented patients were mistakenly diagnosed [3].

Executive function is very complex and relies on the coordination of multiple brain regions. Synaptic dysfunctions were detected in

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the early stages of dementia even before the emergence of any symptoms [4,5]. It has been hypothesized that the disconnection between regions due to the brain's synaptic dysfunctions could disrupt functional connectivity and result in the brain's failure to integrate various regions into effective networks [6]. Progressive deterioration of synaptic plasticity and synaptic connectivity between neurons is a neurophysiological hallmark of brain ageing and has been linked to the severity of dementia [7].

Compensatory remodelling ensures functional maintenance of neurons and constitutes brain reserve. Therefore, neurodegeneration may occur in the absence of symptoms for an uncertain period of time. The onset of functional deterioration in AD is often insidious, as many diseases could cause transient functional decline. The use of EEG markers of AD in conjunction with standard assessments of cognitive functions with neuropsychological batteries could help detect neuronal dysfunction and decreasing brain reserve and thus facilitate earlier recognition of brain neurocognitive disorder.

Numerous studies have examined functional connectivity in AD with EEG [8-10]. EEG coherence represents the functional interaction between two regions [11,12]. It is an advantageous method for exploring neuronal network functioning and could help test the disconnection hypothesis. In our study, we hypothesized that if synaptic disconnection as the neuropathology of AD is responsible for the failure of the brain to integrate various regions into effective networks, then electroencephalographic evidence of the disruption of functional connectivity might be used to diagnose Alzheimer's dementia [13]. We explored the relationship between EEG coherence and executive function in patients with AD and healthy controls.

The four most promising task-related EEG coherence markers were identified as F3-F4 Beta in visual-spatial orientation task (p=0.019), P7-P8 Beta in writing task (p=0.001), T7-T8 Gamma in speech understanding task (p=0.008) and 01-02 Alpha in space orientation task (p=0.020).

Medial temporal lobe atrophy and decreased hippocampus volume are the most typical focused MRI findings in AD [14]. The typical pattern of degeneration follows the temporo-parietal-frontal axis [15]. Although neuronal disconnection in AD is a diffuse prosses, the earliest cortical neuronal degeneration seems to be most prominent in the temporal cortical region. Therefore, the T7-T8 Gamma marker (TG-marker) was chosen for further evaluation.

MATERIALS AND METHODS

The Research Ethics Office of the University of Alberta, Canada, reviewed and approved this study (HREBA.CHC-16-0053).

Participants

The study evaluated 70 participants with different cognitive function levels: individuals with normal cognitive function (control), with AD, vascular dementia, Parkinson's dementia, and depression. Participants were recruited from community care centers and long-term care facilities in Calgary, Alberta. All participants were between the age of 65 and 85, had at least a grade eight education and were fluent in English (Table 1).

Table 1: Demographic information of all study groups (mean ± variance).

Groups	N	Age	Gender/Male	Education
Control	20	77.4 ± 25.30	0.4 ± 0.25	11.6 ± 4.46
AD	12	78.0 ± 24.08	0.5 ± 0.27	10.3 ± 4.97
Vascular D	13	78.0 ± 28.83	0.5 ± 0.26	10.7±5.69
Parkinson's	12	77.7± 8.75	0.5 ± 0.27	10.3 ± 1.33
Depression	13	74.7 ± 23.69	0.5 ± 0.26	11.8 ± 4.30
P-value		0.368026	0.93141	0.175278

The neurocognitive status of all participants was confirmed within three months before the study by the Memory Clinic team in Calgary through a series of functional and cognitive testing repeated at least three months apart in accordance with DSM-5 criteria [16]. Global Deterioration Scale, Mini-Mental State Examination, and Montreal Cognitive Assessment Scale were used to document all participants' cognitive status (Table 2).

Table 2: Neurocognitive statistics for all study groups (mean ± variance).

Groups	N	GDS	MMSE	MoCA
Control	20	1.1 ± 0.09	29.5 ± 0.57	27.0 ± 0.89
AD	12	4 ± 0	21.1 ± 1.42	15.8 ±1.78
Vascular D	13	3.6 ± 0.23	20.9 ±1.07	15.9 ±1.64
Parkinson's	12	3.7 ± 0.21	20.9 ±1.17	16.0 ±1.45
Depression	13	1.8 ± 0.14	28.5 ± 0.93	23.4 ± 6.43

Participants with unstable medical conditions that might affect cognition (e.g. uncontrolled thyroid dysfunction, B12 deficiency, alcohol abuse) or current (within two weeks) psychotropic medication (e.g. anticholinergics, neuroleptics and benzodiazepines) use were excluded. Participants with stable chronic conditions were recruited for the study. Out of 70 participants, there were two members with a history of NSTEMI, eight with controlled hypertension, six with controlled hypothyroidism, twelve with osteoarthritis, and five with GERD. All participants provided written informed consent.

Procedures

Upon recruitment into the study, each participant was assigned a file number. Information regarding the participants' names, medical history, gender and age was concealed, stored separately from the research files and available to the primary clinical investigator only. The primary clinical investigator was excluded from EEG marker identification and analysis of blinded data. On the day of testing, each participant was seated comfortably in a light- and sound-attenuated room. Resting EEG with the participant's eyes closed was recorded for one minute with EMOTIV Epoc+, a portable 14-channel wireless EEG system

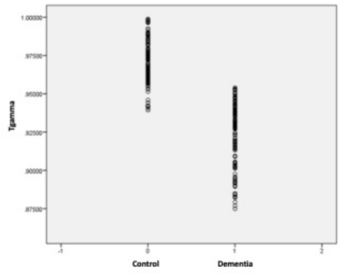
[17]. All participants completed a three-step command test that effectively revealed neuronal disconnection in temporal lobes [13]. The test consists of a verbal three-step command requiring a participant to “take the paper in your right hand, fold it and place it on the table.” A participant listened to the full tree-step direction before proceeding and executing the steps in the order they were listed. The three-step command is a common task in neurocognitive test panels such as the Mini-Mental State Examination [18]. The task recruits left superior temporal and inferior parietal regions.

Statistical analysis

Continuous EEG data were recorded from 14 channels using the Emotiv Epoc+ portable headset, referenced to P3. Data were acquired at a bandpass of 0.3-50 Hz and digitized at a 128 Hz sampling rate. Components containing artifacts associated with eye movements, such as blinks and horizontal eye movements were removed from the dataset. Data were segmented into 1.2-second epochs, and independent component analysis was performed using EEGLAB software [19,20]. MATLAB software was used to generate a numeric average for 50 epochs of EEG coherence values for cross-hemisphere electrode pairs in four brain regions (frontal F3-4, parietal P7-8, temporal T7-8, occipital 01-02) for five EEG frequencies (theta, alpha, beta, gamma, delta) for all 70 participants [21]. Fifty epochs values of TG-marker were identified for each participant. The result was then recorded as TG-Positive (TG-P) and TG -Negative (TG-N) ratio using a cut-off threshold at 0.950. The information on the participants’ status was transferred to the principal investigator, and the study was unblinded.

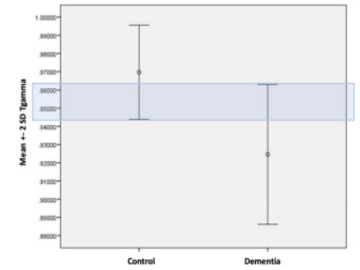
Evaluation of cut-off points as diagnostic test

In order to find potential cut-off points, we analyzed the distribution of the temporal gamma marker values for AD and the control group in our previous study [13,22]. The distributions of the temporal gamma values for the control and dementia groups within ± 2SD of the mean, which contains at least 95% of the values, intersect above 0.940 up to below 0.965. The distribution of the temporal gamma values for the control and dementia groups within ± 2SD of the mean (Figures 1a and 1b).



(1a)

Figure 1a: Distribution of the temporal gamma values for the control and dementia groups.



(1b)

Figure 1b: Distribution of the temporal gamma values for the control and dementia groups within ± 2SD of the mean.

To evaluate the accuracy of the temporal gamma marker as a diagnostic test for AD, we followed the conventional way of describing diagnostic test outcomes (positive/negative results) when compared with “the gold standard”, as demonstrated in Table 3. “The gold standard,” in this case, is the actual clinical diagnosis of the true disease state for dementia.

Table 3: Diagnostic accuracy measures.

Diagnostic test result	Disease status	100%
	Present	Absent
Positive	a (TP)	b (FP)
Negative	c (FN)	d (TN)
Total	n^1=a+c	n^2=b+d

Conventional analyses consider the sensitivity and specificity of a diagnostic test as the primary indices of accuracy since these indices are considered independent of the prior probability of disease (Table 4).

Table 4: Summary indices of test performance.

Diagnostic test	Results
Sensitivity=TP/(TP+FN)=a/(a+c)	Positive predictive value=TP/(TP+FP)=a/(a+b)
Specificity=TN/(FP+TN)=d/(b+d)	Negative predictive value=TN/(FN+TN)=d/(c+d)

Tests that generate results on a continuous scale demand the specification of a test threshold to determine positive and negative results. Changing the threshold alters the proportion of false positive and false negative diagnoses.

We analyzed several cut-off points in multiples of 5 thousandth points (0.940, 0.945, 0.950, 0.955, 0.960 and 9.965) covering an intersecting area of the control and AD groups distributions above 0.940 up to below 0.965 (Table 5).

As demonstrated in Table 5, TG-marker optimal cut-off appears to be at 0.950, for which sensitivity was at 94.4% and specificity at 95.8%. This cut-off point also had both PPV and NPV values at 95%.

Table 5: Sensitivity, specificity, PPV and NPV at various cut-off points of TG-marker.

TG-marker cut-off	True disease state				Total	Sensitivity	Specificity	PPV	NPV
	Dementia (n=160)		Control (n=190)						
	TP (a)	FN (c)	FP (b)	TN (d)					
0.965	160	0	91	99	350	1	0.521	0.637	1
0.96	160	0	48	142	350	1	0.747	0.769	1
0.955	160	0	12	178	350	1	0.937	0.93	1
0.95	151	9	8	182	350	0.944	0.958	0.95	0.953
0.945	141	19	7	183	350	0.881	0.963	0.953	0.906
0.94	128	32	1	189	350	0.8	0.995	0.992	0.855

We also utilize the receiver operating characteristic (ROC) curve to evaluate the accuracy of the TG-marker, where diagnostic accuracy was summarised by combining across a range of thresholds. The classification table produced by logistic regression demonstrated that the TG-marker correctly classified 95% of the cases and matched the outcome of Table 5 for the cut-off point of 0.950 (Table 6).

Table 6: Classification table produced by logistic regression demonstrated that the TG-marker.

Classification table				
Observed		Groups	Predicted	Percentage correct
		Control	Dementia	
Groups	Control	182	8	95.8
	Dementia	9	151	94.4
Overall percentage			95.1	

The ROC curves for both the actual and grouped temporal gamma values are shown in blue and green, respectively. The diagonal line is the reference line for the Area-Under-the-Curve (AUC), which is set by default at 0.50 (Figure 2).

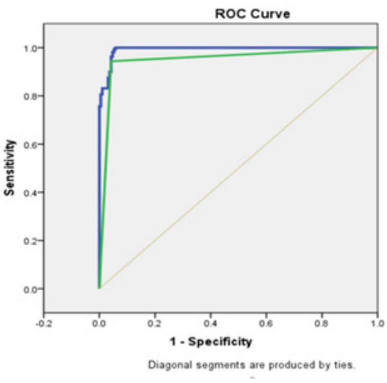


Figure 2: ROC curves for both the actual and grouped temporal gamma. **Note:** (—) Predicated probability; (—) Duct-0.950; (—) Reference line.

The test result variable(s): Dcut-0.950 has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased (Table 7).

Table 7: Diagnostic accuracy measures of TG-marker.

Area Under the Curve (AUC)					
	Asymptotic Sig^b			Asymptotic 95% confidence interval	
Test result variable (s)	Area	Std. error^a		Lower bound	Upper bound
Predicted probability	0.993	0.003	0	0.987	0.998
Dcut-0.950	0.951	0.013	0	0.924	0.977
The test result variable (s)			Dcut-0.950		

Note: a-Under the nonparametric assumption; b- Null hypothesis: True area=0.5

The area under the curve for temporal gamma marker values is 0.993 ($p<0.001$). The logistic regression model classified the group significantly better than mere chance alone. The classification table that resulted for the optimal cut-off point of 0.950 was confirmed by logistic regression and ROC curve analyses. This cut-off point provided 95% correct classification and the corresponding area under the curve 99.3%, exhibiting a nearly ideal differentiation between control and impaired cognitive status.

Since the TG-marker cut point value was established at a single threshold, results obtained from a diagnostic test accuracy study were expressed as TG-positive and TG-negative. As each patient's TG-marker was measured 50 times, the presence of the marker (measure below 0.950) or absence (measure above 0.950) was scored out of 50. Once unblinded, patients' test results were categorized as True Positive (TP), False Positive (FP), True Negative (TN), and False Negative (FN) (Table 8).

Table 8: Summary of TG-marker in all study groups.

Groups	n	TG-P	TG-N
control	20	44	956
AD	12	540	60
Vascular dementia	13	612	38
Parkinson's	12	534	66
Depression	13	136	514

For straightforward and direct interpretation, the results were presented in pairs: Sensitivity and specificity, PPV and NPV, positive Likelihood Ratio (LR) and negative Likelihood Ratio (LR). Sensitivity and specificity are two factors that affect a diagnostic test's validity or its capacity to assess what it is supposed to measure [23]. Sensitivity is the percentage of tests that reveal true positive results for all patients with a condition. Specificity is the proportion of true negative results among all subjects who do not have a condition. PPVs estimate the proportion of true positives out of all positive results; NPVs estimate the proportion of true negatives out of all negative results. PPV and NPV equivalently reflect the probability that a patient with a positive test result has the disease. The Likelihood Ratio (LR) measures the probability that a particular test result would be anticipated in a patient with the target disease. Likelihood ratios are a helpful and practical way to convey the ability of diagnostic tests to increase or decrease the chance of disease. The summary of indexes is presented in Table 9.

Table 9: Diagnostic accuracy measures of TG-marker at cut point value 0.950.

Compared groups	Sensitivity	Specificity	PPV	NPV	LR (+)	LR (-)
AD/control	0.900	0.956	0.924	0.941	20.45	0.1
Vascular D/ control	0.942	0.956	0.932	0.961	21.38	0.06
Parkinson's/ control	0.890	0.956	0.923	0.935	20.2	0.12
depression/control	0.209	0.956	0.755	0.65	4.75	0.83
AD/depression	0.900	0.791	0.798	0.895	4.3	0.12
Neurodegenerative (AD, vasc D, parkinsons)/ control	0.911	0.956	0.974	0.853	20.7	0.09
Neurodegenerative (AD, vasc D, Parkinsons)/	136	136	136	136	136	136
non-neurodegenerative (control, depression)	0.911	0.89	0.903	0.899	8.28	0.1

RESULTS

All five group comparison with ANOVA demonstrated no statistically significant difference among the groups in gender distribution (p=0.931). The participants' age demographic parameters were compatible in all groups with a mean age of 77.2 ± 4.73 (mean ± Std D) (p=0.368). All groups also had similar educational levels with mean years of education of 10.9 ± 2.04 (mean ± Std D) (p=0.175).

TG-marker's sensitivity for detecting AD comparing to a healthy control population was demonstrated at 90% with a specificity of 95%. Predictive value of the marker showed a 92% chance of the illness being present in the presence of the marker and a 94% chance of the illness being absent in the absence of the marker. In the vascular dementia group, the marker performed with 94% sensitivity and 95% specificity, demonstrating a positive predictive value of the marker for dementia at 93% and a negative predictive value at 96%. In the group of Parkinson's dementia, TG-marker had 89% sensitivity with 95% specificity for dementia and PPV 92% and NPV 93%.

We also analyzed TG-marker indices of performance as a marker of neurodegeneration which affects groups with AD, Parkinson's and vascular dementia. In the combined neurodegeneration disorders group, TG-marker demonstrated higher than in AD alone sensitivity of 91% with matching specificity of 95% with PPV 97% and NPV 85%. In all neurodegenerative groups, TG-marker had high positive likelihood ratios of greater than 10. Negative likelihood ratios were strong at or below 0.1 value in all neurodegenerative groups other than Parkinson's group.

In the depression group with pseudo-dementia, the TG-marker was positive in 20% of cases with PPV of only 75% and NPV of 65%. As the negative status of the TG-marker represents the "true" state in non-neurodegenerative depression, we compared depression to AD, in which case TG-marker had 90% sensitivity and only 79% specificity with PPV 78% and NPV 89%.

DISCUSSION

A diagnostic test accuracy research offers evidence of how effectively a test accurately diagnoses or excludes disease and assists doctors and their patients in making future treatment decisions. We expressed the results obtained from our study by comparing them with "the gold standard" of the "true" disease status for each patient that was established prior to each patient's enrolment. To avoid researchers' bias, we blinded EEG data analysts from the patients' "true" status.

The clinically relevant diagnostic threshold has been established at the TG-EEG coherence level below 0.950, based on which the test can categorize patients' results as True Positive (TP), False Positive (FP), True Negative (TN), and False Negative (FN). Diagnostic accuracy was presented using paired results such as sensitivity and specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV), positive likelihood ration and negative likelihood ratio.

We anticipated the threshold of 0.950 to produce an AD marker with sensitivity=94.4% and specificity=95.8%, and both PPV and

NPV values at 95%. Our study demonstrated close to expected TG-EEG marker sensitivity for AD at 90%, matching specificity of 95.6%. Although the neuropathology of AD (neurofibrillary tangles, amyloid plaques, and synaptic dysfunction) has been closely studied, the pathophysiological foundation of cognitive impairment is less clear. The disruption of functional connectivity might be only a part of the complex neuropathology of the disorder. The highest sensitivity of the marker was demonstrated in the vascular dementia group at 94.1%, likely reflecting the neuronal degeneration as a result of vascular compromise and atrophy. In the Parkinson's disease group, the marker demonstrated high sensitivity of 89%, which was expected due to the well-established neurodegenerative nature of the disease.

We also analysed the marker's performance in the joint neurodegenerative disorders group as the marker is reflective of disconnection between neurons and, thus, neurodegeneration. The joint neurodegeneration group combined the participants from AD, vascular dementia and Parkinson's groups. Neuropathology of dementia in all three conditions is likely to involve neuronal degeneration. It is reasonable to consider that even if each neurocognitive disorder could have a distinct cause, the pathophysiology of executive function loss might converge at some point in neurodegeneration and cause a similar clinical and electroencephalographic picture. In the neurodegeneration group, TG-marker demonstrated higher than in AD alone sensitivity of 91% with matching specificity of 95% with PPV 97% and NPV 85%. Disease prevalence in a population affects PPV and NPV. When a disease is highly prevalent, the test is better at 'ruling in' the disease and worse at 'ruling it out' [24,25]. Considering our sample, it is reasonable to assume that some degree of neuronal disconnection could be present in all subjects due to the neurodegenerative nature of their primary diagnosis. Unlike predictive values, similar to sensitivity and specificity, likelihood ratios are not impacted by disease prevalence. In all neurodegenerative groups, TG-marker had high positive likelihood ratios of greater than 10, indicating high probability of the test to be positive in the affected by the pathology population [24].

The clinically relevant diagnostic threshold of TG-marker has been established in our previous study [22]. Changing the threshold alters the proportion of false positive and false negative diagnoses. No diagnostic test has perfect accuracy, and all tests occasionally fail to detect disease or perceive it in healthy patients. However, false negative and false positive diagnoses carry unequal significance. The misclassification cost, the relative importance of a false negative versus a false positive diagnosis, varies according to the disease's effect on patients and the effectiveness of available treatments. Timely detection of a life-threatening disease for which a cure is available, and time-sensitive is likely more important than a false positive diagnosis in a healthy patient. In the case of AD, the false positive diagnosis can trigger immense anxiety in patients and their caregivers and increase the cost to the healthcare system with further investigations. However, the false negative will not cause patients to forgo the benefit of disease-modifying treatment. Recognizing reversible causes of neurocognitive impairment could be even more critical as curative or quality-of-life-improving treatments could be available for pseud-dementias such as those caused by mood disorders and metabolic abnormalities. Thus, the high positive and negative predictive value of the TG-EEG marker is important. The absence of the marker of neurodegeneration in cognitively impaired patients could support investigation for reversible causes and save lives.

In our study, the marker was detected in 20% of people with depression. It is possible that the neurodegenerative process was present in the group in the background of depression and was not yet established due to concurrent mood disorder diagnosis. Treatment of depression with monitoring of cognitive function recovery can clarify the cause of TG-marker presence in depression group.

When the diagnosis of dementia is missed, inappropriate treatment, such as neuroleptics used for delirium treatment, could be harmful to the patients. Investigation of the TG-marker role in ruling out delirium would also be necessary.

TG-marker was detected in 4% of tests in the control group. It would also be interesting to monitor the control group for developing of cognitive impairment to see if the TG-marker of neurodegeneration could be detected prior to clinical conversion to major neurocognitive disorder.

CONCLUSION

The difference in EEG coherence between healthy and AD patients could play an important role in clinical practice. TG-EEG marker is highly sensitive and specific to neurodegenerative changes in the brain. Absence of TG-EEG marker could warrant a search for reversible causes of cognitive decline. Neurodegeneration starts long before clinical manifestations of AD; thus, detecting neuronal disconnection with EEG might be possible even in the preclinical stage. Further evaluation of the markers' sensitivity and specificity to the neurodegenerative process in the preclinical phase of neurodegeneration needs to be conducted.

STUDY LIMITATIONS

The study had limited number of groups with neurocognitive impairment due to pseudo-dementias. It is important to understand presence and significance of TG-marker in delirium, metabolic abnormalities such as B12 deficiency, hypothyroidism and in altered cognitive states caused by medications such as anticholinergics and antihistamines.

Normal aging could also associate with cognitive decline. Exploring role of neurodegeneration and TG-marker in monitoring and predicting progression of normal aging into major neurocognitive disorder is important. TG-marker was not explored in our study as a prognosticative marker. Our study aimed to establish TG-marker as an indicator of AD. However, it became clear that TG-marker is not specific to AD alone and rather better serves as an indicator of neurodegeneration.

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