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ORIGINAL RESEARCH

Neural Biomarkers for Identifying Atopic Dermatitis and Assessing Acupuncture Treatment Response Using Resting-State fMRI

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Purpose: Only a few studies have focused on the brain mechanisms underlying the itch processing in AD patients, and a neural biomarker has never been studied in AD patients. We aimed to develop a deep learning model-based neural signature which can extract the relevant temporal dynamics, discriminate between AD and healthy control (HC), and between AD patients who responded well to acupuncture treatment and those who did not.

Patients and Methods: We recruited 41 AD patients (22 male, age mean ± SD: 24.34 ± 5.29) and 40 HCs (20 male, age mean ± SD: 26.4 ± 5.32), and measured resting-state functional MRI signals. After preprocessing, 38 functional regions of interest were applied to the functional MRI signals. A long short-term memory (LSTM) was used to extract the relevant temporal dynamics for classification and train the prediction model. Bootstrapping and 4-fold cross-validation were used to examine the significance of the models.

Results: For the identification of AD patients and HC, we found that the supplementary motor area (SMA), posterior cingulate cortex (PCC), temporal pole, precuneus, and dorsolateral prefrontal cortex showed significantly greater prediction accuracy than the chance level. For the identification of high and low responder to acupuncture treatment, we found that the lingual-parahippocampal-fusiform gyrus, SMA, frontal gyrus, PCC and precuneus, paracentral lobule, and primary motor and somatosensory cortex showed significantly greater prediction accuracy than the chance level.

Conclusion: We developed and evaluated a deep learning model-based neural biomarker that can distinguish between AD and HC as well as between AD patients who respond well and those who respond less to acupuncture. Using the intrinsic neurological abnormalities, it is possible to diagnose AD patients and provide personalized treatment regimens.

Keywords: Atopic Dermatitis, deep learning, functional MRI, biomarkers, personalized medicine

Introduction

Atopic Dermatitis (AD) is a complex inflammatory skin disease, characterized by intense itching and recurrent eczematous lesions.[1] To treat AD, topical corticosteroids, calcineurin inhibitors, and immunomodulatory agents have been used; however, responsiveness to a treatment can vary.[2] The diagnosis and severity assessment of AD currently relies solely on subjective tools (e.g., patient self-reports, visual inspection of skin).[3] Therefore, attempts have been made to identify more reliable and objective indicators, known as biomarkers, that may help with the diagnosis of AD, and even potentially predict treatment response.[4–6]

Despite studies suggesting neurological dysfunctions in AD patients (e.g., cingulate, dorsolateral prefrontal cortex),[7,8] the use of neural biomarkers in AD patients has never been investigated. In this study, we aimed to investigate whether a neural network model (Long Short-Term Memory; LSTM) can (1) extract the relevant temporal dynamics, which can discriminate

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between mild-moderate AD and healthy control (HC), (2) and between high and low responders to acupuncture treatment in AD patients. We employed recurrent neural networks to the resting-state functional magnetic resonance imaging (rs-fMRI).

Materials and Methods

The study received approval from the institutional review board of Kyung Hee University Korean Medicine Hospital (KOMCIRB 2020-06-003) and was registered with the Korean Clinical Trial Registry (KCT0005422). Furthermore, the study adhered to the principles outlined in the Declaration of Helsinki. We recruited 41 mild-moderate AD patients (22 male, age mean ± SD: 24.34 ± 5.29) and 40 HCs (20 male, age mean ± SD: 26.4 ± 5.32; Table 1). We considered a sample size of at least 18 people per group, based on the SCORing Atopic Dermatitis (SCORAD) total score from the previous study.[9] However, it is important to acknowledge that studies identifying neural biomarkers may necessitate larger sample sizes, often exceeding 100 participants. Therefore, this study is limited by its small sample size. All participants provided informed consent. We obtained resting-state functional magnetic resonance imaging (rs-fMRI) data before the acupuncture treatment (manual acupuncture, 8 sessions, 15 minutes/session). AD participants randomly received real acupuncture (n=27) and sham acupuncture treatment (n=14; see protocol paper for more details;[10] Table 1.), without the incorporation of any additional adjunctive therapies. After the real acupuncture treatment, 11 patients were classified as high responders and 16 as low responders. A patient was classified as a high responder if their SCORAD total score decreased by more than 8.7 on a scale of 0 to 10, according to the minimal clinically important difference.[11]

Table 1 Demographic and Baseline Clinical Characteristics of Participants and Clinical Effects of Real and Sham Acupuncture Treatment in Patients with Atopic Dermatitis

	Healthy Controls (n=40)	AD Baseline (n=41)	AD, Post-Treatment (Real Acupuncture, n=27)	AD, Post-Treatment (Sham Acupuncture, n=14)	$Z^{‡}$ or $U^{†}$, P value
Age (year)	26.4 ± 5.3	24.3 ± 5.2	24.1 ± 5.9	24.7 ± 4.0	1) AD vs HC: Z −1.60, P 0.09 2) AD real vs AD sham: Z −1.18, P 0.24
Sex (m/f)	20 / 20	21 / 20	16/12	6/7	–
BMI (kg/m^2)	22.2 ± 2.7	23.5 ± 3.3	23.2 ± 2.9	24.1 ± 4.1	1) AD vs HC: Z 1.76, P 0.08 2) AD real vs AD sham: T −0.81, P 0.42
Duration of AD (year)	-	20.4 ± 8.7	20.3 ± 8.5	20.5 ± 9.7	AD real vs AD sham: T −0.14, P 0.89
SCORAD	-	31.2 ± 8.7	24.5 ± 8.3	26.7 ± 10.6	1) AD real baseline vs post-treatment: T −4.91, P < 0.001 2) AD sham baseline vs post-treatment: T −2.88, P 0.04
EASI	-	4.6 ± 3.4	4.3 ± 3.9	4.7 ± 3.4	1) AD real baseline vs post-treatment: T −2.42, P 0.03 2) AD sham baseline vs post-treatment: T −0.03, P 0.98
VAS (itching)	-	5.5 ± 1.9	3.7 ± 2.1	3.2 ± 2.1	1) AD real baseline vs post-treatment: T −3.89, P < 0.001 2) AD sham baseline vs post-treatment: T −3.60, P 0.01
VAS (insomnia)	-	3.5 ± 2.2	2.1 ± 1.9	2.9 ± 2.2	1) AD real baseline vs post-treatment: T −2.93, P 0.01 2) AD sham baseline vs post-treatment: T 0.04, P 0.97

Notes: All data are presented as mean ± standard deviation. †Mann–Whitney *U*-test; ‡Paired or two-sample *t*-test.

Abbreviations: AD, Atopic Dermatitis; BMI, Body Mass Index; BDI, Beck Depression Inventory; EASI, Eczema Area and Severity Index; SCORAD, SCORing Atopic Dermatitis scale; VAS, visual analogue scale.

Neuroimaging Acquisition and Analysis

All images were obtained with a 3T scanner (Siemens Trio Tim). A T1-weighted anatomical image was recorded (repetition time=2000ms, echo time=2.37ms, voxel size=0.9×0.9×1mm3). Whole brain blood oxygenation level–dependent data were obtained with the use of the standard T2*-weighted echo planar sequence (150 volumes, repetition time=2000ms, echo time=30ms, voxel size =3.8×3.8×4.0mm3). Data were preprocessed with the FMRIB's Software Library, and the pipeline involved the motion correction, spatial smoothing, and registration. LSTM models keep the contextual information of the input sequences, therefore, the use of LSTM was appropriate to capture dynamic brain activity over time. LSTM models keep the contextual information of the input sequences,[12] therefore, the use of LSTM was appropriate to capture dynamic brain activity over time. An LSTM was used to extract the relevant temporal dynamics for classification using scikit-learn,[13] Keras,[14] and TensorFlow[15] libraries in Python 3.8.10 (Figure 1). The preprocessed rs-fMRI data were used as input for the neural network sequential model, which has two LSTM layers and one dense layer. We applied Power's 38 pre-defined regions of interest (ROIs, Table 2).[16] The significance of the classification accuracy and area under receiver operating characteristic curve (AUC), obtained from bootstrapping (n=100) and 4-fold cross-validation, were tested to a chance level (0.5) using a *t*-test with a significance level of $p < 0.05$.

Results

Neural Biomarker for Atopic Dermatitis

The model evaluation results are shown in Figure 2. For the identification of AD patients and HC, we found that the left supplementary motor area (SMA; mean accuracy 0.85, mean AUC 0.85), right posterior cingulate cortex (PCC; 0.82,

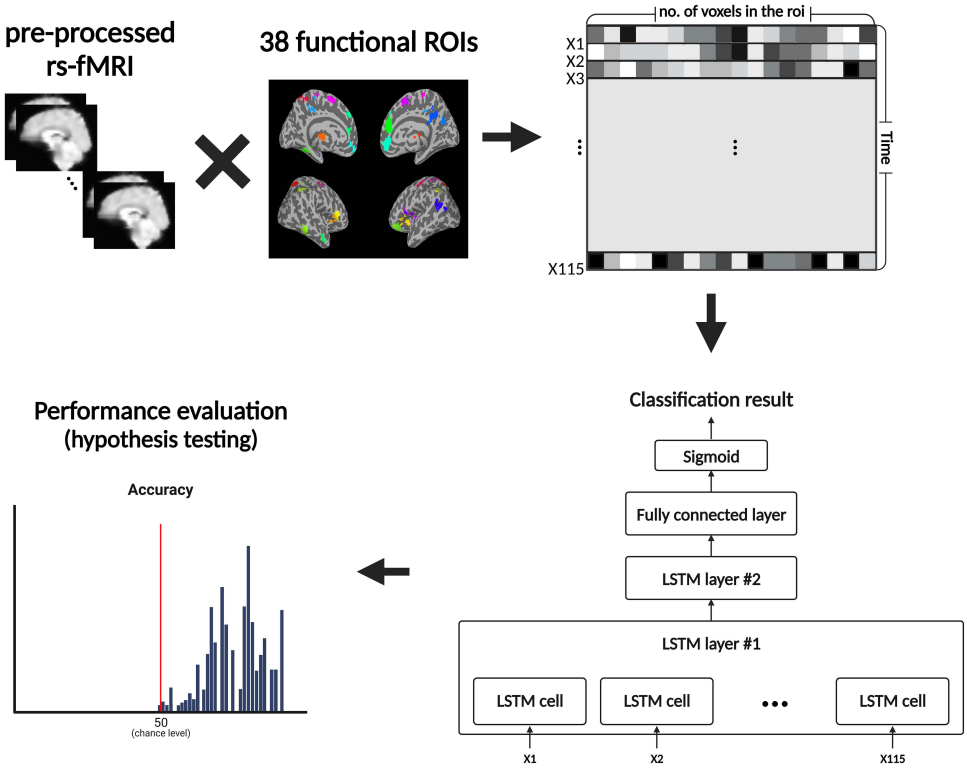

Figure 1 The Long Short-Term Memory analysis procedure. The resting-state fMRI data (Atopic Dermatitis [AD] n=41, healthy controls n=40) was pre-processed using FSL to remove artifacts, correct motion, smooth spatially, and functional data were registered to standard space. Blood oxygen level-dependent signals of each time point (n=115) were extracted for 38 pre-defined regions of interest (ROIs) of Power's functional atlas. We identified two Long Short-Term Memory (LSTM) models; a model to identify mild-moderate AD patients and healthy controls and another model to identify high and low responders to acupuncture treatment among AD patients. The signals were input into a dual-layer LSTM network designed to capture temporal dependencies within the fMRI data. Each layer is composed of multiple LSTM cells that process data from the corresponding time points, allowing the network to retain information over time. The final layer's output is forwarded through a fully connected layer followed by a sigmoid activation function to generate the classification result. We tested models' prediction performance of each ROI based on the classification accuracy and area under receiver operating characteristic curve, assessed from a 4-fold cross-validation test. A *t*-test against a chance level (0.5) was conducted for the accuracy, computed by bootstrapping (n=100). The significance threshold was set at $p < 0.05$.
Abbreviations: LSTM, Long Short-Term Memory; no., number; ROI(s), region(s) of interest; rs-fMRI, resting-state functional magnetic resonance imaging.

Table 2 Functional Regions of Interest Employed in Long Short-Term Memory Models for AD Patients

No.	MNI Coordinates (X, Y, Z)	Regions	Functional Networks
1	−7.12, −52.22, 60.71	Precuneus (left)	Somatosensory-motor
2	−39.63, −19.04, 54.21	S1/M1 (left)	Somatosensory-motor
3	44.34, −7.55, 56.98	M1 (right)	Somatosensory-motor
4	−29.1, −43, 60.66	M1-sup. parietal cortex (left)	Somatosensory-motor
5	2.4, −27.94, 60.15	Paracentral lobule (right)	Somatosensory-motor
6	−2.88, 2.38, 53.21	Supplementary motor area (left)	Somatosensory-motor
7	6.52, 7.69, 50.58	Supplementary motor area (right)	Somatosensory-motor
8	25.34, −58.18, 60.34	Sup. parietal gyrus (right)	Somatosensory-motor/attention
9	−16.5, −58.57, 64.46	Sup. parietal gyrus (left)	Somatosensory-motor/attention
10	−35.44, 20.03, 0.07	Ant. insula (left)	Salience
11	35.91, 21.91, 2.62	Ant. insula (right)	Salience
12	−44.76, 0.1, 8.83	Mid. insula (left)	Salience
13	−10.28, −18.48, 7.04	Thalamus (left)	Somatosensory-motor
14	11.75, −17.18, 7.54	Thalamus (right)	Somatosensory-motor
15	−51.26, 8.26, −2.06	Inf. operculum – sup. temporal gyrus – ant. insula (left)	Salience
16	23.33, 33.07, 47.68	Sup-mid. frontal gyrus (right)	Default mode
17	−16.4, 28.52, 53.05	Sup. frontal gyrus (left)	Default mode
18	−35.36, 19.86, 50.8	Mid. frontal gyrus (left)	Default mode
19	6.11, 63.98, 21.96	Sup. med. frontal gyrus (right)	Default mode
20	−2.06, 37.85, 36.34	Sup. med. frontal gyrus (left)	Default mode
21	26.07, 49.56, 26.58	Mid. frontal gyrus (right)	Salience
22	47.6, 22.16, 9.74	Inf. frontal gyrus (right)	Salience
23	−42.09, −54.98, 44.74	Inf. frontal gyrus (left)	Fronto-parietal task control
24	−17.65, 63.19, −9.17	OFC (left)	Default mode
25	−46.17, 31.26, −13.03	OFC (left)	Default mode
26	−3.06, 44.41, −9.46	OFC-ACC (left)	Default mode
27	−2.5, 41.7, 16.05	ACC (left)	Salience
28	7.51, 42.49, −5.35	ACC (right)	Salience
29	12.25, 35.63, 20.3	ACC (right)	Salience
30	7.94, −48.37, 30.57	PCC (right)	Default mode
31	15.12, −63.09, 25.98	Precuneus (right)	Default mode
32	−2.2, −36.68, 43.85	PCC-precuneus (left)	Default mode
33	−45.79, −60.69, 20.85	TPJ (left)	Salience/attention
34	−43.58, 11.99, −34.15	Temporal pole (left)	Default mode
35	64.64, −11.8, −19.3	Mid. temporal gyrus (right)	Default mode
36	58.31, −52.79, −13.61	Inf. temporal gyrus (right)	Fronto-parietal
37	43.93, −52.95, 46.95	Inf. parietal gyrus (right)	Fronto-parietal
38	−33.93, −38.06, −15.6	Lingual-parahippocampal-fusiform gyrus (left)	Default mode

Abbreviations: ACC, anterior cingulate cortex; ant., anterior; inf., inferior; med., medial; mid., middle; MNI, Montreal Neurological Institute; M1, primary motor cortex; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; sup., superior; S1, primary somatosensory cortex; TPJ, temporo-parietal junction.

0.81), left superior/middle frontal gyrus (0.81, 0.81, $p < 0.001$/0.80, 0.80, $p < 0.01$), temporal pole (0.79, 0.80), PCC (0.82, 0.81), precuneus (0.79, 0.80), right SMA (0.78, 0.78), dorsolateral prefrontal cortex (0.78, 0.78, $p < 0.001$), middle temporal gyrus (0.77, 0.78), and superior medial frontal gyrus (0.75, 0.75, $p < 0.01$) showed significantly greater prediction accuracy than the chance level.

Neural Biomarker for Treatment Responses

For the identification of high and low responders to acupuncture treatment, we found that the left lingual-parahippocampal-fusiform gyrus and superior frontal gyrus (0.90, 0.89, $p < 0.01$), right middle temporal gyrus (0.89, 0.89, $p < 0.001$), SMA (0.87, 0.87), superior middle frontal gyrus (0.84, 0.83, $p < 0.01$), left superior medial/middle

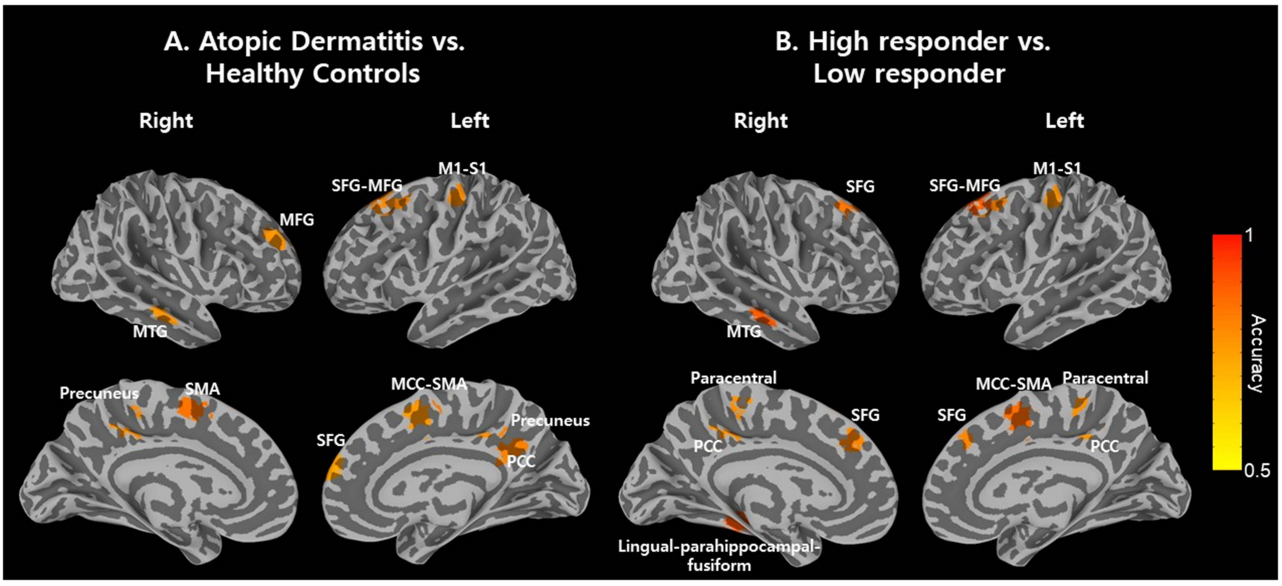

Figure 2 Neural biomarkers classification accuracies achieved by Long Short-Term Memory Models. We observed that patients with Atopic Dermatitis (AD) were accurately distinguished, and the outcomes of their acupuncture treatment were solely determined by the signals from resting-state functional magnetic resonance imaging (rs-fMRI) and long short-term memory models. (**A**) We identified distinct temporal features in the left supplementary motor area (SMA; mean accuracy 0.85, mean area under receiver operating characteristic curve [AUC] 0.85), right SMA (0.78, 0.78), right middle/posterior cingulate cortex (0.79–0.82, 0.79–0.81), left superior/middle/medial frontal gyri including the dorsolateral prefrontal cortex (0.71–0.81, 0.79–0.81), right superior/middle frontal gyrus (0.75–0.78, 0.75–0.79), left precentral gyrus (0.80, 0.80), right temporal pole (0.77, 0.77), left fusiform gyrus (0.74, 0.74), and right precuneus (0.71, 0.70) between patients with AD and healthy participants. These differences contributed to the classification of AD patients from healthy controls. (**B**) Using rs-fMRI signals obtained even before the acupuncture treatment, it was revealed that the right lingual-parahippocampal-fusiform gyrus (0.90, 0.89), right SMA (0.87, 0.87), left fusiform gyrus (0.90, 0.89), right superior middle frontal gyrus (0.84, 0.83), left superior/middle frontal gyrus (0.81–0.82, 0.80–0.84), left posterior cingulate cortex and precuneus (0.79, 0.68) have temporal characteristics that can distinguish high and low responders to acupuncture treatment in AD patients. The brain regions identified for diagnosing and predicting treatment responses may provide a basis for further research on the neural mechanisms of AD and the exploration of innovative treatment modalities in the future.
Abbreviations: MCC, midcingulate cortex; MFG, middle frontal gyrus; MTG, middle temporal gyrus; M1, primary motor cortex; PCC, posterior cingulate cortex; SFG, superior frontal gyrus; SMA, supplementary motor area; S1, primary somatosensory cortex.

frontal gyrus (0.82, 0.80/0.81, 0.84), PCC and precuneus (0.79, 0.68, $p < 0.05$), right paracentral lobule (0.78, 0.68), and left primary motor (MI) and somatosensory cortex (SI; 0.78, 0.67, $p < 0.01$) showed significantly greater prediction accuracy than the chance level.

Discussion

This study represents the novel investigation to identify neural biomarkers that could be beneficial for patients with AD using brain imaging data and deep learning algorithms. We found that the neural network model successfully captures differentiating dynamic brain activities, which can distinguish AD patients from HC and predict responses to acupuncture treatment. The most important features were found in the default mode and somatosensory-motor networks, which implies that AD patients and their response to a treatment might be mediated by the neural processing of their internal and external body state and sensations. The majority of significant regions discovered by deep learning models have been associated with the processing of itches, including the SMA, MI, SI, prefrontal cortex, and PCC.[17] Although the results suggest the potential for temporal properties of these regions to be used as a biomarker for AD, additional study is required to replicate and generalize our findings.

Upon examination of prior studies employing machine learning or deep learning algorithms for prediction research on patients with AD to identify potential biomarkers, it becomes apparent that these studies primarily utilize skin and serum samples[18,19] or skin lesion images.[3,20] Most studies have focused on diagnosing AD,[3] predicting its severity,[19,20] or forecasting the efficacy of treatments such as dupilumab,[18] similar to our study. However, our study demonstrates the feasibility of identifying neural biomarkers in patients with AD by solely utilizing neuroimaging data to predict diagnosis and acupuncture treatment outcomes. Particularly, the brain regions that can be commonly used for diagnosing and predicting treatment outcomes may serve as a foundation for future research on the brain mechanisms of AD and the

development of new treatments. For example, this could include devices designed to alleviate itching by stimulating the brain directly or by targeting specific areas of the skin, known as acupoints in acupuncture treatment, to alleviate itching through brain mechanisms. As we used rs-fMRI without a task, our method has a distinct advantage as a useful biomarker for clinical application. As more healthcare devices have become available in recent years, a wearable and wireless instrument which measures and analyzes intrinsic neuronal activity may help in the early identification and treatment of AD in near future. We also suggest that patients would benefit more from using a cost-effective neuroimaging technique, such as Functional Near-Infrared Spectroscopy (fNIRS). For instance, to propose optimal diagnostic and treatment methods for patients, neuroimaging techniques can be utilized. Initially, utilizing MRI machines with superior spatial and temporal resolution, neural biomarker regions and signal characteristics can be identified. Following this, the results can be applied to research utilizing a brain imaging device that is more clinically accessible, such as fNIRS, which offers ease of installation, portability, and adaptability to diverse experimental and clinical settings.

This study has two limitations: a small sample size, and a lack of fresh data validation. A larger clinical trial is necessary to confirm the models' accuracy and reliability. The findings, in our opinion, suggest potential applications for intrinsic neural distortions as well as potential research targets for certain regions of the brain. For instance, given that we have identified several cortical areas that can be measured by fNIRS, such as the frontal gyrus, SMA, primary motor, and somatosensory cortex, further investigation is required to determine whether the models can be successfully applied to signals from more approachable and cost-effective neuroimaging techniques to offer individualized diagnosis and treatment for patients with AD.

Conclusion

Our neural network model effectively distinguishes AD patients from healthy controls, predicting responses to acupuncture treatment. Key features in the default mode and somatosensory-motor networks suggest a link between AD and neural processing of body states. Significant regions, particularly in itch processing, may serve as potential biomarkers for AD. Our rs-fMRI approach, without a task, provides a valuable clinical biomarker. With the rise of wearable devices, a tool analyzing intrinsic neuronal activity could aid in early AD identification and treatment. Further studies are needed for validation and generalization.

Data Sharing Statement

All data presented in the manuscript, including fMRI and clinical data devoid of identifiable participant information, may be shared solely for research purposes. Requests from other parties will be directed to the corresponding authors for consideration.

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Disclosure

The authors report no conflicts of interest in this work.

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