Neural Mechanism Underlying Successful Classification of Amnestic Mild Cognitive Impairment Using Multi-Sensory-Evoked Potentials

Lei Zhang[1], Malcom Binns[1,2], Ricky Chow[1], Rahel Rabi[1], Nicole D. Anderson[1,3,6], Jing Lu[4,5], Morris Freedman[1,7,8,9], and Claude Alain[1,3,10,11]

[1]Rotman Research Institute, Baycrest Academy for Research and Education, Ontario, Canada, M6A 2E1

[2]Dalla Lana School of Public Health, University of Toronto, Ontario, Canada, M5T 3M7

[3]Department of Psychology, University of Toronto, Ontario, Canada, M5G 3G3

[4]MOE Key Lab for Neuroinformation, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, China, 611731

[5]Center for Information in Medicine, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, China, 611731

[6]Department of Psychiatry, University of Toronto, Ontario, Canada, M5T 1R8

[7]Department of Medicine (Neurology), Baycrest Centre, Ontario, Canada, M6A 2E1

[8]Department of Medicine (Neurology), Mount Sinai Hospital, Ontario, Canada, M5G 1X5

[9]Department of Medicine (Neurology), University of Toronto, Ontario, Canada, M5S 3H2

[10]Institute of Medical Science, University of Toronto, Ontario, Canada, M5S 1A8

[11]Music and Health Science Research Collaboratory, University of Toronto, Ontario, Canada, M5S 2C3

Correspondance: Claude Alain, Ph.D.
Rotman Research Institute
Baycrest Academy for Research and Education
3560 Bathurst Street
Toronto, Ontario, M6A 2E1
Canada
(416) 785-2500 ext. 3523 (telephone)
(416) 785-2862 (fax)
Email: calain@research.baycrest.org

Lei Zhang, Ph.D.
Rotman Research Institute
3560 Bathurst Street
Toronto, Ontario, M6A 2E1
Canada
(416) 785-2500 ext. 2103 (telephone)
Email: lzhang@research.baycrest.org

Abstract

Introduction

The diagnosis, prognosis, and management of amnestic mild cognitive impairment (aMCI) remains challenging. Early detection of aMCI is crucial for timely interventions.

Method

This study combines scalp recordings of auditory, visual, and somatosensory stimuli with a flexible and interpretable support vector machine classification pipeline to differentiate individuals diagnosed with aMCI from healthy controls.

Results

Event-related potentials (ERPs) and functional connectivity (FC) matrices from each modality successfully predicted aMCI. We got optimal classification accuracy (96.1%), sensitivity (97.7%) and specificity (94.3%) when combining information from all sensory conditions than when using information from a single modality. Reduced ERP amplitude, higher FC in frontal region which predicted worse cognitive performance, and lower FC in posterior regions from delta to alpha frequency in aMCI contributed to classification.

Conclusions

The results highlight the clinical potential of sensory-evoked potentials in detecting aMCI, with optimal classification using both amplitude and oscillatory-based FC measures from multiple modalities.

Background

Amnestic mild cognitive impairment (aMCI) represents an intermediate stage between healthy aging and dementia, typically due to Alzheimer's disease (AD), the most common cause of dementia in the aging population. Individuals with aMCI show impairment in episodic memory and sometimes in additional cognitive domains such as executive functioning and language,[1-3] with preserved functional independence in daily activities.[4] The diagnosis, prognosis, and management of aMCI remain challenging. Timely identification and intervention in aMCI are pivotal for its effective clinical management. The present study contributes to this critical need by introducing a cutting-edge framework that integrates the power of support vector machine (SVM) algorithm with a novel multisensory evoked potential (MSEP) paradigm.

Scalp-recording of event-related potentials (ERP) may help identify individuals with aMCI. Relative to healthy controls, individuals with MCI (including amnestic and non-amnestic subtypes that are prodromal to all-cause dementia) show significant reductions in N2 and P3 amplitude, as well as delayed P3 latency, signifying deficits in inhibitory control.[5-12] Multivariate classification of cognitive ERPs has been shown to correctly discriminate participants with MCI from healthy controls with an accuracy ranging from 70% to 80% depending on the task.[13-15] However, Cognitive ERP recordings can be time-consuming due to variability in amplitude and latency, requiring numerous trials for reliable signal-to-noise ratios. Additionally, cultural factors like language, education, and literacy can influence performance on cognitive ERP paradigms.[16]

To overcome these limitations, we developed the MSEP paradigm,[17] which provides a means to delineate normal from impaired sensory processing. In this paradigm, lateralized

80 auditory, visual, and somatosensory stimuli are presented sequentially at a high rate (e.g., 3-5
81 stimuli per second) and in random order. This approach minimizes neural adaptation, thereby
82 ensuring reliable and fairly quick (~15 minutes) measurements of sensory-evoked responses
83 from three sensory modalities. These three measurements may then have potential for
84 differentiating individuals with aMCI from healthy older adults. Because these sensory-evoked
85 responses are recorded while participants sit quietly in the absence of a task (i.e., no response
86 required), there are no concerns related to task complexity, or difficulty understanding complex
87 instructions, making it easy to administer to older adults. Therefore, the design of this paradigm
88 provides practicality in clinical settings as this paradigm is short in length, accessible and
89 inclusive for older adults, and can provide reliable measures of brain functioning.

90 The MSEP paradigm has been developed in light of prior ERP studies using either
91 auditory,[5,18,19] visual[20-22] or somatosensory[23,24] stimuli, which have revealed aberrant
92 (hypersensitive and/or delayed responses) sensory-evoked responses in older adults. Sensory-
93 evoked response amplitude may be linked to widespread structural changes in prefrontal
94 regions of individuals with MCI.[25-35] Notably, lesions to prefrontal cortices have been associated
95 with an increase in amplitude of auditory, visual and somatosensory ERPs, which was attributed
96 to deficits in inhibitory control.[36,37] Moreover, sensory evoked response amplitude have been
97 associated with deficits in memory tasks.[38-40] Given these findings from studies measuring
98 sensory evoked response amplitude from a single sensory modality, we foresee that using
99 measurements from auditory, visual and somatosensory systems could significantly enhance
100 the sensitivity of EEG measures in detecting aMCI.

Evidence suggests that SVM algorithm can successfully identify older adults with MCI (including amnestic and non-amnestic subtypes) from healthy controls with accuracy ranging from 75% to 98% using speech-evoked responses[41] or resting-state EEG[42-44] depending on the number and type of EEG features analyzed. A recent study applying parameter optimized SVM classifiers to oscillatory-based functional connectivity data showed hearing status could be decoded during a speech categorization task solely using network-level descriptions.[45] Extending prior work,[45] we used adjusted connectome-based predictive modeling with SVM classifiers to distinguish older adults with a diagnosis of aMCI from healthy controls using EEG functional connectivity measures during processing of auditory, visual, and somatosensory stimuli. Given prior findings of aberrant sensory evoked responses in single sensory modalities, we hypothesize that correct classification of aMCI will increase when combining information for multiple sensory modalities compared to using information from a single sensory modality.

Methods

Participants

Participants were recruited if they were native English speakers or learned English before the age of five, had normal or corrected-to-normal vision (e.g., no history of degenerative conditions, glaucoma, cataracts significant enough to impede vision, or color blindness), and reported no significant hearing loss, no history of learning disabilities, stroke, transient ischemic attack, traumatic brain injury with loss of consciousness greater than five minutes, substance abuse disorder, history of intracranial surgery, and any other diagnosis of major neurological or psychiatric disorder. Participants were excluded if they had a history of myocardial infarction, coronary artery disease, or bypass surgery. Participants were also

excluded if they were prescribed hearing aids, taking medication known to possibly affect cognitive functioning including antidepressants, anticonvulsants, antipsychotics, or consuming recreational drugs either concurrently or within the year prior to testing. An inclusion criterion for older adults was scoring above the cut-off on the Telephone Interview for Cognitive Status-Modified (TICS-M).[46] Our final sample included 44 individuals with aMCI (62-88 years, 23 males), and 35 healthy older adult controls (60-88 years, 20 males). Participants were recruited from the Rotman Research Institute participant database. The study protocol was approved by the Research Ethics Board of the Rotman Research Institute at Baycrest. All participants provided informed written consent, and were compensated a modest stipend for their participation and out-of-pocket expenses incurred (e.g., parking).

Neuropsychological assessment

Preceding the recording of neuroelectric activity, participants were administered a battery of standardized neuropsychological tests in the domains of intellectual functioning, memory, language, processing speed, and executive functioning. The neuropsychological assessment took place on a separate day from measurements of sensory-evoked responses to prevent fatigue effects. Diagnosis of single-domain or multiple-domain aMCI was verified by a registered neuropsychologist. A full description of the administered neuropsychological assessments have been previously reported in Chow et al[47] and Rabi et al.[48] Demographic, neuropsychological, and clinical data for individuals with aMCI and age-matched controls are displayed in Table 1. The aMCI and control groups did not statistically differ in age, sex, or years of education.

Stimuli and multi-sensory evoked paradigm

The visual stimulus was a 5 by 10 square black and white checkerboard pattern presented at 50ms in duration that spanned the entire height and approximately 40% of the width of a 19-inch computer monitor that extended from either the left or right edge of the monitor. The entire checkerboard stimulus subtended a visual angle of 14.3° by 28.1°, with each checkerboard square subtending a visual angle of 2.9° by 2.9°. The auditory stimulus was a monoaural harmonic complex tone (50 ms in duration, 5 ms rise/fall time). It comprised five tonal elements (200, 400, 600, 800, and 1000 Hz) and had a fundamental frequency of 200 Hz. The tone was presented to the left or right ear through ER-3A insert earphones (Etymotic Research Inc., Elk Grove, IL, USA). The sound intensity was set at 85 decibels (dB) sound pressure level (SPL) as measured by a Larson Davis 824 SPL meter using a 2cc coupler. The somatosensory stimulus consisted of pneumatic tactile stimulation delivered simultaneously to the tips of all four fingers (thumb excluded) of the left or right hand. The somatosensory stimulation was delivered from a puff-type pressure stimulator from a compressed air tank with electromagnetic air valves kept constant at 30 psi through plastic tubes to 8 pneumatically driven inflatable circular plastic membranes with a diameter of 1 cm each. Each membrane was worn on the participant's fingers at the distal interphalangeal joint. During somatosensory stimulation, the valves were activated to periodically inflate the membrane and deliver brief pressure pulses of 50 ms duration to the fingertips.

Procedure

To measure sensory-evoked potentials, we used a continuous, rapid serial event-related paradigm in which lateralized visual, auditory, and somatosensory stimuli were presented sequentially in a randomized order. The paradigm was administered with participants seated in

167 a sound-attenuated booth. Before recording sensory evoked potentials, participants were
168 presented with a 10-second sample of the paradigm to ensure that they could clearly perceive
169 the auditory, visual, and somatosensory stimulation from both left and right hemispace. During
170 the stimulus presentation, participants were instructed to gaze on a fixation dot 0.60 cm in
171 diameter at the center of a 19-inch computer screen set at 100% contrast level and placed 60
172 cm from participants. The stimulus onset asynchrony varied between 200 and 340 ms (20 ms
173 steps, rectangular distribution). The stimulus presentation lasted approximately 12 minutes,
174 with a total of 1440 stimuli (480 trials per sensory modality) evenly distributed between left
175 and right laterality. Stimuli were presented using Presentation software (version 13,
176 Neurobehavioral Systems, Albany, CA).

177 **EEG Acquisition and Preprocessing**

178 Neuroelectric brain activity was recorded continuously using a 76-channel BioSemi
179 ActiveTwo acquisition system (BioSemi, Amsterdam, The Netherlands) with a sampling rate of
180 512 Hz. Sixty-six electrodes were positioned on the scalp using a BioSemi headcap according to
181 the standard 10-20 system with a pair of Common Mode Sense active electrode and Driven
182 Right Leg passive electrode serving as ground. Ten additional electrodes were placed below the
183 hairline (i.e., mastoids, pre-auricular points, two lateral ocular sites, two inferior ocular sites,
184 and two additional frontal-lateral electrodes) to monitor eye movements and cover the whole
185 scalp evenly. EEG recordings were preprocessed offline using FieldTrip toolbox[49] and custom
186 scripts.

187 The EEG data were first re-referenced to the average of all electrodes. Then,
188 independent component analysis was performed to remove the artifacts caused by eye blinks,

eye movements, and heartbeat. Next, the EEG data were bandpass filtered from 1 to 40Hz. Filtered data were parsed into 500 ms epochs time-locked to stimulus onset, including 100 ms of pre-stimulus activity and baseline corrected using pre-stimulus interval (-100 to -20 ms). Lastly, the preprocessed data were visually inspected to identify trials contaminated with artifacts and noisy electrodes; these trials were then rejected from subsequent analysis. Noisy electrodes were interpolated, with no more than 10% of the channels interpolated per participant.

We did not have a priori hypotheses regarding possible stimulus lateralization. Hence, as a dimension reduction method and to improve the signal-to-noise ratio, epochs of lateralized sensory-evoked potentials were averaged together in a transposed montage such that right-lateralized responses (elicited by left-lateralized stimuli) were kept untransposed, and left-lateralized evoked potentials (elicited by right-lateralized stimuli) were transposed across laterality. This transposition method allowed us to combine the evoked responses from lateralized stimuli, thereby significantly increasing the number of trials per modality.

Electrode-level functional connectivity matrix construction

A surface Laplacian method was applied to reduce the effect of volume conduction on functional connectivity estimates.[50] The surface Laplacian is a spatial filter that computes the second spatial derivative of the scalp potential, which provides a measure of the local current source density. Then, for each sensory modality, phase locking value (PLV), which estimated the phase synchronization of two signals, was calculated for estimating the functional connectivity between pairs of electrodes across 12 frequency bands ranging from 2.5 Hz to 30 Hz, with each band being 2.5 Hz in width (i.e., 2.5 Hz, 5 Hz, 7.5 Hz … 27.5 Hz, 30 Hz). Consequently, for each

participant, twelve 72 by 72 functional connectivity matrices were created for each stimulus modality per participant.

Adjusted connectome-based predictive modeling (CPM)

We adjusted the procedure from CPM[51] and used it with SVM learning to classify each participant as belonging to either the aMCI group or control group (Fig. 1). Functional connectivity matrices of each modality and frequency band were separately entered into the classification analysis. Leave-one-subject-out (LOSO) cross-validation was employed to evaluate classification performance (i.e., classification accuracy) for each electrode under each sensory condition. Specifically, for each cross-validation fold, matrices from 78 participants were used to build the model and the matrix from the left-out participant was used to test model performance. For each matrix, we first performed a two-sample independent *t*-test (two-tailed) on each edge between aMCI and healthy control groups using the training set. Edges that showed sufficient group difference ($p_{uncorrected} < 0.05$) were selected for training the SVM classification model with a linear kernel. A parameter search was performed using training data to optimize the cost value, which balanced the margin and training error, for each model and each stimulus modality (thereby maximizing the average accuracy of the top three frequency bands over the range $2^{-6}, 2^{-5}, \ldots, 2^{5}$). After training the model, the edges from the left out participant were used to test the model. With the LOSO cross validation procedure, every participant would be predicted to be in the aMCI or control group using the model trained by the selected functional connectivity edges of all other participants. Classification accuracy was calculated by averaging the accuracy across all folds. SVM classification analysis was conducted

using the LIBSVM package.[52] The selected edge masks in each fold were kept for visualizing the important edges that contributed to the classification.

We performed permutation testing to determine the statistical significance of the classification accuracy of each frequency band for each sensory modality. The labels of the participants were shuffled and used to perform the classification analysis described above. The number of permutations was set at 2000, which allowed us to separately construct the null distributions of classification accuracy for each frequency band under three sensory modalities. Permutation-based statistics were calculated based on the following formula:

$$\frac{accuracy_{real} - mean(accuracy_{permutation})}{standard\ deviation\ (accuracy_{permutation})}$$

The frequency-level permutation-based statistics was followed by cluster-based permutation tests to correct for multiple comparisons across frequency bands. The sums of the permutation-based statistics of contiguous frequencies that were significant ($p_{permutation} < 0.05$) were computed. Then, 2000 permutations were conducted and the largest permutation-based statistics-mass for each permutation was extracted to get the null distribution of the cluster level mass. Significance was set at a family-wise corrected *p*-value of $p_{fwe} < 0.05$ cluster-mass corrected.

SVM classification with sensory-evoked response amplitude

Besides functional connectivity matrices, we also performed SVM classification analysis using the amplitude of sensory-evoked potentials (Fig. 1). Averaged amplitudes for each modality were separately entered in the classification analysis. For each electrode, classifiers were trained using SVM algorithm with a linear kernel separately for the three modalities.

Similarly, LOSO cross-validation was employed to evaluate classification performance (i.e., classification accuracy) for each electrode in each sensory modality. A parameter search was also performed using training data to optimize the cost value for each model and each stimulus modality (thereby maximizing the average accuracy of top ten electrodes over the range $2^{-3}, 2^{-2}, \ldots, 2^{5}$). We used cluster-based permutation testing to determine the statistical significance of the classification accuracy of each electrode for each modality. Channel neighbors were defined by the FieldTrip function "ft_prepare_neighbours" with the "triangulation" method.[49] The sums of the permutation-based statistics of contiguous channels that were significant ($p_{permutation} < 0.05$) were computed. Then, 2000 permutations were conducted and the largest permutation-based statistics-mass for each permutation was extracted to get the null distribution of the cluster-level mass. Significance was set at $p_{fwe} < 0.05$ cluster-mass corrected.

Voting method for classification combining multiple modalities

We used voting strategies to combine the classification results from different modalities and indices. The frequency bands or electrodes that showed highest classification accuracy in each sensory modality were selected and entered in the voting procedure. We employed two strategies in the voting procedure: majority rule or one-vote veto rule. The majority rule denotes that whether a given participant is classified as belonging to the aMCI or control group is determined by most supporters (i.e., a participant was classified as belonging to one group if they were also identified as belonging to the same group in two or all three modalities). As for the one-vote veto rule, a given participant was classified as belonging to the aMCI or control

group only when all involved classifiers agree on aMCI status. The left-out participants were labelled as undetermined participants and were not included in the accuracy calculation.

Group comparison of evoked response from three modalities

Averaged sensory-evoked responses in the significant clusters under each modality were entered into the group comparison analysis between aMCI and control groups. Note that the participants with more than one channel that misclassified the participants were not included in the group comparison since they could not be classified with high consistency across channels. Independent-sample *t*-tests were performed to compare the group-averaged sensory-evoked amplitudes among significant clusters between aMCI and controls. Cluster-based permutation testing was performed to find clusters that showed significant group difference of sensory-evoked response amplitude between the two groups.

Brain-behavior correlation

Linear regression models were fit to examine the relationship between neural indices (functional connectivity estimates of the important edges, sensory-evoked response amplitude of significant clusters) and composite scores from the neuropsychological assessment (Table 1). Group variable (aMCI/healthy older adults) was set as the control variable in the linear regression models.

Results

Classification with unisensory prediction models

Firstly, with the adjusted CPM approach, we trained the SVM learning classifiers to predict whether a given participant belonged to the aMCI or control group separately with

294 unisensory functional connectivity matrices (visual, auditory, or somatosensory). We found
295 frequency clusters that showed significantly greater classification accuracy than chance for all
296 three sensory modalities (Fig. 2A). For visual stimuli, functional connectivity matrices from 2.5
297 Hz to 10 Hz and from 15 Hz to 17.5 Hz significantly predicted correct classification (i.e., whether
298 a participant belonged to the aMCI or healthy control group, 2.5hz-10hz: $p_{fwe} = 0.007$, 15hz-
299 17.5hz: $p_{fwe} = 0.040$). For auditory stimuli, the significant frequency bands were from 2.5 Hz
300 to 7.5 Hz and 12.5 Hz (2.5hz-7.5hz: $p_{fwe} < 0.001$, 12.5 hz: $p_{fwe} < 0.001$). For somatosensory
301 stimuli, the significant frequency bands were from 2.5 Hz to 12.5 Hz ($p_{fwe} < 0.001$).

302 Figure 2A shows classification accuracy per frequency band. Classification accuracies
303 tended to be higher for lower frequencies (i.e., delta, theta, and alpha) in all three modalities,
304 with the highest classification accuracy at 5 Hz (Fig. 2D, 69.6% for visual stimuli, $p_{permutation} =$
305 0.004, 89.9% for auditory stimuli, $p_{permutation} < 0.001$, 92.4% for somatosensory stimuli,
306 $p_{permutation} < 0.001$). The sensitivities of all three modalities were high, while the
307 specificities were relatively low (Fig. 2D, for visual stimuli, 79.5% vs. 57.1%; for auditory stimuli,
308 95.5% vs. 82.9%; for somatosensory stimuli, 95.5% vs. 88.6%). In other words, the fitted model
309 seemed to show good detection of participants with aMCI (i.e., better able to detect true
310 positives) but relatively poor detection of healthy older adults (i.e., resulting in a few false
311 positives).

312 We employed a voting method to combine the predictive power from three modalities.
313 With majority rule, the accuracy, sensitivity, and specificity of the model was similar to the
314 somatosensory modality, which showed the best performance (i.e., Fig. 2E, Accuracy: 91.1%;
315 Sensitivity: 95.5%; Specificity: 85.3%). The classification accuracy was calculated based on the

subset of participants for whom prediction from all involved classifiers were consistent. Therefore, there exists accuracy-proportion of predictable participant trade-off with one-vote veto rule. We found a slight increase of the performance compared to somatosensory classifier, but only 68.4% of participants could be accurately identified (Fig. 2E, F, Accuracy: 94.4%; Sensitivity: 100%; Specificity: 85.7%). With a voting procedure that combined three modalities, we found that specificity was still relatively low.

Functional connectivity strength predicted cognitive performance

We extracted all of the masks used for each fold. Since LOSO cross-validation was used in SVM classification, 79 masks were generated in the analysis. Masks were slightly different for each fold because training sets varied for each fold. We kept the edges that were preserved in most folds (> 90%), which were more important for the classification analysis than the rest edges.

We divided the electrode montage into five regions of interest (ROIs): frontal (frontopolar, anterior-frontal and frontal channels), temporal (frontotemporal and temporal-parietal channels), central (frontocentral and central channels), parietal (centroparietal and parietal channels), and occipital (parietal-occipital and occipital channels). Then, we summarized the positive and negative edge numbers that were kept according to the five ROIs separately for each sensory modality and significant frequency band. Note that, positive edges refer to the edges where aMCI showed higher functional connectivity estimates than healthy older adults, while negative edges refer to the edges where aMCI showed lower functional connectivity estimates.

Within lower frequency bands (i.e., delta, theta, and alpha bands), we found similar pattern of connectivity for the three modalities (Fig. 2B and 2C). That is, the aMCI group showed stronger functional connectivity than healthy older adults within frontal electrodes, as well as connectivity from frontal and central electrodes to posterior electrodes. Meanwhile, within beta band, we also found that aMCI showed greater functional connectivity than controls across the whole brain with visual stimuli. Besides the increased connectivity, we also observed weaker edges in the aMCI group that connected posterior regions like occipital, temporal, and parietal areas within lower frequency bands. Within beta band, we found increased frontal-central and temporal-parietal connectivity in the aMCI group.

Linear regression analysis was performed to investigate the relationship between functional connectivity of the important edges and cognitive performance from neuropsychological assessments. We separately summed the positive or negative important edges for three modalities as the independent variable in the linear regression analysis. Group variable was inputted to the model as the control variable. We found that functional connectivity that was higher in the aMCI group than healthy older adults predicted worse cognitive performance within both frequency bands (Table2, EF: Delta-Theta-alpha band: Visual: $\beta = -4.37$, $p = 0.005$; Somatosensory: $\beta = -3.60$, $p = 0.017$; Beta band: Visual: $\beta = -5.39$, $p = 0.010$). The higher functional connectivity in aMCI may reflect a loss of complexity in EEG dynamics, which has been associated with difficulties to adapt to new situations and could be a potential biomarker for aMCI diagnosis.[53-55] However, for functional connectivity that was lower in the aMCI group, we observed different results. Within beta band, weaker functional

connectivity between frontal and posterior areas predicted better performance on tests of language (Table2, Language: β = -5.92, p = 0.006).

Classification with unisensory evoked response amplitude

We also trained the SVM classifiers to predict whether the participant belonged to the aMCI or control group using the amplitude of sensory evoked responses (visual, auditory, or somatosensory stimuli). Compared to a null distribution of classification accuracy generated by permutation testing, we found significant clusters that showed significantly greater classification accuracy than null distribution under all three sensory modalities conditions (Fig. 3A-C). With visual stimuli, we found clusters that showed significant classification accuracy in left central-frontal areas (FP1, AF7, AF3, F3, FC3, $p_{fwe} = 0.003$) and right parietal areas (CP6, CP4, P6, CP2, P4, $p_{fwe} = 0.001$). With auditory stimuli, we found significant clusters in bilateral central areas (FC5, FC3, C1, Cz, C2, $p_{fwe} < 0.001$), left temporal-parietal areas (P7, PO7, PO9, TP9, $p_{fwe} = 0.020$, and right parietal areas (P6, P8, PO8, PO4, O2, $p_{fwe} < 0.001$). With somatosensory stimuli, we found significant cluster in right occipital areas (Iz, O2, $p_{fwe} = 0.040$).

As shown in Fig. 2D, with three modality stimuli, electrodes that showed highest classification accuracy were for visual stimuli (P8, classification accuracy = 79.7%; sensitivity = 81.8%; specificity = 77.1%), with auditory stimuli (P4, classification accuracy = 76.0%; sensitivity = 88.6%; specificity = 60.0%), and with somatosensory stimuli (Iz, classification accuracy = 79.7%; sensitivity = 84.1%; specificity = 74.3%). Again, similar to the model trained by functional connectivity matrices, specificity of the model is lower than the sensitivity.

Models trained with unisensory evoked response amplitude were not as good as models trained with unisensory functional connectivity. However, as for EEG connectivity, model performance increased significantly after combining three modalities using the voting procedure. With majority rule among classifiers of all three modalities, classification accuracy increased to 87.3% (Fig. 3E, accuracy = 87.3%, sensitivity = 93.2%, specificity = 80.0%). With one-vote veto rule, the model performance slightly increased compared to the model trained by functional connectivity. Classification accuracy increased to 97.5% (Fig. 3E-F, sensitivity = 100%, specificity = 92.3%) at the expense that only 50.6% of participants could be determined.

Reduced sensory evoked response amplitude in aMCI

To unravel what contributes to the predictability of the SVM classifier trained by averaged evoked responses from three sensory modalities, we compared the averaged sensory-evoked response amplitude among the significant clusters between the aMCI group and healthy older adults. Only clusters that contained no more than one electrode that generated false prediction were included.

With visual stimuli, we found a larger early positive component in healthy older adults than those with aMCI (Fig. 3G, from -28ms to 50ms, $p_{fwe} = 0.003$) over the frontocentral region ipsilateral to stimulus presentation. However, we did not find a significant difference in contralateral parietal areas. With auditory stimuli, we found that older adults showed greater amplitude in positive and negative waveforms peaking at about 200 and 300 ms after sound onset, referred to as P2 and N3, respectively (Fig. 3H, P2: from 171ms to 238ms, $p_{fwe} = 0.004$; N3: from 294ms to 338ms, $p_{fwe} = 0.004$) in central cluster, greater P2 amplitude (Fig. 3I, from 172ms to 249ms, $p_{fwe} = 0.002$) in a left temporal-parietal cluster, and greater P2 amplitude

(Fig. 3J, from 238ms to 283ms, $p_{fwe} = 0.016$) in right parietal cluster. With somatosensory stimuli, we failed to find any difference between two groups in lateral occipital regions.

Next, we employed linear regression to investigate the relationship between significant clusters and cognitive performance in older adults. After controlling for group as the control variable, we found that a greater N3 amplitude of the auditory evoked response in central regions significantly predicted higher speed composite scores ($\beta_{AEP} = -0.36, p = 0.029$).

Combining classification models trained by functional connectivity and ERPs

Since both models that were trained by connectivity measures and ERP amplitude after combining three modalities and the specificity were both relatively low with majority rule, we combined the six models (3 modalities × 2 neural indices) with voting procedure. With one-vote veto rule, only 35.4% of participants could be determined and therefore the model showed little utility. With majority rule, classification accuracy was 96.1%, and we got balanced sensitivity and specificity (Fig. 4A-B, sensitivity = 97.7%, specificity = 94.3%).

Discussion

In this study, we employed the SVM algorithm to classify individuals with aMCI and healthy older adults with electrode-wise functional connectivity matrices and sensory-evoked responses from auditory, visual, and somatosensory systems. We found that healthy older adults and those with aMCI could be reliably classified using neural indices for each sensory modality alone. However, we observed a significant increase in classification accuracy after combining both neural indices under all three sensory conditions with the majority rule voting

422 procedure, which yielded optimal classification accuracy (96.1%), sensitivity (97.7%), and
423 specificity (94.3%). With adjusted CPM analysis, we identified increased functional connectivity
424 within frontal and central regions in a lower frequency band and whole-brain functional
425 connectivity in the beta band, which were the major contributing features in classification.
426 Meanwhile, a group comparison of sensory-evoked response amplitude between correctly
427 classified participants with aMCI and healthy older adults showed smaller response amplitude
428 in the aMCI group than healthy older adults at central, frontal, parietal, and temporal
429 electrodes. Notably, these increases and reductions in connectivity were correlated with better
430 cognitive performance, namely executive functioning and speed, which suggest these features
431 could be sensitive to cognitive impairment that is often associated with aMCI.

432 Since individuals with aMCI often experience difficulty with complex decision-making,
433 experimental paradigms that are easy, fast, and require low cognitive demands are often used
434 in clinical assessment of aMCI. Hence, investigating resting-state brain activity, which is simple
435 and task-free, is popular in studies aiming to develop biomarkers for distinguishing aMCI from
436 healthy controls.[56,57] However, recent studies found that task-induced functional connectivity
437 may capture more behaviour-related information than resting-state functional connectivity,
438 even if the tasks during scanning are not directly relevant to the behavioral tasks.[58-60] For
439 example, Finn and Bandettini[59] found that functional connectivity during movie watching could
440 better predict watchers' trait-like phenotypes in both cognition and emotion domains than
441 resting-state connectivity. In the current study, we designed a paradigm for the passive
442 perception of simple stimuli from three different modalities. Our MSEP paradigm is as simple,
443 fast, and low in cognitive demand as the resting-state paradigm. Besides the well-performed

classification, we also found robust correlations of sensory-induced functional connectivity to cognitive performance. These results support that sensory-induced neural activities could capture some changes in cognitive performance associated with aMCI, even though these cognitive functions are irrelevant to the perceptual stimuli per se.

Neural indices from all three modalities provide information for distinguishing between older adults with and without a diagnosis of aMCI. However, the amount of information varies between modalities, leading to different classification accuracies ranging from 69.6% to 92.4% (sensitivity: from 79.5% to 95.5%; specificity: from 57.1% to 88.6%). This is consistent with previous finding that neural responses to single modal stimuli could be used to classify aMCI from healthy controls.[41,61-63] With our MSEP paradigm, we could obtain neural responses to different modalities in a single recording session, which enables us to combine informative component from different modalities for a better classification performance. Previous studies merging features from different modalities or sources usually combine features in the feature selection and model training stage and predict samples using the combined features. [41,42,61] The present study combines different features (i.e., amplitude of the evoked response, functional connectivity) under three sensory conditions in the prediction output session. With our strategy, model prediction performance markedly improved in accuracy, sensitivity, and specificity (accuracy = 96.1%, sensitivity = 97.7%, specificity = 94.3%).

The first advantage of our pipeline is the high flexibility. In the model training and test stages, the SVM algorithm could be replaced with any other machine learning or deep learning algorithms such as logistic regression or artificial neural networks. Then, permutation testing and the voting procedure could be performed in the same way as this study. Furthermore, the

voting procedure is a highly flexible method to combine information from different features because it does not require merging different features before or during the model training and testing phases. Therefore, any model or pipeline that produces a prediction label for each sample will apply to the voting procedure. This feature provides the advantage that different neural indices could be trained and tested using different algorithms since the optimal algorithm is not necessarily the same across different neural indices due to their divergent data characteristics and task types.[64]

One of the main challenges in applying machine learning methods to psychological or medical research is interpretability.[65] Another advantage of our analysis pipeline is providing insight into the neural mechanisms underlying successful classification. The adjusted CPM provides important edges that contribute to successful classification. A group comparison of neural indices among the correctly classified samples identifies significant components that distinguish the two groups. Therefore, these extracted components enable brain-behavior analyses to explore how changes in functional connectivity seen in aMCI are associated with cognitive impairment in this population.

Using PLV, we found that aMCI was associated with greater functional connectivity within central-frontal electrodes and greater functional connectivity from central-frontal electrodes to temporal electrodes including parietal, temporal, and occipital electrodes in the theta to alpha frequency bands. Meanwhile, older adults diagnosed with aMCI exhibited greater whole-brain functional connectivity in the beta band. Our findings complement prior research on resting-state functional connectivity in MCI, showing hypo- and hyper-connectivity in MCI compared to controls.[56] A recent meta-analysis of functional near infrared spectroscopy studies showed that

aMCI was associated with weaker functional connectivity between prefrontal and posterior parietal regions during resting state than healthy older adults.[66] However, for task-induced functional connectivity, older adults with aMCI showed stronger connectivity between medial left frontal cortex and temporal regions compared to healthy controls during tasks of working memory and naming.[66] These opposing results may reflect different constructs of brain functioning captured by resting-state functional connectivity and task-induced functional connectivity. Weaker functional connectivity at rest may suggest that aMCI-related deficits in the stability of intrinsic organization, while higher functional connectivity may suggest a loss of neural complexity in aMCI in service of sensory perception and goal-oriented tasks. Our correlation analyses of the most important edges to cognitive tasks also supports that the increased functional connectivity was correlated to impaired cognitive function in the aMCI group.

Besides functional connectivity, we also found that sensory-evoked response amplitude under all three sensory conditions are significant predictors of aMCI status. By comparing group differences in sensory-evoked responses, we found reduced amplitude at various latencies in all three sensory modalities. These results are consistent with previous studies investigating auditory- and visual-evoked response alterations in older adults diagnosed with MCI and early Alzheimer's disease compared to healthy controls.[67-70]

Previous EEG studies found that older adults displayed enhanced early sensory evoked response amplitude compared to young adults, which has been attributed to reflecting changes in sensory regulation mediated by the PFC.[17,36] The decreased amplitude of sensory-evoked responses in individuals with aMCI may also reflect further deficits in frontal regulation of

sensory responses attributed to early Alzheimer's disease-related degeneration of frontal and temporal areas. This result also is consistent with deficits in frontal functioning in aMCI, such as inhibition,[2] working memory,[71] and executive function.[72]

In this study, we introduced the novel MSEP paradigm that is suitable for the aMCI population and a classification analysis pipeline that enables researchers to flexibly combine features from different modalities and further explore the neural mechanism underlying the classification performance. Here, we employed the MSEP paradigm and classified older adults with aMCI from healthy older adults. Classification performance increased substantially after combining features from evoked potentials of multiple sensory modalities. Additionally, we found that the reduced sensory ERP amplitudes and increased functional connectivity in individuals with aMCI were the main contributors to the successful classification. These findings provide new insights into how EEG may be used to support the diagnosis and identification of neural biomarkers for aMCI and potentially other neurological disorders. Until now, past research has focused on examining sensory-perceptual processing in a single modality. Our study is the first to combine modalities providing a more comprehensive picture of sensory-processing deficits which improves classification accuracy of aMCI.

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Conflicts of Interest

The authors declare no conflicts of interest.

Consent Statement

All participants provided informed consent for participation.

Keywords: Aging, Evoked Potentials, EEG, sensory perception, mild cognitive impairment

Table 1

Participant Demographic and Neuropsychological Data

Variable	aMCI Means (SD) *n = 44*		HC Means (SD) *n = 35*	
	Raw	Scaled	Raw	Scaled
Demographics				
Age (years)	76.00 (5.82)	--	75.86 (6.99)	--
Education (years)	15.36 (2.76)	--	16.34 (2.29)	--
Sex (F:M)	20:20	--	15:20	--
TICS-m *	32.53 (3.49)	--	37.03 (3.04)	--
MoCA *	22.43 (2.97)	--	27.09 (2.34)	--
Estimates of IQ				
WAIS-III Matrix Reasoning *	21.30 (5.15)	13.09 (2.27)	24.14 (5.26)	14.40 (2.67)
Shipley Vocabulary	34.41 (3.77)	11.39 (2.93)	35.94 (3.28)	12.54 (2.70)
Memory				
CVLT-II Learning *	26.02 (8.13)	5.83 (2.14)	49.29 (9.77)	13.20 (2.96)
CVLT-II Short Delay FR *	2.43 (2.35)	3.83 (2.97)	10.31 (3.26)	12.40 (3.07)
CVLT-II Long Delay FR *	2.85 (2.47)	4.05 (2.89)	10.57 (3.32)	11.54 (2.82)
WMS-R Visual PA I *	7.61 (4.23)	8.89 (2.62)	11.97 (3.29)	11.71 (2.47)
WMS-R Visual PA II *	3.14 (1.85)	9.80 (2.21)	4.97 (1.40)	11.97 (1.72)
WMS-R Verbal PA I *	10.72 (6.40)	5.42 (2.73)	16.03 (2.96)	9.94 (2.25)
WMS-R Verbal PA II *	4.42 (1.92)	8.19 (3.07)	6.77 (1.17)	11.54 (2.49)
WAIS-III Digit Symbol IL FR *	4.70 (2.22)	7.07 (3.06)	7.31 (0.93)	10.43 (1.07)
WAIS-III Digit Symbol IL PR *	4.36 (4.50)	6.52 (3.47)	11.89 (4.32)	10.40 (1.42)
Language				
BNT-15	50.18 (8.71)	9.82 (3.38)	53.71 (4.93)	10.94 (2.82)
Phonemic Fluency (FAS)	40.41 (12.28)	9.93 (3.12)	47.40 (13.16)	11.46 (3.46)
Semantic Fluency (Animals) *	13.16 (4.56)	6.66 (3.18)	19.00 (5.27)	10.47 (3.59)
Executive Functioning and Processing Speed				
WAIS-III Digit Symbol *	49.70 (15.44)	10.57 (2.95)	60.97 (14.42)	12.80 (2.77)
D-KEFS Trails Numbers *	51.74 (21.40)	11.02 (3.51)	38.97 (12.18)	12.94 (2.18)
D-KEFS Trails Letters *	54.90 (23.32)	10.71 (3.11)	37.74 (11.41)	12.89 (1.64)
D-KEFS Trails N-L Switch *	142.60 (62.42)	9.18 (4.34)	98.97 (37.95)	12.03 (2.51)
D-KEFS CWIT Colour *	34.40 (7.88)	10.00 (3.03)	30.55 (5.59)	11.54 (2.22)
D-KEFS CWIT Word	25.82 (8.27)	10.20 (3.59)	22.85 (4.56)	11.17 (2.93)
D-KEFS CWIT Inhibition *	75.29 (26.53)	10.59 (3.24)	57.59 (13.69)	12.91 (1.90)
Alpha Span Stop Point	21.41 (6.19)	8.46 (2.58)	28.51 (9.28)	10.60 (3.10)
WCST Perseverative Errors % *	23.12 (12.65)	9.93 (3.43)	14.12 (10.19)	13.20 (4.41)

WCST Categories	3.93 (2.29)	--	4.66 (1.94)	--
Questionnaires				
HADS Anxiety	4.74 (3.67)	--	4.69 (2.89)	--
HADS Depression	2.74 (2.25)	--	2.51 (2.16)	--
EPW	5.81 (4.15)	--	6.69 (2.96)	--
PSQI	5.05 (2.74)	--	5.76 (2.99)	--
MAC Abilities *	59.85 (9.29)	8.22 (2.41)	68.86 (9.75)	10.69 (2.44)
FAQ	1.81 (2.29)	--	--	--

Note. TICS-m = modified Telephone Interview of Cognitive Status; MoCA = Montreal Cognitive Assessment; WAIS-III = Wechsler Adult Intelligence Scale, 3rd edition; CVLT-II = California Verbal Learning Test, 2nd edition; FR = Free Recall; WMS-R = Wechsler Memory Scale – Revised; PA = Paired Associates; PR = Paired Recall; IL= Incidental Learning; BNT-15 = Boston Naming Test, short form; FAS = phonemic fluency to the letters F, A, and S; D-KEFS = Delis Kaplan Executive Functioning System; CWIT = Colour-Word Interference Test; N-L = Number-Letter; WCST = Wisconsin Card Sorting Test; HADS = Hospital Anxiety and Depression Scale; EPW = Epworth Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index; MAC = Memory Assessment Clinics Self-Rating Scale; FAQ = Functional Assessment Questionnaire. Scaled scores: mean =10, SD = 3. For normed assessments, tests of significance were run on scaled scores. *aMCI ≠ HC, $p < .05$

Table 2

Linear regression results. Regression coefficients and corresponding p values (in parenthesis) between summed functional connectivity and cognitive performance after controlling group.

	Edge Strength	Memory	Speed	EF	Language
Delta-Theta-Alpha band	V: aMCI > HC	0.03 (0.982)	-2.09 (0.099)	-4.37 (0.005)	-2.07 (0.264)
	A: aMCI > HC	1.00 (0.554)	-1.57 (0.306)	-3.57 (0.063)	-2.38 (0.284)
	S: aMCI > HC	-0.28 (0.833)	-1.18 (0.328)	-3.60 (0.017)	-1.74 (0.321)
	A: aMCI < HC	2.13 (0.243)	0.50 (0.764)	1.19 (0.569)	0.34 (0.889)
	S: aMCI < HC	1.88 (0.272)	2.44 (0.115)	2.68 (0.172)	1.29 (0.571)
Beta band	V: aMCI > HC	-2.71 (0.143)	-3.17 (0.058)	-5.39 (0.010)	-3.65 (0.135)
	V: aMCI < HC	-0.01 (0.993)	-2.15 (0.154)	-2.55 (0.180)	-5.92 (0.006)

Note: EF = executive functioning; HC = healthy control;

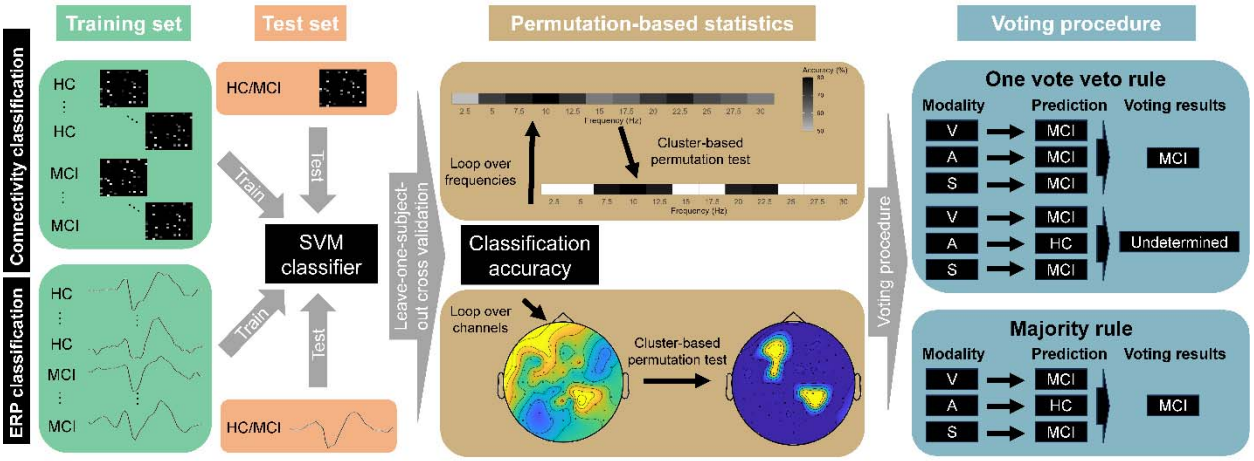

Fig. 1. Classification procedure illustration. We separately performed SVM classification analyses using functional connectivity matrices or ERP for each sensory modality (for details, please see methods). With leave-one-subject-out cross validation, we obtain classification accuracy of each frequency or electrode for each sensory modality. Next, we performed permutation-based test for the significance and statistics of each frequency or electrode for each sensory modality (for details, please see methods). Lastly, we employed the voting procedures to combine the output from difference neural indices evoked by stimuli from difference sensory modalities to perform the prediction.

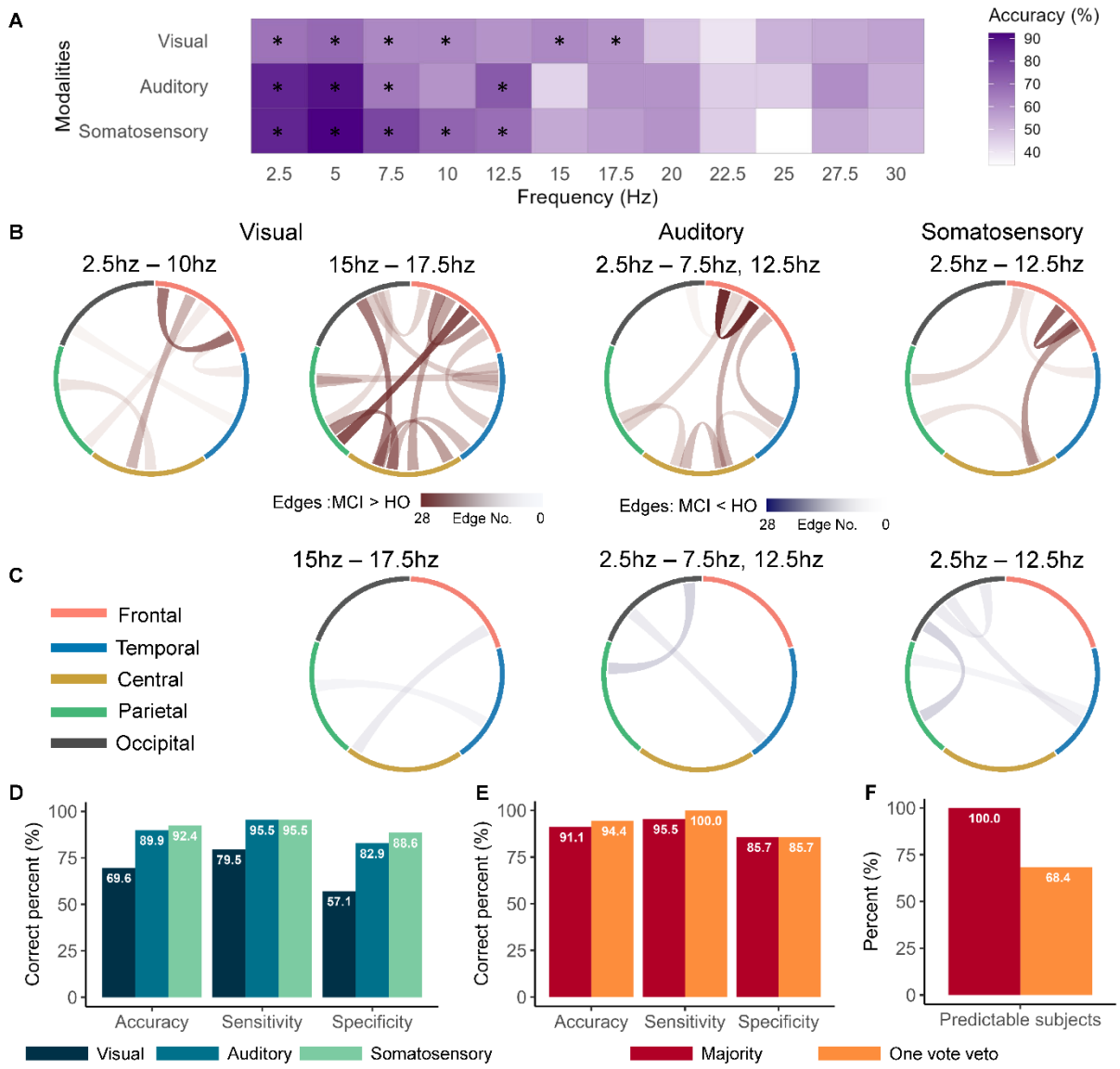

Fig. 2. Classification results using functional connectivity matrices. A. Classification accuracy at different frequency bands for three modalities. *denotes the significant frequencies for each modality after cluster-based correction. B-C, Summarized the positive (B) and negative (C) important edge numbers that were kept according to the five ROIs (frontal ROI: frontopolar, anterior-frontal and frontal channels, temporal ROI: frontotemporal and temporal-parietal channels, central ROI: frontocentral and central channels, parietal ROI: centroparietal and parietal channels, and occipital ROI: parietal-occipital and occipital channels), Important

connectivity edges were those edges that preserved in more than 90% folds. D-F, Classification accuracy, sensitivity, and specificity of the top frequencies (D), voting results combining three modalities (E), predictable subject percent (F).

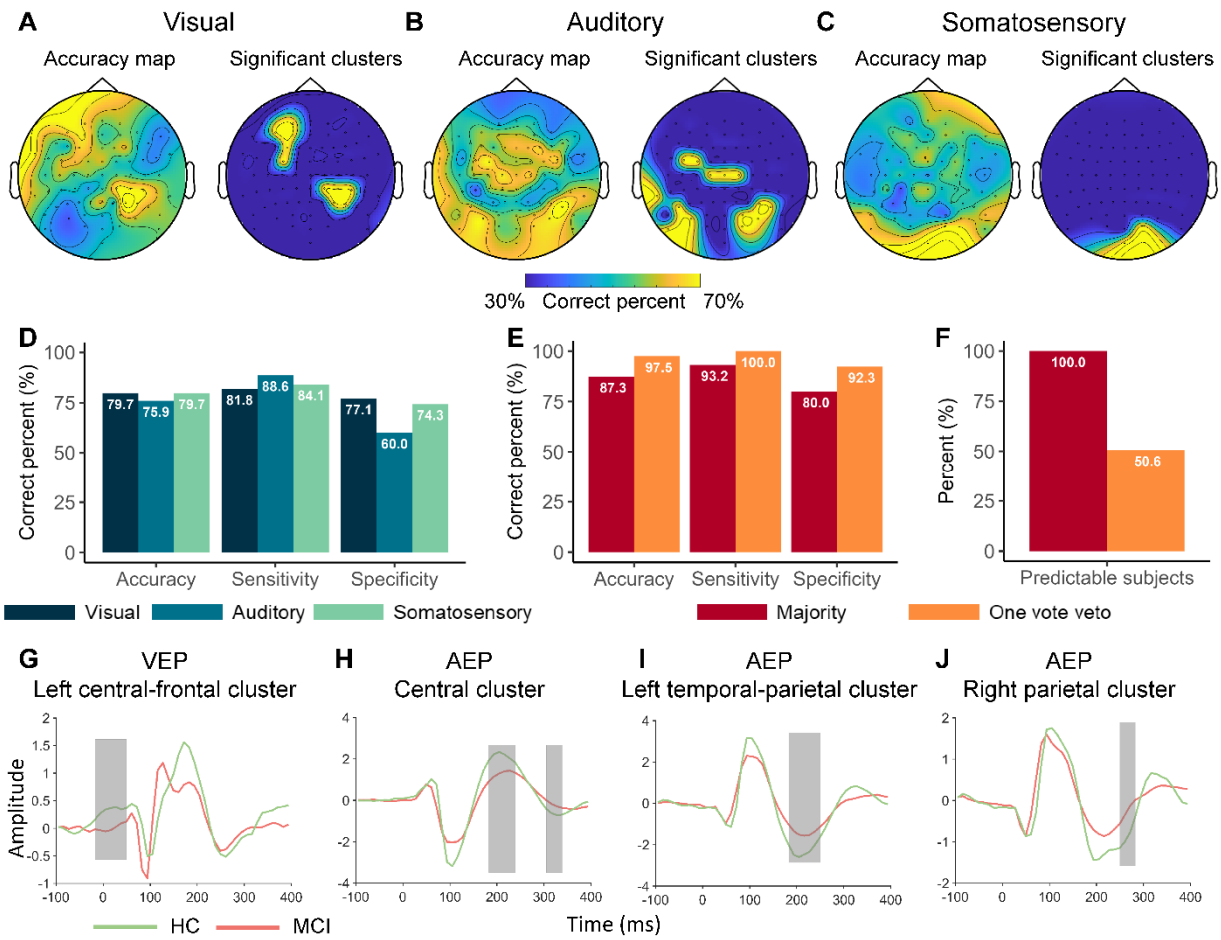

Fig. 3. Classification results using ERP. A-C, Topoplot (left: unthresholded accuracy map; right: significant clusters) of prediction accuracy for visual (A), auditory (B), and somatosensory (C) modalities. D-F, Classification accuracy, sensitivity, and specificity of the top electrodes (D), voting results combining three modalities (E), predictable subject percent (F). G-J, Averaged ERP of the significant clusters.

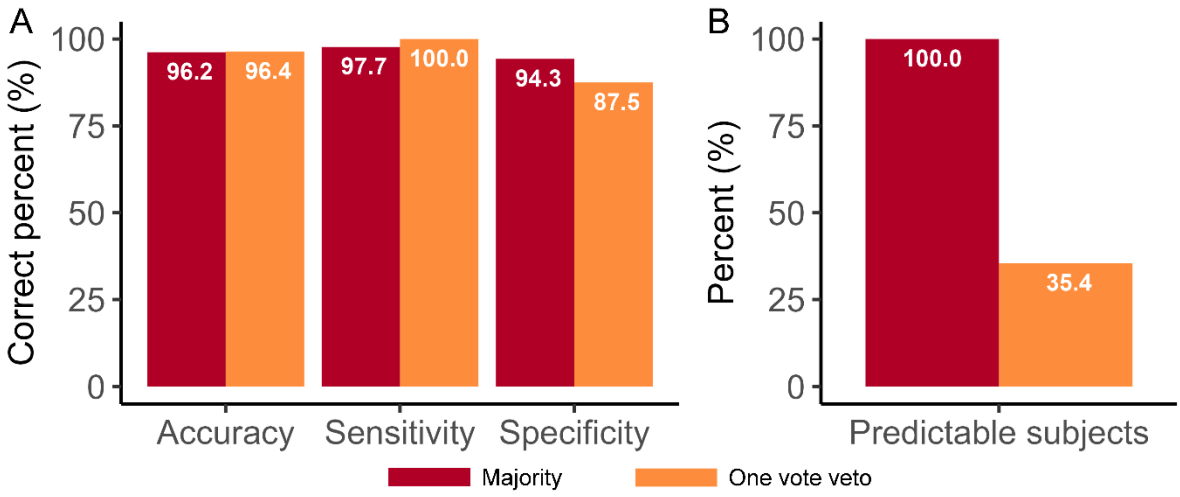

Fig. 4. Voting results combining six models. We employed majority rules and one vote veto rules to make predictions based on the predictions from the models trained by functional matrices or ERP evoked by visual, auditory, and somatosensory modalities. A-B, Classification accuracy, sensitivity, and specificity of voting results combining three modalities (A), predictable subject percent (B).