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Advances in Computational Psychophysiology

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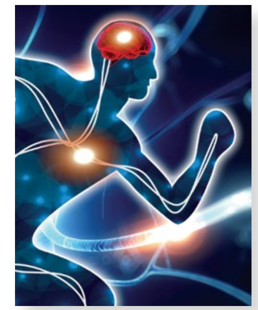
Advances in Computational Psychophysiology



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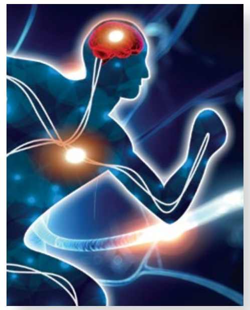

When the old becomes new again

In the West in general, and the United States in particular, the last few decades have seen a rise in the acceptance of many seemingly new customs and cultures from the East.

For all the talk these days about the differences between nations and peoples across the globe, there exists far more sharing of cuisines, religions, ideas, and cultures than ever before. In the West in general, and the United States in particular, the last few decades have seen a rise in the acceptance of many seemingly new customs and cultures from the East. Putting aside for the moment the fact that many of these beliefs and practices are found among Native Americans, to the majority of the U.S. population, they are unfamiliar.

One such belief is that of the mind–body connection. Although taken for granted in Eastern philosophies, this concept can be foreign to many living in Westernized nations, where the mindset seems to be more towards reductionism than holistic thought. Psychophysiology is essentially the study of this mind–body connection, or the relationship between the physiological and the psychological. The first known use of the term was in 1839[1] and its popularity grew rapidly in the 1960s, peaking around 1980 and then going into a steady decline.[2] However, this is apparently not a reflection on the field of psychophysiology, which is quite active and boasts a number of international journals covering the topic.

What is new in this *Advances in Computational Psychophysiology* supplement is the marrying of psychophysiology with the relatively recent surge in the power of computers. This has allowed psychophysiology researchers to perform far more complex analyses of their data, as well as incorporate technologies that can provide much richer information and therefore a deeper understanding of the processes involved. Powerful imaging technologies such as positron emission tomography and functional magnetic resonance imaging are enabling researchers to look inside the brain with unprecedented clarity, as well as in real time. This technology is allowing them to better understand and potentially treat a range of neurological disorders including neurodegenerative diseases, mild cognitive impairment, attention deficit hyperactivity disorder, psychiatric disorders, stroke, autism, and depression, among others. Much of this work is translational in nature, with a clear focus on helping patients in a fundamental way.

This research also has ramifications for how we might interact with computers in the future through brain–machine interfaces. The ability to collect and analyze multimodal measurements/inputs, in combination with advanced machine learning techniques may lead to a better grasp of the complexities of human emotions and how we both experience emotion and perceive it in others. In the future, machine learning technology could even conceivably aid in the diagnosis of depression and predict suicidal tendencies.

This supplement touches on a number of these topics and provides just a sample of the many ways in which the field of computational psychophysiology is growing and maturing. In addition to shedding light on many important areas of psychology, it may also provide a medium through which the mind-body connection can be appreciated and understood by a broader audience.

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[1] www.merriam-webster.com/dictionary/psychophysiology
[2] Google Books Ngram Viewer, bit.ly/1PBxyNB

Introducing computational psychophysiology

The majority of the papers presented in this volume emphasize how important bodily measures are for the study of a wide variety of mental and physical disorders.

Advances in Computational Psychophysiology reflects an intention on the part of the authors to introduce a new interdisciplinary field. Naming subfields within the disciplines of psychology and neuroscience has played an important role in directing research efforts.

Both the terms psychophysiology and computation have long been used in the study of human behavior, and the combination seems apt. The majority of the papers presented in this volume emphasize how important bodily measures are for the study of a wide variety of mental and physical disorders—a very traditional use of psychophysiology—and the incorporation of quantitative methods for interpreting data is clearly important.

The authors surely intend to provide methods and direction to researchers who are examining the nonbrain physiological processes, as a response to the findings that many of our thought processes draw on metaphors based upon the structure and behavior of the human body (*1*). The study of the embodied mind has resulted from, and increased research into, these ideas. This goal is most explicitly stated by Van Dam et al. (p. 16), who argue that the default state of brain activity can best be seen as a bodily state that produces changes in brain networks (*2*).

These articles also promote quantitative methods that summarize the output of various measures of the body and brain. For example, Zhang et al. (p. 30) advocate for single-trial analysis of electroencephalographic oscillations to study decision making, and Zhang et al. (p. 40) use neurofeedback as a method to improve working memory. Further, novel methods for acquiring data are discussed, such as use of the Internet (Zhao et al., p. 51), musical stimulation (Lu, Wu, and Yao, p. 47), and acupuncture (Qin et al., p. 38).

This supplement highlights how the synthesis of new measurement methods, quantitative analyses, and awareness of the interaction between the body and the brain can illuminate the way specific operations and tasks are carried out in the brain, such as conflict processing (Yang et al., p. 33) and implicit sequence learning (Fu et al., p. 22). Notably, Woo and Wager summarize the development of predictive methods, including multivoxel pattern analysis for magnetic resonance imaging (p. 18).

It may be well to consider both the intended consequences of introducing the topic of computational psychophysiology, but also the unintended consequences. It would be unfortunate, for example, if an increased emphasis on this field led researchers to substitute peripheral measures in place of brain-imaging methods. As the field progresses, researchers will need to find a good balance between now traditional imaging methods with those introduced in this volume.

Although understanding the embodied mind is essential, proponents of the computational psychophysiology approach should remember that the brain is also an organ that is a part of the body.

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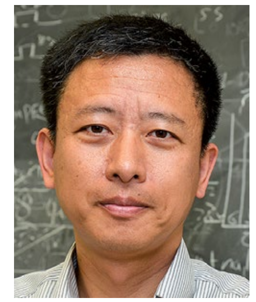

Computational psychophysiology

Working at the intersection of the mind and body, psychophysiology studies the effects of psychological states on physiological processes and vice-versa.

We are pleased to introduce this special supplement, *Advances in Computational Psychophysiology*, which encompasses contemporary research using computational methodologies to explore psychophysiological processes related to the interaction among the human brain, body, mind, and behavior. This special supplement also explores novel applications of computational psychophysiology, such as biomarker identification for mental illness.

The field of psychophysiology investigates the physiological basis of psychological processes. Working at the intersection of the mind and body, psychophysiology studies the effects of psychological states on physiological processes and vice-versa. In its nascent stages, psychophysiological research predominantly focused on relatively peripheral markers of autonomic nervous system activity by measuring fluctuations in a subject's electrodermal activity (EDA), electromyogram (EMG), electrogastrogram (EGG), electrocardiogram (ECG), heart rate, heart rate variability (HRV), respiration rate, electrooculogram (EOG), and pupillary dilation. In recent years, psychophysiology has begun to focus on the central nervous system, partially as a result of increasing accessibility and growth in measures of brain activity, such as event-related potentials (ERPs), magnetic encephalography (MEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). These methodologies offer more proximal measurement of brain (and mind) activity than indicators of the autonomic nervous system, which require inferences from fluctuations in peripheral responses.

To study the human brain, mind, and behavior, autonomic and central psychophysiological indices must be analyzed in combination, a feat that requires advanced computational approaches. The implementation of these approaches in psychophysiology is the focus of this supplement. Computational psychophysiology is an interdisciplinary research field that employs methods from the disciplines of psychology, physiology, neuroscience, computer science, mathematics, physics, and others to model physiological activity in relation to the psychological components of human behavior. Computational modeling provides a framework for understanding the numerous physiological processes underlying complex human mental states and behavior. Computational models can be used to simulate and predict psychological outcomes based on different physiological states or experimental manipulations.

This new direction will broaden the field of psychophysiology by allowing for the identification and integration of multimodal signals to test specific models of mental states and psychological processes. Additionally, such approaches will allow for the extraction of multiple signals from large-scale multidimensional data, with a greater ability to differentiate signals embedded in background noise. Further, these approaches will allow for a better understanding of the complex psychophysiological processes underlying brain disorders such as autism spectrum disorder, depression, and anxiety. Given the widely acknowledged limitations of psychiatric nosology and the limited treatment options available, new computational models may provide the basis for a multidimensional diagnostic system and potentially new treatment approaches.

Applying computational data analysis and modeling to psychophysiological signals may thus help to identify new phenotypes for normal and abnormal psychological functions. The further development of computational strategies has the promise of providing large-scale models of the neural substrates of human behavior.

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Brain disorders

Computational psychophysiological approaches can be used to investigate the cognitive processes and mechanisms underlying disorders that cause mental health issues.

Magnetic resonance imaging of mental disorders: A multimodal approach for psycho-radiology

Su Lui[1], Du Lei[1], Weihong Kwuang[2], Hua Ai[3], Feng Bi[4], Zhongwei Gu[3], Qiyong Gong[1*]

Magnetic resonance imaging (MRI) is an emerging and powerful tool for noninvasively examining the structure and function of the brains of patients with mental disorders. Over the past two decades, the number of psychiatric MRI studies has increased dramatically, largely due to the significant advances in technical and methodological improvements in MRI modalities. This has led to a wide range of applications for clinically oriented research on mental disorders.

The development of the multimodal MRI has enabled the precise quantification of brain tissue at the structural, functional, and molecular levels (*1–6*). Using high-field MRI (i.e., 3.0 Tesla MR), for instance, the structural and functional correlates underlying a number of mental disorders have been identified. Taking advantage of novel approaches and techniques for the acquisition and analysis of MRI data, a number of clinical studies have revealed imaging biomarkers in populations that are at high risk for developing mental disorders (*7–12*). Moreover, such biomarkers for mental disorders provide further insight into their underlying pathological mechanisms (*13–21*). The results not only support the U.S. National Institute of Mental Health (NIMH)'s recent Research Domain Criteria (RDoC) project, which focuses on investigating the biological underpinnings of mental disorders (*22*), but also provide a preliminary step toward the translational use of high-field MRI for diagnosing, predicting, and monitoring a patient's response to treatment.

For example, multimodal MRI neuroimaging of treatment-naïve patients with first-episode schizophrenia gave us the opportunity to examine fundamental brain changes caused by the disease, unrelated to medication (*13, 23, 24*). Both the short-term and long-term effects of antipsychotic treatments on a patient's brain can be investigated using a connectivity analysis of resting state functional MRI (R-fMRI) data (*25, 26*). One such analysis revealed elevated prefrontal brain connectivity in patients with schizophrenia, which appears to be a robust biomarker associated with the clinical severity of the disorder (*26*); however, this directly contrasts the results of other studies (*14, 21, 27*). Sun et al. at the West China Hospital of Sichuan University recently carried out a cross-sectional diffusion tensor imaging study of a large cohort of 113 medication-naïve patients with first-episode schizophrenia and 110 demographically matched healthy control individuals (*28*). By employing a data-driven analysis scheme, they identified two subgroups of patients with schizophrenia defined by different patterns of white matter abnormalities. The group with more severe and widespread white matter pathology had more severe negative symptoms, such as reduced social engagement and emotional expression, and lack of motivation. The findings suggest that patterns of white matter abnormalities may provide a promising biomarker for subtyping patients with schizophrenia for studies investigating the disease's underlying mechanisms, as well as for quantitative phenotyping for genetic research.

Furthermore, how the disorder and treatments affect different brain regions over the long term are key issues under investigation. Zhang and colleagues have begun to address these questions with a study of 25 chronic patients with untreated schizophrenia over a duration of 5 to 47 years who were compared with 33 demographically matched (age, sex, and years of education) healthy individuals. The group reported an increased rate of prefrontal and temporal cortical thinning and striatal hypertrophy that may represent key changes in brain pathophysiology over the disorder's progression, effects that could not be attributed to antipsychotic treatment. No doubt, their findings provide important insights into the course and regional specificity of progressive brain changes associated with schizophrenia in the decades following onset (*29*).

In summary, efforts by researchers to better understand and treat psychiatric disorders have been increasing, reflecting the greater awareness of mental illness worldwide. This is best exemplified by the psychoradiological (i.e., psychiatric imaging) research that allows us to obtain various objective radiological signs (i.e., imaging biomarkers) of mental disorders, which could be used in a clinical context. For example, the application of functional imaging biomarkers has enabled the quantitative prediction of post-traumatic stress disorder (PTSD) symptoms in the individual psychopathology of trauma survivors, as assessed by a 17-item self-report measure of PTSD symptoms (*11*). In addition to the aforementioned major mental illnesses, psychiatric MRI findings and relevant methodological developments have been reported for other disorders, e.g., obsessive-compulsive disorder

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and attention deficit hyperactivity disorder (*19, 20, 30–33*). The results—especially those using MRI to predict the treatment response for individual patients with depressive disorder—may represent an initial step toward the use of psychoradiological findings to inform early clinical diagnoses as well as effective treatment for patients with mental disorders (*18*). Additionally, recent advances in MRI tools, such as the development of novel imaging probes (*34–37*), are enabling the underlying neuropathology of psychiatric disorders to be investigated at the molecular level. In particular, the development of novel quantitative MRI methods such as macromolecular tissue volume estimation (which is a consistent quantitative measure of brain anatomy and can be obtained across a range of scanners) (*1*), and magnetic resonance fingerprinting (which permits the noninvasive quantification of multiple material or tissue properties simultaneously through a new approach to data acquisition, post-processing, and visualization) (*2*), if validated clinically, will no doubt expedite the translation of psychoradiological discoveries into patient care.

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Multiscale neuroimaging analysis in Alzheimer's disease and mild cognitive impairment

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Alzheimer's disease is the most common form of dementia and impedes the daily life of patients by disrupting their cognition and memory. Clinical symptoms include a decline in memory, learning, communication, and reasoning. In the Western world, approximately two-thirds of patients with dementia who are over 60 years old have Alzheimer's disease (*1, 2*). At present, it is incurable and effective treatments are not available (*3*).

Mild cognitive impairment (MCI) is an early stage in the transition to Alzheimer's disease, and people with MCI have a high risk of acquiring Alzheimer's disease (*4, 5*). MCI is characterized by mild clinical symptoms involving cognitive impairments that are not significant enough to interfere with daily activities (*4*). Neuroimaging technologies can provide biomarkers that are potentially useful for providing early alerts as to the likelihood of a patient presenting with Alzheimer's disease. They can also provide a means for identifying Alzheimer's disease at the earliest stage possible, which is critical for developing treatments that will slow its progression.

Neuroimaging technologies such as structural and functional magnetic resonance imaging (MRI) and positron emission tomography (PET) (*5–7*) are increasingly effective and precise. Using these techniques, we have carried out voxel-based studies and analyzed the surface-based morphology and brain networks within regions of interest (ROIs) in subjects with MCI and Alzheimer's disease, and in healthy controls. These studies have successfully detected abnormalities in brain volume, cerebral cortex thickness, structural and functional connectivity, and the topology of structural and functional networks (*4, 6, 8–10*). The data are available in the open access Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu/).

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In this review, we discuss how neuroimaging technologies are being used to understand the effects of MCI and Alzheimer's disease on brain structure, function, and metabolism. Such methods could potentially be used to identify biomarkers that can help classify and predict the stages of these diseases.

Mesoscale: Voxel-based morphology analysis

Technologies that monitor mesoscale changes in the brain can provide data reflecting properties that are regionally specific. One such method is voxel-based morphology analysis. This technique has been used to measure the progression of mesoscale changes in patients with MCI and Alzheimer's disease and has revealed that these patients undergo a loss of gray matter volume in specific brain regions, including the parahippocampal gyrus, hippocampus, left amygdala, and left fusiform gyrus (*9*). These studies have shown that patients with Alzheimer's disease have alterations in the surface morphology of the cerebral cortex, loss of gray matter volume, atrophy of cortical thickness, and a decline in cerebral glucose metabolism (Figure 1) (*6–9*).

MRI-based neuroimaging technologies can also be used to explore the relationship between brain structure and function and to investigate atrophy within particular brain regions in patients with MCI and Alzheimer's disease (*11*). Interestingly, our analysis of surface-based morphology using structural MRI data has revealed atrophy in the parahippocampal gyrus, a brain region in the cerebral cortex known to be influenced by MCI and Alzheimer's disease. Moreover, our longitudinal studies have shown that the rate of atrophy in the parahippocampal gyrus in patients with amnestic MCI is more pronounced than in control patients (Figure 1D) (*6*). Voxel-based analyses of PET data have also indicated that, concordant with changes in the morphology of the cerebral cortex, the brains of patients with Alzheimer's disease show reduced metabolism in the parahippocampal gyrus (Figure 1C) (*7*).

Detection of regional homogeneity (ReHo) and fraction amplitude of low-frequency fluctuations (fALFF) represent other powerful tools for characterizing properties of regional brain activity (Figure 1B) (*8*). ReHo evaluates resting-state brain activity (*5*), whereas fALFF measures the ratio of the fluctuant amplitude in a low-frequency band to the fluctuant amplitude in the total frequency band (*8*). A study comparing the ReHo values in subjects with Alzheimer's or MCI with healthy controls showed the values were significantly decreased in the patients' medial prefrontal cortex, the bilateral posterior cingulate gyrus/precuneus, and the left inferior parietal lobule (IPL), and were increased in the left IPL (Figure 1A) (*5*). Additionally, subjects with MCI alone had lower fALFF values in the postcentral gyrus, the right inferior temporal gyrus, and the left inferior occipital gyrus as compared with healthy controls (*8*).

Macroscale: Brain network visualization

Macroscale analysis depends on the correlation of data from spatially separate brain regions that can be

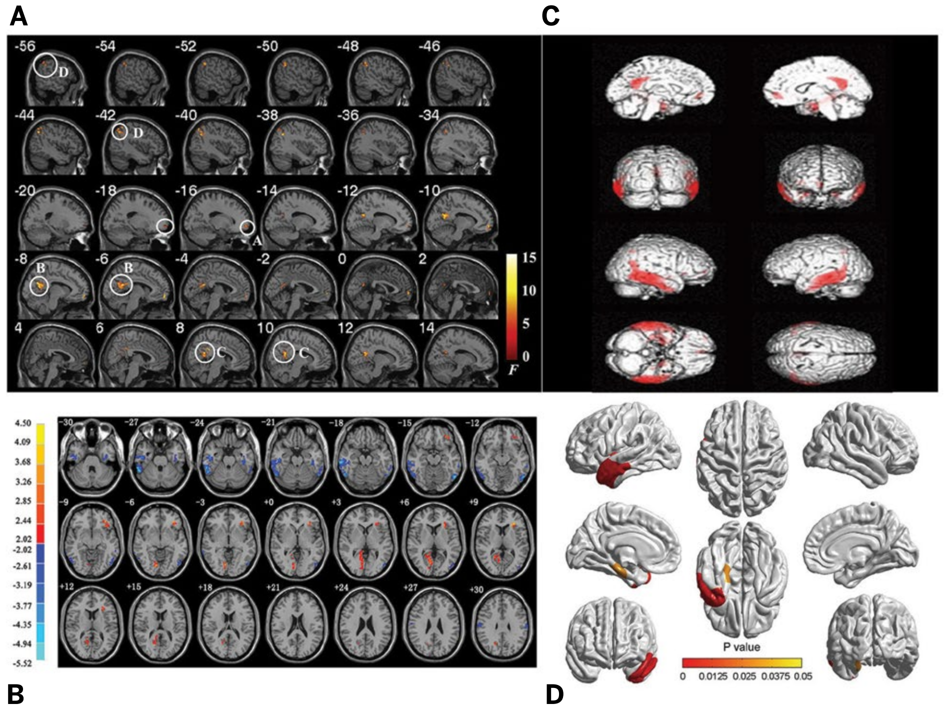
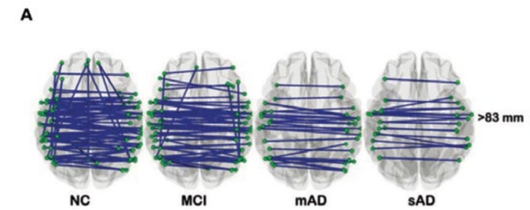


FIGURE 1. Differences in regional properties between patients with Alzheimer's disease, mild cognitive impairment (MCI), and normal controls (NCs). (A) Significant differences in regional homogeneity in patients with Alzheimer's disease and MCI (*5*). **(B)** Significant differences in fraction amplitude of low-frequency fluctuations (fALFF) between amnestic MCI (aMCI) and NC groups (*8*). **(C)** Differences in metabolism in brains of patients with Alzheimer's disease compared to normal controls (*7*). **(D)** Differences in rate of atrophy between aMCI and NC groups (*6*).

integrated to study whole-brain networks, or the human "connectome" (the connection matrix, Figure 2). Brain networks can be constructed from neuroimaging data, wherein ROIs are defined as "nodes." ROIs can be created by segmenting readily available atlas images (such as those from Automated Anatomical Labeling, Brodmann, and Harvard-Oxford) or by extracting spatial components by independent component analysis [ICA, a multivariate and data-driven method extracting independent resting-state networks (RSNs) from the Blood Oxygen Level Dependent (BOLD) time series].

We and others have shown that patients with MCI and Alzheimer's disease have abnormalities in specific structural and functional brain networks (*4, 10*). Using structural and functional MRI, we have defined several common differences between patients with MCI and Alzheimer's in brain covariance networks, as constructed by correlations between ROIs. The most significant of these common differences is a disruption of relatively long-distance connections (>83 mm, the mean physical distance between brain regions, Figure 2A and B) (*4, 10*). The disruption of long-distance connections represents the loss of global efficiency. However, networks with small-world topology—brain networks that are graphically represented by high clustering coefficients and low characteristic path lengths—have higher efficiency at lower connection costs. In such small-world networks, most nodes that are not close to one another can be reached from every other node by a small number of steps. In patients with MCI or Alzheimer's disease, increases in the clustering coefficients and shortest paths have been reported. Specifically, in functional and structural networks, clustering coefficients were significantly increased among Alzheimer's subjects compared with healthy controls (*4, 12*). Clustering coefficients are related to local efficiency. Information dissemination and information processing may be more efficient in a network with a shorter absolute path length and higher global efficiency (*4*). Furthermore, an analysis of voxel-based structural networks showed that in subjects with MCI, the clustering coefficient and the shortest path length of the cortical network fell between the median values of healthy controls and patients with Alzheimer's disease. This data supports the concept that MCI is a transition stage from the normal state to Alzheimer's disease (*4*). Furthermore, the data from these voxel-based structural networks are consistent with those from cerebral cortex thickness-based networks studies, in which increased clustering coefficients and shortest path lengths were also reported (*13*). Reduced efficiency of networks was associated with cognitive impairment in the Alzheimer's disease and MCI patient groups. More severe forms of Alzheimer's disease are related to fewer long-distance connections (*10*).

The metric used to measure the importance of a region within a brain network is betweenness, a measure of the centrality of a node in a graph. The betweenness of a node is defined as the number of shortest paths that are between any two other nodes and that run through the node. Important brain regions are termed hub regions, for which betweenness values exceed twice the average of the betweenness value of the network. Interestingly, subjects with MCI and Alzheimer's disease show a loss of hub



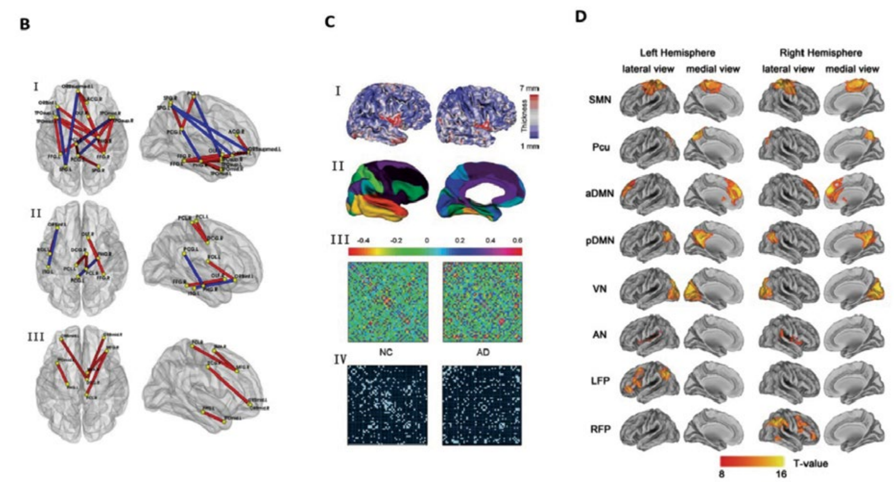


FIGURE 2. Depiction of "connectome" network, based on structural and functional MRI, highlighting the differences in small-world properties. (A) Long-distance connections in normal controls (NC) as well as patients with mild cognitive impairment (MCI), mild Alzheimer's disease (mAD), or severe Alzheimer's disease (sAD) (*10*). **(B)** Differences in interregional connectivity between patients with Alzheimer's or MCI, and NCs: Panel I shows significant changes between the NC and Alzheimer's disease groups; Panel II shows significant changes between the NC and MCI groups; Panel III shows significant changes between the MCI and Alzheimer's disease groups (*4*). **(C)** Construction of structural cortical networks in patients with Alzheimer's disease and NCs (*13*): Panel I shows representating cortical thickness maps for a control subject (left) and for an Alzheimer's disease subject (right) obtained from structural MRI; Panel II shows the cerebral cortex segmented into 54 cortical areas, each color representing an individual region; Panel III shows the correlation matrices from calculating the partial correlation coefficients between regional thickness across subjects within the control group (left) and the Alzheimer's disease group (right); Panel IV shows the binarized matrices (left for the control group and right for the Alzheimer's disease group) by a sparsity threshold of 13%. **(D)** Resting State Networks (RSNs) based on independent component analysis in all subjects including NC, amnestic MCI, and Alzheimer's disease. Extracted RSNs included anterior default mode network (aDMN), auditory network (AN), left frontoparietal network (LFP), precuneus network (Pcu), posterior default mode network (pDMN), right frontoparietal network (RFP), sensorimotor network (SMN), and visual network (VN) (*14*).

regions within the frontal lobe as compared with controls (*4*). Further, ICA, a form of data-driven analysis, has been used to define information about RSNs or intrinsic connectivity networks (ICNs) (Figure 2D). In subjects with Alzheimer's disease, functional network connectivity (FNC) is significantly decreased between the anterior and posterior default mode networks and between the visual network and the left front parietal network (*14*).

In the multiscale analysis of neuroimaging data described in this review, some abnormal regions simultaneously presented at both the mesoscale and macroscale, including the parahippocampal gyrus and the posterior cingulate gyrus/precuneus. In patients with MCI and Alzheimer's disease, the morphology, metabolism, and connections related to these regions have been found to be damaged, reflective of cognitive impairment and memory decline. Moreover, the posterior cingulate gyrus/precuneus also appear to play an important part in the structural and functional networks as shown by these studies. Further defining these regions by multiscale analysis, using the approaches discussed in this review, will help to elucidate the underlying pathology of Alzheimer's disease.

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Using motor patterns for stroke detection

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Stroke is a leading cause of death and severe disability in the elderly, and poses a major challenge for public health. In recent years, there has been a rapid increase in the number of stroke victims in many countries, due to the aging population (*1, 2*). Moreover, stroke survivors are at a higher risk of suffering another stroke. Indeed, studies report that up to 40% of survivors suffer a new stroke within one year of a diagnosed stroke. Therefore, early detection of stroke in at-risk patients, including stroke survivors, is an important health challenge.

Previous studies have shown that the Trail Making Test (TMT) is an important means to detect stroke (*1, 3*). However, conducting a traditional TMT requires the assistance of doctors, which is not always convenient. In this paper, we describe an accurate approach for automating stroke detection through a computer-based, body sensing game-based Trail Making Test (BSG-TMT), which in theory will allow for timelier intervention implementations. Our results demonstrate that the accuracy of a stroke diagnosis can be as high as 91% using only four selected motor pattern features (*4*). This accuracy can be significantly improved by including medical history features. These findings verify clinical observations and highlight the importance of using fine motor pattern features of the upper limbs and medical history features for detecting strokes.

Motor pattern feature selection

As shown in Figure 1, the proposed stroke detection framework consists of four steps: (1) data acquisition—collecting raw motion data using the proposed robust fingertip tracking method (*5*); (2) feature extraction—extracting the potential motor pattern features related to stroke from the raw motion data collected in Step 1 and identifying the patient's medical history features; (3) feature selection—applying a mutual information-based feature selection method to obtain the most representative features; and (4) classification—validating the discrimination ability of the selected features.

In Step 1 of the proposed detection framework, a Microsoft Kinect unit is used to collect raw depth sensor data while each subject is taking the BSG-TMT (*4*). The BSG-TMT is designed based on the widely accepted clinical TMT. The TMT requires the subject to connect a set of *N* dots, numbered 1, 2, … , *N*, in a strictly sequential order (starting with dot 1) as quickly as possible. In the BSG-TMT, the pen and paper used for traditional TMTs are replaced by the subject's fingertip and a computer screen, respectively. As illustrated in Figure 1, the fingertip is represented by the red bullet symbol and the numbered dots are represented by the numbered squares. If the subject is currently on dot *N* and makes a mistake by next connecting to a dot other than dot *N* + 1, we say that a connection error has occurred. In this event, the subject has to retry until he connects to dot *N* + 1. The test ends when the subject connects to dot *N*. Because it is difficult to identify patients who will suffer a stroke in the future, we collected data from stroke patients who had been recently discharged from the hospital and used the data to approximate the data for potential stroke patients. These selected patients are known to have a high likelihood of a new stroke occurrence, which provides us with a reasonable proxy for at-risk patients.

In Step 2, potential stroke-related motor pattern features are extracted from the data collected in Step 1. These features include the time the subject took to complete the BSG-TMT (A-Time); the test accuracy (T-Accuracy); the time the subject took to correct a connection error (C-Time); the mean (M-R-Length) and variance (V-Length) of the *N*–1 ratios of the fingertip movement path length to the straight-line distance between two consecutively numbered dots; the mean (M-Fingertip) time duration spent by fingertips at the dots; and the mean (M-R-Time) and variance (V-Time) of the ratios of the time needed to connect two consecutively numbered dots to the fingertip movement path length between the two dots. Medical history features, such as history of strokes, hypertension (HT), hyperglycemia (HG), coronary heart disease (CHD), and diabetes were also retrieved. In total, 13 features were studied.

To determine the most representative features for stroke detection, in Step 3 we adopted the mutual information-based feature selection method. This method automatically measures the importance of the 13 features, retaining the most representative features and discarding unnecessary ones. Initially, we used the finger motor pattern features to build the stroke detection model and tested the discrimination ability using 10-fold cross validation (*6*). We then ranked the combination of features in the order of testing accuracy. For each combination, we applied the 10-fold cross validation again to get the final testing accuracy and selected the most discriminative combination as the final feature set. Similarly, we ranked the discrimination ability of the medical history features. We added the medical history features to the selected feature set one by one until no further classification performance improvements could be obtained.

In Step 4, the effectiveness of the selected features was validated through a recognition test on the subjects.

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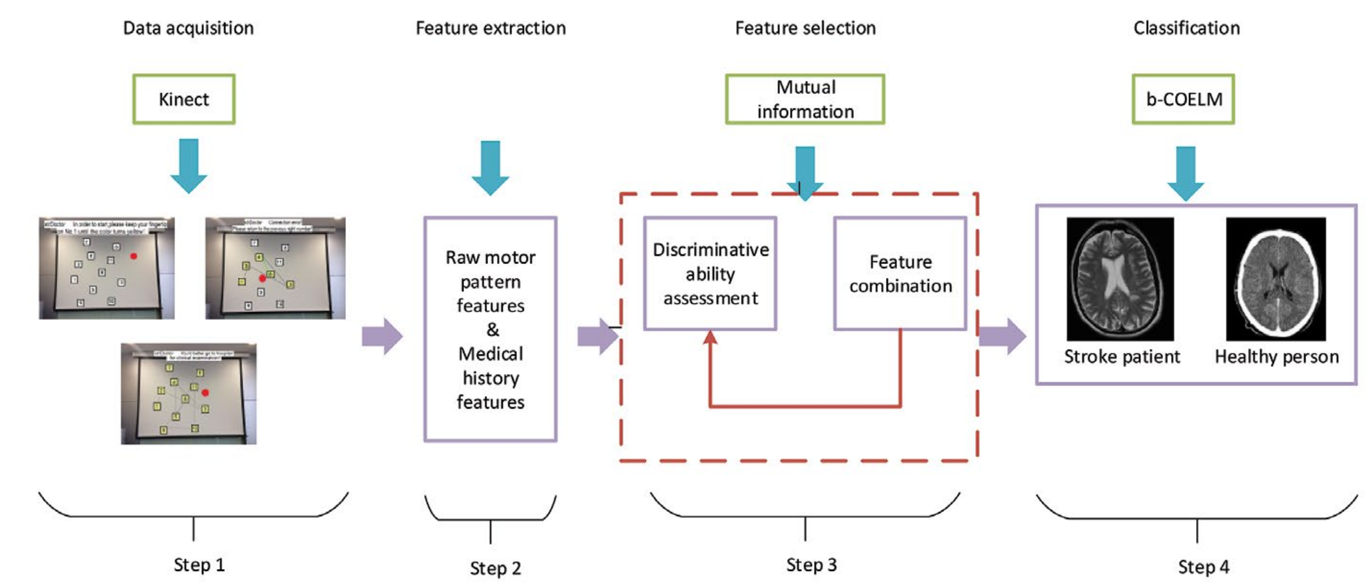
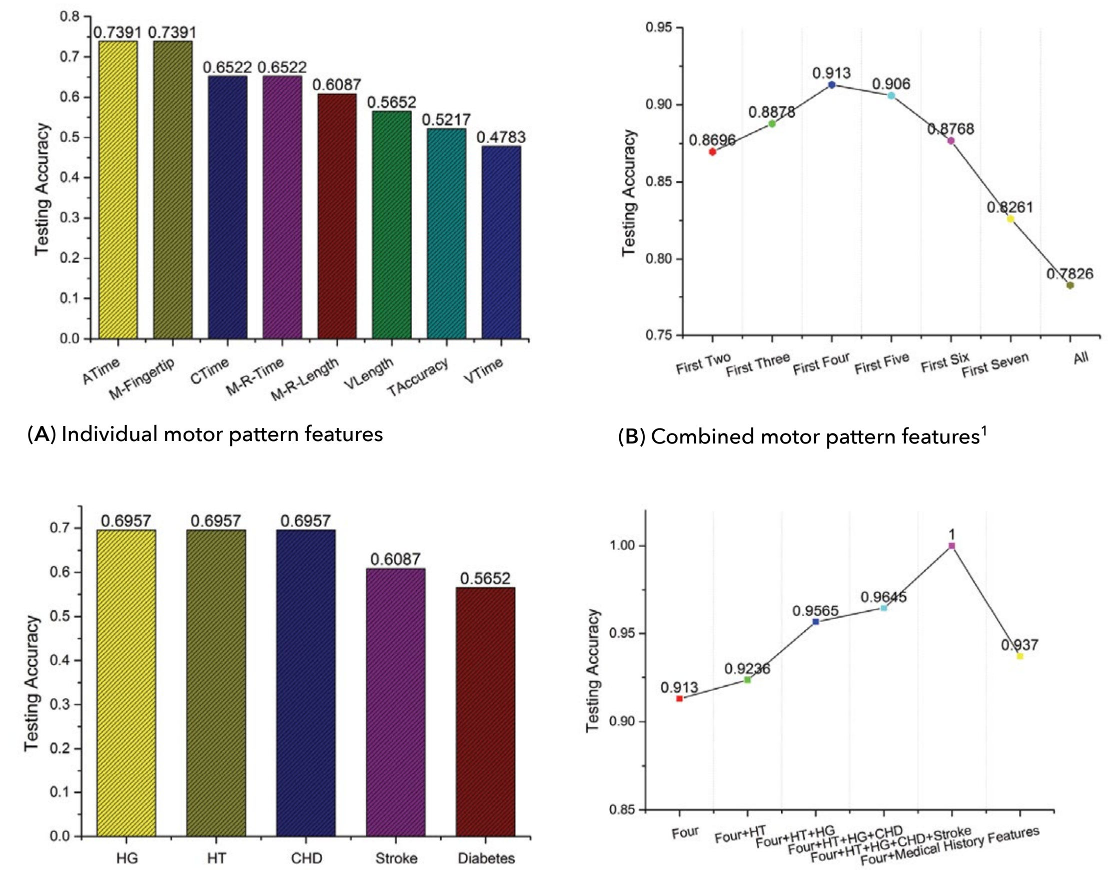


FIGURE 1. The proposed stroke detection framework.



(A) Individual motor pattern features

(B) Combined motor pattern features[1]

(C) Individual medical history features[2]

(D) Combined motor pattern and medical history features

FIGURE 2. Results showing the accuracy of test data when selecting for representative features (*4*).

[1]"First Two," "First Three," etc. correspond to eight features listed left to right in graph (A).
[2]HG=hyperglycemia; HT=hypertension; CHD=coronary heart disease.

TABLE 1. Eight most discriminant features for stroke detection.

Category	No.	Feature name	Feature description
Motor pattern features	1	A-Time	Time the subject takes to complete the BSG-TMT
	2	M-Fingertip	Mean time that fingertips are on the dots
	3	C-Time	Time the subject takes to correct a connection error
	4	M-R-Time	The mean of the ratio for the time needed to connect two consecutively numbered dots to the path length taken between the two dots
Medical history features	5	HT	Whether the subject has hypertension
	6	HG	Whether the subject has hyperglycemia
	7	CHD	Whether the subject has coronary heart disease
	8	Stroke	Whether the subject has previously had a stroke

We employed a single-hidden-layer neural network, b-COELM (*7*), which is very efficient and effective when the training set is small (*8*), to train a binary classifier to distinguish stroke patients from the control subjects based on the selected features.

Experimental analysis

We designed a study using human subjects to demonstrate the effectiveness of the proposed stroke detection method. Fifty stroke patients (16 women and 34 men, from ages 52 to 81) and 55 healthy elderly subjects (25 women and 30 men, from ages 30 to 68) were recruited for our experiments. Each subject was asked to take the BSG-TMT, and the entire session was automatically recorded by the system.

A feature selection experiment was then performed on the data. As shown in Figure 2, after seven iterations, the four most representative motor pattern features were selected, which improved the classification accuracy from 74% to 91%. After combining these features with the four selected medical features, the accuracy improved to nearly 100% (*4*). Table 1 shows the eight selected features. Our results indicate that motor pattern features are sufficient to detect stroke with reasonable accuracy, and the accuracy can be further improved by also considering the subjects' medical history. The experimental results have demonstrated for the first time that through combining motor pattern features and a patient's medical history features, a stroke can be accurately detected.

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Cognition and behavior

Computational psychophysiological models can be used to better understand social behavior and how psychophysiological signals are related to mental states and cognitive processes.

The embodied mind: Using psychophysiological signals to inform brain activity and connectivity during rest

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In the 17th century, the philosopher René Descartes famously established the mind–body problem by proposing that individual existence could be affirmed by thought ("*cogito ergo sum*"), but that the embodied self could be illusory. In the late 20th century, Descartes' argument was modernized in the form of the "brain in a vat" proposition (*1*), whereby a brain removed from the body and sustained on appropriate "life support" was hypothesized to still experience consciousness and recapitulate what an embodied brain can do. There is a division among scientists and philosophers: Some believe that consciousness is mainly driven by events localized in the brain (*2*), and others argue that consciousness must be the result of an embodied brain supported by the physiological processes of the body (*3*). Regardless of the minimum substrates necessary for consciousness, the concept of self relies greatly on the ability of the brain to process signals emanating from the body (*4*). The body and brain cannot be separated without loss of meaningful information. Thus, rather than simply considering the mind–body or mind–brain, in this review, we consider the mind–brain–body context: How do the mind, brain, and body interact with each other, and how does this system as a whole, process, predict, and act in the world?

Unfortunately, some research ignores the fact that the brain, and therefore the mind, is part of an interdependent system: the body. This problem is especially evident in functional neuroimaging studies, in which signals from the body are usually treated as noise. For example, in resting state functional magnetic resonance imaging (R-fMRI) research, blood oxygen level dependent (BOLD) signals are used as a measure of neural activity. However, body-related contributions to BOLD signals, such as respiration and heart rate, are usually discarded (5). This practice leads to the loss of important data. Here we argue that psychophysiological processes, grounded in the autonomic nervous system (ANS), are key contributors to cognitive and affective functions, and they can serve as indices for psychological processes.

We draw an important distinction between physiological processes, which relate to biological functioning of the body, and psychophysiological processes, which relate to the biological underpinnings of psychological functions. For example, the heartbeat (i.e., the pulsatile rhythm) is physiological, while variations in heart rate (i.e., the changing interval between heart contractions) are modulated by the ANS, the latter of which is influenced by arousal and other psychological factors. Psychophysiological signals vary dramatically as a function of individual differences in autonomic reactivity and baseline activity levels, as well as different psychological states (*6*). In contrast to the prevailing view that physiological signals (including their psychophysiological components) are merely noise, we propose that psychophysiological signals can inform the psychological processes underlying the activity and functional connectivity observed in brain imaging studies.

R-fMRI is conducted by implementing a resting condition, whereby participants are explicitly instructed to rest with eyes closed or open, or to fix their gaze on a crosshair. Participants are also commonly instructed to remain as still as possible and not to think about or do anything specific. However, the resting state observed in R-fMRI is more akin to an extremely complex task condition than a task baseline. Numerous studies have shown that during rest, the brain is actually undergoing interesting patterns of intrinsic activity and connectivity, reflecting spontaneous mentation and other internally directed mental operations (*7*). The brain at rest appears to be constantly monitoring and processing stimuli from internal and external environments to predict and meet environmental demands (*8*), a process which is estimated to account for 95% of the brain's overall energy consumption (*9*). As the richness of resting state data has become apparent, scientists have begun developing methods that utilize this information to study the brain's networks (*10*). For instance, spontaneous, low frequency fluctuations of the BOLD signal can be used to define resting state networks (RSNs) of spatially distinct brain regions exhibiting temporally synchronous oscillations.

The default mode network (DMN), one of two large RSNs, has emerged as consistently deactivated by tasks and activated (or less deactivated) during rest (*11, 12*). The DMN comprises primarily the posterior cingulate cortex (PCC), ventromedial prefrontal cortex, and dorsomedial prefrontal cortex (*13*). These regions exhibit coherent oscillations at rest and an apparent "deactivation" during task engagement that is inversely correlated with regions of the task-positive network (TPN), the second of two large RSNs. The TPN includes cortical areas along the intraparietal sulcus, the anterior cingulate cortex (ACC), the anterior insular cortex (AIC), and the frontal eye fields (*12*). The DMN appears to be

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involved in emotional processing, self-referential mental activity, and recollection of past experiences (*8, 13, 14*). Given the importance of the functions attributed to the DMN for understanding the self (i.e., the mind), tools to index psychological states (e.g., psychophysiological measures) during rest are invaluable.

Although resting neural activity and connectivity is a rich source of information, differentiating signal from noise in R-fMRI is challenging (*5, 7, 15*). Noise often arises from the very nature of the methodology employed and can include head motion during acquisition or anatomical misalignment during analysis. The development of methods to maximize the signal and minimize the potential effects of noise is thus a topic of great interest (*5, 7, 15*). In many cases, however, it is unclear to what extent measurements reflect signal or noise. For example, recent work has demonstrated that measures of physiology, as well as head motion, exhibit patterns similar to those of RSNs (*16*). Thus a fair bit of caution is needed in adjudicating signal and noise in studies employing R-fMRI. Some physiological measures may not only correlate with a "signal," but could actually contribute to it meaningfully. More specifically, psychophysiological signals may be useful indices of mental processes during R-fMRI.

Given no specific task manipulations during R-fMRI, it is difficult to understand the psychological implications of neural activity and connectivity. As such, to gain further insight into the state of the mind during rest, a thorough understanding of the brain–body interaction is required. The central nervous system, especially the brain, interacts with the body through the peripheral nervous system. The peripheral nervous system is further divided into the somatic and autonomic nervous systems, which interact with the external and internal environments, respectively. The primary role of the somatic nervous system is to coordinate the action of the skeletal muscles, thus alterations to this system can dramatically impact RSNs (*17*). Here we focus on ANS signals because they are easily measured in human populations and can index psychological processes. The sympathetic and parasympathetic branches of the ANS regulate internal physiology in a hierarchical manner, spanning the levels of the spinal cord, brainstem, and cerebral cortex (*18, 19*). The ANS provides an essential, reciprocal link between the brain and body. Moreover, the ANS regulates physiological reflexes, maintaining homeostasis in response to environmental demands. It also operates centrally to integrate homeostatic needs with the modulations necessary to support physical, social, emotional, and cognitive functions (*18, 19*), thereby creating an intimate interaction among the autonomic activity governing the body, the processing of information in the brain, and the psychological context of the mind (*19*).

Whereas psychophysiological indices are increasingly used in analyses alongside task-based fMRI, there is a dearth of such inclusion in R-fMRI, where these indices may actually be most informative. An illustrative example of the use of psychophysiological signals to understand R-fMRI activity and connectivity patterns is our study examining the associations between nonspecific (nontask related) skin conductance responses (SCRs, a sensitive index of ANS activity) and brain activity and connectivity during rest (*20*). Our results have demonstrated that SCRs are associated with activation of the TPN (especially AIC and ACC) and deactivation of the DMN (especially PCC and precuneus). The coherence within the DMN and the magnitude of the anti-correlation between the DMN and TPN was modulated by SCRs, such that they both were enhanced by the psychological context that the SCRs indexed. These findings suggest that the pattern of activity and connectivity within and between the DMN and TPN may be driven by autonomic activity, which reflects autonomic arousal and potential psychological processes during rest. These results may provide an important framework for understanding mental states and operations during rest.

The need to understand differences in the mental states of individuals during rest is particularly pronounced for group comparisons. Given evidence of altered ANS functioning, along with related differences in mental states across many forms of psychopathology, we have found that psychophysiological differences during rest may partly explain the observed differences in RSNs between clinical populations and controls. Namely, recent work from our group has demonstrated differences between individuals with autism spectrum disorder (ASD) and typically developing controls in ANS activity and its relation to brain activity and connectivity. Individuals with ASD exhibited reduced ANS activity, as indicated by a reduction in the number of nonspecific SCRs, along with decreased correlations of SCRs with brain regions reflecting autonomic signal processing (e.g., thalamus, dorsal ACC, supplementary motor area, AIC) and self-referential processing (e.g., medial prefrontal cortex). Importantly, reduced DMN connectivity in ASD was associated with less modulation by ANS activity (*21*). Therefore, this study provides evidence that differences in RSN connectivity between patient populations and controls may be related to differences in psychophysiological activity.

The data we have discussed in this review suggest that the mind, brain, and body comprise a dynamic system that is constantly active and interactive. Thus, whereas physiological signals are commonly removed in R-fMRI studies and referred to as "noise," the psychophysiological aspects comprising data on bodily and psychological states are in fact critical. This body of work suggests that examining psychophysiological signals can provide important clues to the function of the mind and brain during rest.

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The predictive mapping approach in neuroimaging

Choong-Wan Woo and Tor D. Wager*

For the past 20 years, neuroimaging techniques have transformed how we study psychology and medicine. Data from neuroimaging can constrain psychological theories, resolve some theoretical debates, and be used to develop new hypotheses about human cognition and emotions by providing a grounding in neurophysiology (*1*). In medicine, neuroimaging provides promising measures that can serve as biomarkers for brain-related disorders, such as psychiatric and neurologic disorders (*2*, *3*). Neuroimaging can also connect psychology to biology and medicine, which can help researchers understand how the mind and the body interact and thereby treat medical conditions more effectively (for example, understanding the placebo effect) (*4*).

Despite these promises, neuroimaging has not followed the quick and easy path to success that was initially envisioned. One important reason is that too little effort has gone into developing neuroimaging markers that are sensitive and specific to particular mental processes or health-related outcomes and can be prospectively applied to new data. The dominant paradigm in neuroimaging has focused on brain "maps," not markers. Brain maps identify anatomical regions associated with particular mental processes. This paradigm does not adequately address the many-to-many relationships between brain regions and mental processes: One brain region can be involved in multiple processes, and one process can be distributed across many regions. Thus, we cannot make inferences about which mental process is engaged based on brain maps. Markers, by contrast, are multivariate patterns of brain activity optimized to be sensitive and specific to a particular type of mental process. Without markers, the inferences we can make about brain representations are fundamentally limited (*5*).

Do we really have neuroimaging markers?

It might seem that neuroimaging markers for mental processes already exist, but in fact, we have been using neuroimaging findings as brain markers without properly assessing their sensitivity and specificity. For example, amygdala activity has often been used as a brain marker for negative emotion. However, the amygdala is a large anatomical structure comprising heterogeneous neuronal populations that encode various physical and mental events (*6*). Therefore, averaged functional brain activity within this region is not very useful as a brain marker because of its low specificity (*7*).

In order to be considered as a marker, the brain measure used should show high sensitivity and specificity to the mental event or process of interest. Sensitivity accounts for whether a test—in this case, a brain marker—shows positive results when a target psychological or behavioral process is engaged, while specificity describes whether the test shows positive results that are exclusive to the target process being engaged. Sensitivity and specificity can tell us the diagnostic performance of the brain measure in question and enable us to make inferences or predictions about mental processes or outcomes of interest.

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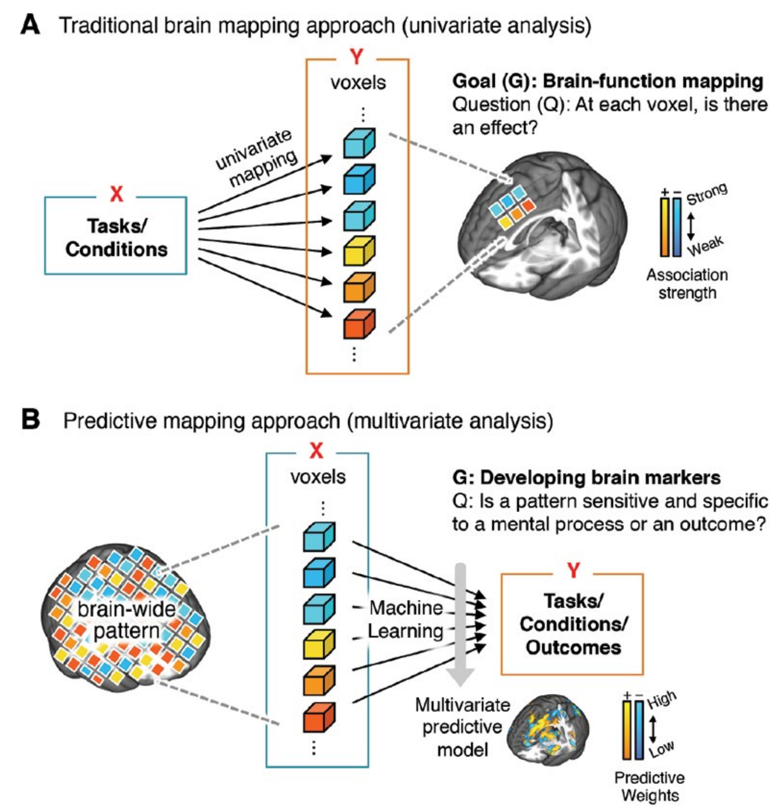
FIGURE 1. Traditional versus predictive mapping. (A) Traditional mapping approaches (including univariate analysis) aim to obtain the functional architecture of the brain by localizing effects in the brain. This approach often entails low sensitivity and specificity. **(B)** The predictive mapping approach aims to develop a multivariate, brain-wide predictive (decoding) model that is sensitive and specific to the outcome of interest.



Traditional brain mapping approaches

Traditional brain mapping approaches—often called "mass-univariate analysis" or "statistical parametric mapping"—have been extremely useful in the development of neuroimaging. However, these approaches are of little help in identifying and utilizing brain markers with established sensitivity and specificity. The main goal of the traditional approach is to map different mental functions onto specific brain regions to localize brain functions. As Figure 1A demonstrates, in this framework, tasks or conditions are independent variables, and each voxel's fMRI signal becomes a dependent variable. The most important question answered by the traditional approach is whether there is an effect in each voxel or region.

This traditional approach has, at best, low sensitivity to the effects of task conditions because it assumes independence among voxels or regions. However, psychological and behavioral processes and related outcomes result from integrated circuit dynamics. Thus, the effects of task conditions—and the relationships between brain activity and behavioral/psychological outcomes—are likely to be distributed across brain regions and voxels. Analyses that consider only information in a single voxel or region, as the mass-univariate approach does, are unlikely to capture the full effects of tasks. In addition, the univariate approach involves a large number of statistical tests and requires a correction for multiple comparisons (*8*). The correction for multiple tests focuses on controlling false positives and in turn increases false negatives, which results in low sensitivity (*8*). With low sensitivity, many of the voxels activated in relation to a task or outcome will be missed, providing a poor assessment of the pattern across the brain. This, in turn, undermines efforts to establish replicability across studies (*9*, *10*). Furthermore, as illustrated in Figure 2, traditional brain mapping has a limited ability to detect the unique relationships between mental functions and brain regions, which could undermine the specificity of the resulting brain maps.

Developing neuroimaging markers: The predictive mapping approach

The predictive mapping approach can resolve the issues described above and provide neuroimaging markers with quantitatively characterized measures of diagnostic performance. Predictive mapping aims to develop multivariate, systems-level predictive models (or decoding models) that are sensitive and specific to particular outcomes of interest (see, for example, *11*). As Figure 1B shows, one of the main features that distinguishes predictive mapping from traditional

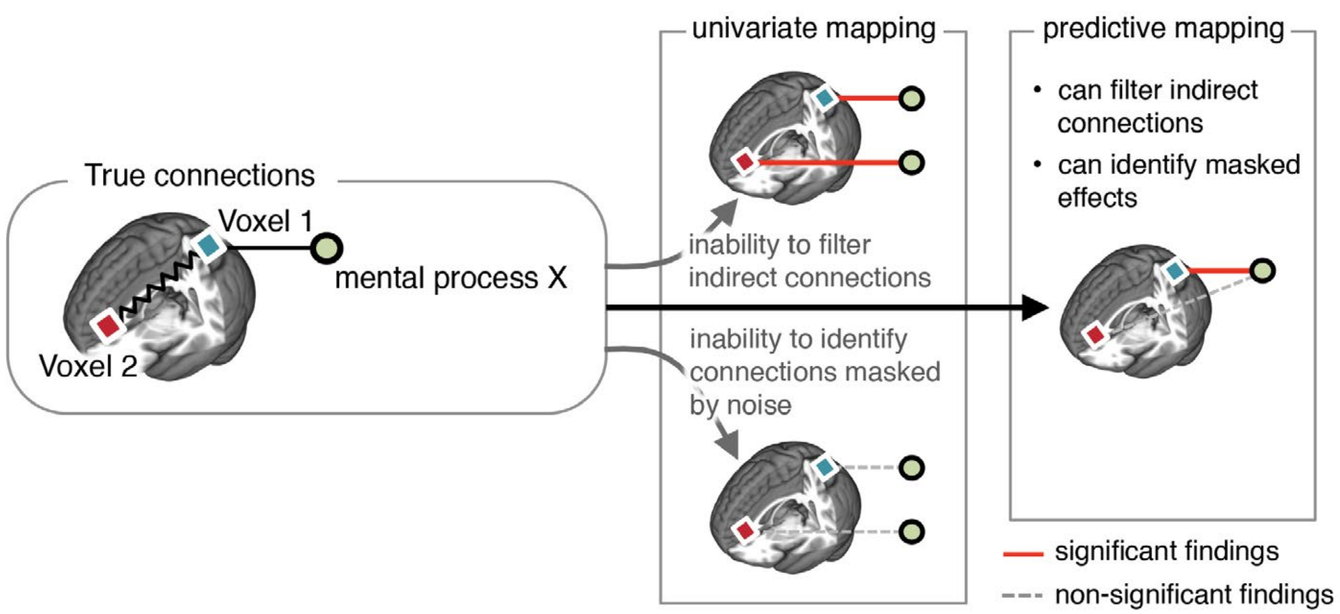


FIGURE 2. Benefits of predictive mapping. There are a number of scenarios under which predictive mapping yields higher power and more accurate representation of brain-outcome relationships than traditional mapping. We illustrate one such scenario here, in which there is a direct relationship between Voxel 1 and the outcome (mental process X), and a correlation between Voxel 1 and Voxel 2 that reflects a common source of noise unrelated to the outcome. In the center top panel, univariate mapping may identify significant effects of both voxels, as it cannot separate regions with indirect connections to X from those that have more direct relationships. The predictive mapping approach controls for Voxel 1 when assessing the effects of Voxel 2, and so will not spuriously identify Voxel 2 as significant. In addition, controlling for Voxel 2 can remove some of the noise in Voxel 1, which may otherwise mask the relationship between Voxel 1 and X and prevent Voxel 1 from reaching significance (center bottom panel). For both reasons, under this scenario, the predictive mapping approach has a greater chance of identifying true brain-outcome relationships.

approaches is that the assignment of independent and dependent variables is reversed.

The predictive mapping approach helps to solve the low sensitivity and specificity problem of traditional mapping in several ways. First, it can identify voxels that have selective relationships with the outcome (see Figure 2). Second, it uses distributed signals across many voxels without requiring thresholding and correction for multiple comparisons. Third, it is sensitive to information at multiple spatial scales, including large-scale information distributed across multiple systems and mesoscale information below the resolution of the imaging itself (so-called fMRI hyperacuity) (*12*). Assessing multivariate patterns rather than individual voxels is critical if information about outcomes is encoded in neuronal population codes (*13*). Furthermore, assessing large-scale patterns across systems is critical if mental states are encoded across systems (*14*). A related approach, called information-based mapping (*15*), also uses multivariate patterns to predict outcomes. However, it still focuses on local effects (using searchlights, or spatial moving windows), and thus is subject to limited sensitivity and massive multiple comparisons. In contrast, the predictive mapping approach focuses on developing one unified predictive model based on brain-wide patterns of brain activity.

In the predictive mapping approach, machine learning techniques become crucial because analyses based on large-scale population codes are subject to the high-dimensionality problem. High-dimensional data, in which there are many more predictors than observations ($p \gg n$; often called the "curse of dimensionality"), causes problems with model optimization because the parameter space is underconstrained by the data (*16*). Some machine learning algorithms, such as support vector machines and regularized regression, can provide stable prediction models even for the high-dimensional data with a guarantee of good generalization capacity (*17, 18*).

Precisely defined model and prospective testing: benefits for translational research

In addition to benefits in sensitivity and specificity, the predictive mapping approach can provide precisely defined models that can be prospectively tested on new datasets.

In traditional mapping approaches, replication and hypothesis testing depends heavily on anatomical definitions that are often heuristic and ambiguous, leading to flexibility in how researchers identify what counts as an a priori hypothesis and, in turn, increases in false positive results and reduced specificity (*19*). For example, "amygdala activity" does not provide a reproducible definition of precisely (a) which voxels in the amygdala should be activated (there are typically hundreds); and (b) the relative expected intensity of activity across each voxel. *Any* significant result anywhere in the amygdala can count as amygdala activation, and this flexibility leads to spurious findings. In contrast, the predictive mapping approach can minimize biases in measuring, testing, and replicating effects in new individuals and studies through predictive models defined by precise patterns of brain activity, which can provide a priori predictions and testing procedures.

Precisely defined predictive models (based on multivariate patterns of neuroimaging data) provide several advantages for basic and translational research. First, hypotheses are precisely specified in terms of spatial patterns, and responses in these patterns are falsifiable and readily testable, providing a foundation for strong inference (*20, 21*). Second, precisely specified models are research products that can be shared and tested across laboratories, enabling a cumulative understanding of their properties across test conditions and study populations. Third, some predictive models can be prospectively applied to new individual participants, which is critical for clinical and legal applications. Fourth, well-defined predictive models can serve as a means of bringing together basic and clinical research, as diverse research groups can communicate with each other through tests of predictive models, facilitating translation of findings from one setting (e.g., basic research) into new contexts (e.g., clinical assessment).

Conclusions

Recent advances have provided promise and hope that we can use neuroimaging to better understand the human mind, including the neurophysiology that underlies behavior and brain-related illnesses. However, a wide gap still exists between neuroimaging data and the mental processes we want to measure. Part of the problem is that we do not have neuroimaging markers that are sensitive and specific enough to accurately indicate when a particular class of mental process is engaged. The predictive mapping approach we outline here can be used to develop neuroimaging markers that have better sensitivity and specificity compared to the traditional univariate mapping approach. The predictive mapping approach can also provide precisely defined predictive models that can be prospectively tested in new individuals and studies, and thereby turn the predictive models into research products and/or clinical tools. This characteristic can allow neuroimaging markers to be easily accessed and tested by other researchers and laboratories, promoting replicability and facilitating translation from laboratory to clinic. All together, the predictive mapping approach has the potential to facilitate neuroimaging marker discovery and validation for both basic and clinical science.

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Computational models of implicit sequence learning: Distinguishing abstract processes from chunking processes

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Implicit learning refers to all unintentional learning, in which knowledge of the structure of an environment is incidentally acquired (*1, 2*). Implicit learning produces a tacit knowledge base, which can be acquired independently of intentional efforts to learn and can be transferred implicitly through novel circumstances (*3, 4*). However, despite decades of research, it remains controversial whether abstract knowledge can be acquired through implicit learning. An abstractionist view of knowledge acquisition assumes that it can be unconsciously received and is "deep, abstract, and representative of the structure inherent in the underlying invariance patterns of the stimulus environment" (*5*). Much of the evidence supporting the abstractionist view comes from artificial grammar learning tasks (*6*). In contrast, the nonabstractionist view assumes that implicit learning is based on storing memories in specific exemplars, chunks, or fragmentary sequences (*7*). Recent studies on sequence learning seem to support the latter view (*2, 8–10*).

Chunking and abstract processes in implicit sequence learning

Sequence learning is one of the most widely used implicit learning tasks, in which a stimulus appears at one of four locations and subjects are asked to respond to the stimulus location. Recently, studies investigating sequence learning have adopted two sequences, namely SOC1 (3-4-2-3-1-2-1-4-3-2-4-1) and SOC2 (3-4-1-2-4-3-1-4-2-1-3-2), that consist exclusively of so-called second-order conditional (SOC) transitions, in which each location is determined by the previous two. When the stimulus location follows the order of one SOC sequence (called the training sequence) but rarely switches to the order of the other SOC sequence (the transfer sequence), subjects respond more quickly to the training sequence than the transfer sequence, indicative of learning (*9–12*). Because the only difference between the two sequences is in their SOC structure (e.g., transition 3–4 was followed by a 2 in SOC1, but by a 1 in SOC2), the learning effect indicates that subjects have acquired chunk knowledge, i.e., a collection of information stored and retrieved as a unit.

To address whether abstract knowledge can be acquired during sequence learning, Goschke and Bolte (*13*) asked subjects to name the everyday objects shown in line drawings from one of four (semantic) categories. The objects were presented in a random order, but the categories followed a repeating sequence. This study found that the reaction times (RTs) slowed when the repeating category sequence changed to a random category sequence; however, when participants were asked to verbally articulate the repeating category sequence, they performed no better than chance. These results provided convincing evidence that abstract knowledge about the deep structure underlying a sequence of specific stimuli can be acquired through implicit learning.

If both chunk and abstract knowledge can be acquired implicitly during sequence learning, one could argue that test subjects should be acquiring abstract knowledge during the sequence learning of the SOC structures. Indeed, using SOCs as learning materials, it has been found that subjects can acquire two types of knowledge during implicit sequence learning: (1) knowledge relevant to being able to distinguish between the training and the transfer SOC sequences, i.e., concrete triplets or chunks; and (2) knowledge about properties common to both the training and transfer SOC sequences, i.e., abstract structures (*2*). Moreover, when including yet another (deviant) sequence that was different in structure from both the training and transfer sequences, but was presented with a low probability of presentation (same as the transfer sequence), we found that RTs to the transfer sequence were much faster than they were to the deviant sequence, confirming that both chunk and abstract knowledge is acquired during implicit sequence learning tasks (*14*).

Computational models of implicit sequence learning

To elucidate the type of knowledge gained during an implicit sequence learning task, researchers have used various computational models. The simple recurrent network (SRN) is one of the most widely used models of implicit learning. It is trained to use the current stimulus to predict the next stimulus, utilizing a so-called backpropagation algorithm (*15–18*). To make the prediction possible, the model is set up as a three-layer feedforward network that includes context units used to copy the network's pattern of activity elicited by the stimulus over the hidden layer each time the stimulus is presented (see Figure 1). Information processing in the SRN can be formulated as follows:

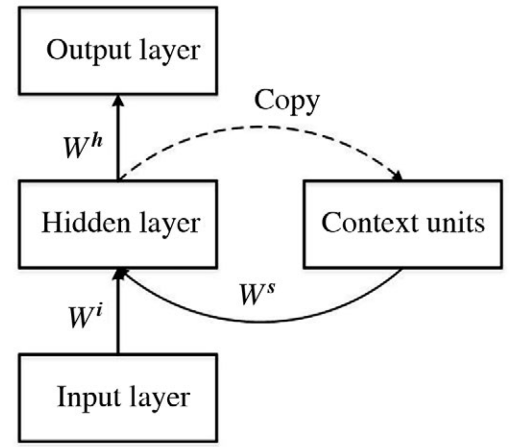

FIGURE 1. Schematic diagram of the simple recurrent network (SRN). The weight connections between different layers are denoted as W^i, W^h, and W^s. The SRN is trained to utilize the current stimulus to predict the next stimulus using a backpropagation algorithm. To make the prediction possible, the context units continuously record a copy of the network's pattern of activity elicited by the stimulus over the hidden layer.

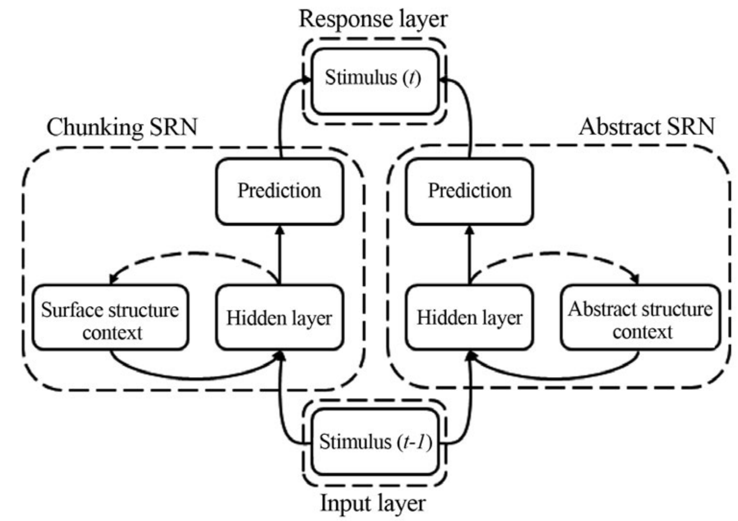

FIGURE 2. Schematic diagram of the dual simple recurrent network (DSRN). The chunking SRN encodes specific stimuli and learns to predict the next specific stimulus, whereas the abstract SRN encodes the abstract properties of the current stimulus and learns to predict the abstract properties of the next stimulus. The response layer is designed to integrate different predictions in order to make a final prediction.

$$\begin{cases} a^o(t) = f(W^h a^h(t)) \\ a^h(t) = f(W^i a^i(t-1) = W^s a^s(t)), \\ a^s(t) = a^h(t-1) \end{cases}$$

where a^o, a^h, a^s, and a^i refer to the activation of the output layer, hidden layer, context units, and input layer, respectively; W^h, W^i, and W^s refer to the weight connections between different layers or units; and *f* refers to the activation function. Through training, the SRN can learn to improve prediction accuracy by refining the connection weights between the hidden layer and the input or output layer, and long-term knowledge is represented by the weights' value (*18*). Thus, without any further assumptions, the SRN captures two important characteristics of implicit learning: (1) that implicit learning is incidental and mandatory; and (2) that the resulting knowledge is unconscious or difficult to articulate.

To simulate RT performance in sequence learning, it is assumed that the normalized activity of the output layer is inversely proportional to RT (*15*). This assumption allows the SRN model to simulate most of the results seen in sequence learning experiments (*16, 18, 19*). To simulate how abstract sequential structures can be acquired in implicit sequence learning tasks, the SRN was assumed to be sensitive to the gap between successive occurrences of the same stimulus (*20*), an example of structure information. However, abstract structure can be defined by the relationship between repeating sequence elements (*21*). To better simulate how different types of knowledge are gained during sequence learning, a dual process model was introduced in which surface learning or chunk learning was based on an SRN model, and abstract learning depended on a short-term memory mechanism that encoded previous responses and a recognition mechanism that compared the current response to the stored short-term memory responses to detect any repeated elements (*21*). This dual process model has clearly demonstrated that surface structure can be learned implicitly, whereas abstract structure can also be learned, but only under explicit conditions. Nonetheless, this model cannot account for the evidence of implicit abstract learning found in other studies (*2, 13*).

To address this discrepancy, we proposed a dual simple recurrent network (DSRN) model (see Figure 2), in which surface learning and abstract learning are based on different SRN models. The chunking SRN encodes the specific stimulus and learns to predict the next specific stimulus. The abstract SRN encodes the abstract property of the current stimulus and learns to predict the abstract property of the next stimulus. To integrate the different predictions of the two SRNs, we added a response layer that produces the final prediction of the next stimulus using the equation: $a_i(t) = \rho a_i^l(t) + (1-\rho) a_i^r(t)$, where $a_i(t), a_i^l(t)$, and $a_i^r(t)$ refer to the activation of the response layer, prediction layer of the chunking SRN, and prediction layer of the abstract SRN, respectively, and ρ refers to the prediction weight of the chunking SRN. After the DSRN

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has made its prediction, the backpropagation processing provides a learning opportunity for each SRN. Following training, the DSRN responds to the training sequence more quickly than to the transfer or other sequences.

To simulate generation performance in an inclusion test, in which subjects were asked to generate a sequence that resembles the training sequence as much as possible, and in an exclusion test, in which subjects were asked to avoid generating the training sequence, we assumed that (1) each unit in the response layer has an attribute called "activation state" to indicate whether it is activated or not and this activation state can be calculated by the equation $s_i(t) = \begin{cases} 1, & a_i(t) \geq \varepsilon \\ 0, & a_i(t) < \varepsilon \end{cases}$, where ε is a constant parameter; and (2) the activation state of each response unit in the response layer determines which response is made. Because there are 36 concrete triplets for surface learning, but only two abstract structures for abstract learning, abstract structures will be learned much faster and more accurately and will more quickly come to consciousness. Because conscious and unconscious knowledge play different roles in generating the training sequence in the inclusion and exclusion tests, we can manipulate the prediction weight of each SRN to simulate generation performance of the training sequence in the inclusion and exclusion tests.

Compared with previous computational models of implicit sequence learning, the DSRN model has two advantages. First, the DSRN can successfully model how surface and abstract structures are acquired implicitly in different sequence learning situations. This not only extends the SRN's ability to learn, but also demonstrates that surface learning and abstract learning may use similar computational principles. Second, the separation of surface and abstract SRNs allows us to investigate whether the degree of abstraction determines the conscious status of the acquired knowledge—an area in which there has been an ongoing debate. Nonetheless, it has its own disadvantages. No guidelines have been set up with respect to how to determine the value of free parameters (e.g., learning rate, number of layers, and number of units in each layer) by users of the DSRN; rather, these need to be individually determined. Further, although this model provides a new way to simulate RTs and generation performance of the training sequence, it still has difficulty in clearly distinguishing implicit learning tasks from explicit testing tasks, a calculation that remains too complex for our present models.

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Self-regulation of aversive emotion: A dynamic causal model

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The ability of humans to regulate emotion is a fundamental prerequisite for maintaining intact social lives that impacts both emotional and mental well-being (*1*). Generally, emotion regulation includes processes that amplify, attenuate, or maintain an emotion (*2*). An inability to effectively down-regulate (attenuate) negative emotions when they arise distinguishes those who are vulnerable to emotional disorders—such as anxiety disorders and major depressive disorder (MDD)—from emotionally healthy individuals, and this is thought to underlie the pathogenesis of mental disorders (*3*). Therefore, unraveling the neural mechanisms underlying emotion regulation is key to furthering our understanding of emotional disorders. Theoretically, one important dimension of emotion regulation is the discrepancy between conscious regulation (i.e., guided by explicit intentions and accessible to one's own awareness) and automatic regulation (i.e., guided by implicit intentions or outside one's awareness) (*1*). Although both forms of regulation are interesting and important, there is a lack of neuroscience-based studies addressing the latter issue (*4*). That is, studies have shown that when subjects are faced with a specific task requirement (e.g., "imagine that the crying woman in the picture is an actress who is performing"), they use top-down cognitive regulation of their emotion that recruits the cognitive system (e.g., attention or memory). The instruction provided along with the image actively elicits emotion regulation and changes the way the subject appraises the meaning of an emotional stimulus. This task is followed by what we term a "modulated recovery period" from the emotional response since the instruction necessitates that the subjects change their emotion when confronted with the emotional stimulus. If no such instruction is provided, the subsequent recovery is instead regarded as a natural recovery period. As our recent study on the self-regulation of aversive emotion shows, there is a lack of research regarding whether cognitive regulation is required during natural recovery (*5*). Therefore, we have reanalyzed the data from this study on the self-regulation of aversive emotion to also investigate the emotion regulation processes underlying the natural recovery period. Moreover, we have proposed a model to explain the dynamic neural activity involved in self-regulating aversive emotion. Here, we discuss both our data reanalysis and our new model.

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Self-regulation of aversive emotion

In our recent study investigating brain responses to aversive stimuli using functional magnetic resonance imaging (fMRI), 20 healthy volunteers were recruited to investigate the discomfort induced by viewing aversive pictures (those with fear-inducing or disgusting content) and the emotional self-regulation during the natural recovery period (resting state) that followed (*5*). We collected multiple measurements from the sample group, including a pretest that displayed only neutral pictures without inducing emotion and a posttest that displayed only aversive pictures that aroused aversive emotions. For each test, volunteers were asked to concentrate on 15 pictures sequentially for 1 minute (4 seconds per picture) and then rest (recover) for 4 minutes. The two tests were separated by a 15-minute interval. Using fMRI to measure each subject's brain activity, the blood oxygen level dependent (BOLD) responses were compared for each condition, either aversive or neutral pictures. The data indicated that the subjects' brain activity was significantly greater during the posttest compared with the pretest. This result was observed for both the emotional responses to aversive stimuli (corresponding to the 1-minute period of picture viewing) and the self-recovery period (corresponding to the 4-minute period of rest). In addition, we observed increased activation in the striatal region when subjects were viewing the aversive pictures, suggesting that this region plays a functional role in generating emotions (*7*). This activation continued even after the display of the aversive pictures had ceased, suggesting this subcortical region is also used for bottom-up regulation of emotion and is driven by the direct perception of aversive stimuli and spontaneous suppression (holding back) of emotion. The striatum has been linked to this type of emotion suppression because it has been shown to play a role in anticipating aversive stimuli (*8*) and manual response inhibition (constraining body movement) (*9*). Furthermore, the data also indicated that the aversive stimuli condition induced significantly increased activation in the dorsolateral prefrontal cortex (DLPFC) during the late period of rest. The DLPFC controls higher cognitive functioning along with several other regions within the executive control network (*6*). These data suggest that top-down regulation—initiated from higher cognitive brain regions—is also involved in emotional self-recovery. Finally, we observed a gradual decrease in the BOLD signal in the striatum as well as a continuous increase in the BOLD signal in the DLPFC. Taken together, it seems reasonable to assume that the

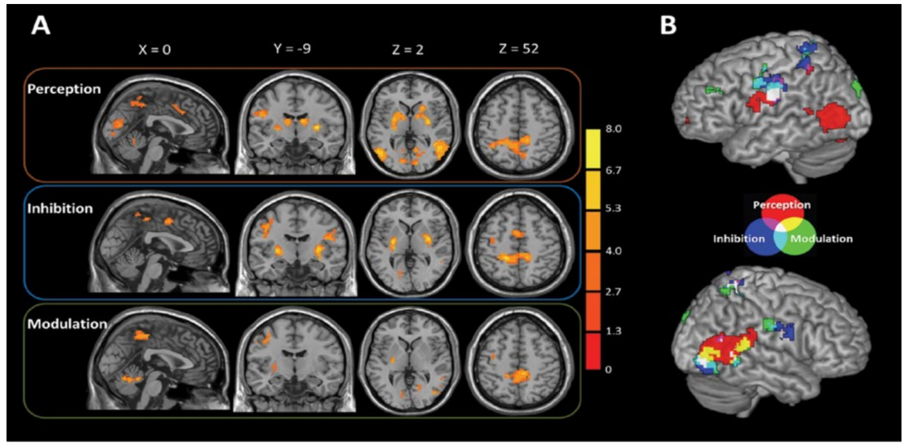

FIGURE 1. Functional magnetic resonance imaging (fMRI) images of subjects viewing aversive pictures compared with neutral pictures. Aversive stimuli induced significant brain activation that differed across regions depending upon three states: perception, inhibition, and modulation. **(A)** Significant activation at (0, -9, 2/52), displayed in Montreal Neurological Institute (MNI) coordinates, is shown in sagittal, coronal, and axial planes. Activation in each region reached statistical significance of $P < 0.05$ [false discovery rate (FDR), corrected], cluster size $k > 10$ voxels. **(B)** The brain regions where significant activation occurred during the three states are depicted on the surface of the brain in different colors.

subjects' strategies for self-regulating emotion transitioned from attempting to suppress the emotion to a cognitive control strategy. Therefore, we propose that the subjects' brain activity went through three states: perceiving the emotional stimuli, suppressing the induced emotions, and regulating the emotions through cognitive control. These data demonstrate that both bottom-up and top-down controls are involved in emotional self-recovery.

Dynamic causal modeling of emotion regulation

Because conventional methods for analyzing fMRI data have limited ability to show causal relationships between brain functions, the results of our previous study were insufficient to thoroughly interpret how the independent bottom-up and top-down systems interact at the cellular level. To investigate this further, the data from the same group of 20 volunteers were reanalyzed for the time period during which subjects were viewing the pictures using dynamic causal modeling (DCM) (*10*). This approach for analyzing effective connectivity can show the transmission of neural signals between brain regions (which reflects how a former cognitive activity influences a latter cognitive activity, i.e., causality between cognitive processes), depict the influence that one neuronal system exerts on another, and evaluate how well a particular model explains the observed data.

Similar to the results from Yang et al. (*5*), the results of this analysis demonstrate that there were shifts in how the brain controls emotion when viewing the pictures (Figure 1). These shifts corresponded to three states: the initial response to the aversive pictures (perception and encoding of stimuli), which activated the visual and encoding regions; response suppression (inhibition), which induced significant activation in the ventral striatum (VS) and supplementary motor area (SMA); and response modulation, which led to significant activation in the DLPFC [$P < 0.05$, false discovery rate (FDR) corrected, for each state when compared with neutral images]. The dynamic causal connections (or directional interactions) were modeled for the four regions that were activated during the specific time intervals of the three states: ventrolateral prefrontal cortex (VLPFC), dorsal part of anterior cingulate cortex (dACC), VS, and DLPFC (*1, 4*). Because the precise function of these four regions and their interactions are still being debated (e.g., whether the VLPFC is involved in the generation of emotion or whether the DLPFC modulates the VS in a direct way), 50 models were chosen to cover each of the hypotheses, and the optimal model that represented the best fit to the data was identified using Bayesian model selection (BMS) (*11*).

As a result, bidirectional endogenous connections were identified between the pairs of VS and VLPFC, VS and dACC, VS and DLPFC, VLPFC and DLPFC, and dACC and DLPFC (Figure 2A). The overarching idea is that the prefrontal and cingulate systems support the control processes that modulate activity in subcortical systems, which generate emotional responses (*4*). Although the amygdala is more commonly reported to be activated during emotion generation than the VS, our study did not find significant activation in this region. However, the data verified our previous results in which the VS was associated with both emotion generation and bottom-up regulation via suppression. Moreover, emotion-inducing stimuli were only associated with the VS and not the VLPFC, which refutes the possibility that the VLPFC is engaged when generating emotions (*1*). The stimuli also led to a self-connection within the VS (Figure 2A), which causes a self-inhibition that prevents uncontrolled outbursts of neural activity. However, the aversive emotion induced by viewing pictures in our study was intense enough to override this inhibition and enabled the activation of the DLPFC via two indirect paths: the dACC and the VLPFC. The DLPFC exerted modulatory effects on the VS directly, which down-regulated the subjects' emotional responses. During indirect transmission of emotional signals from VS to DLPFC, the VLPFC and dACC are involved in evaluating the positive or negative valence of afferent signals and monitoring conflicts between the responses to the

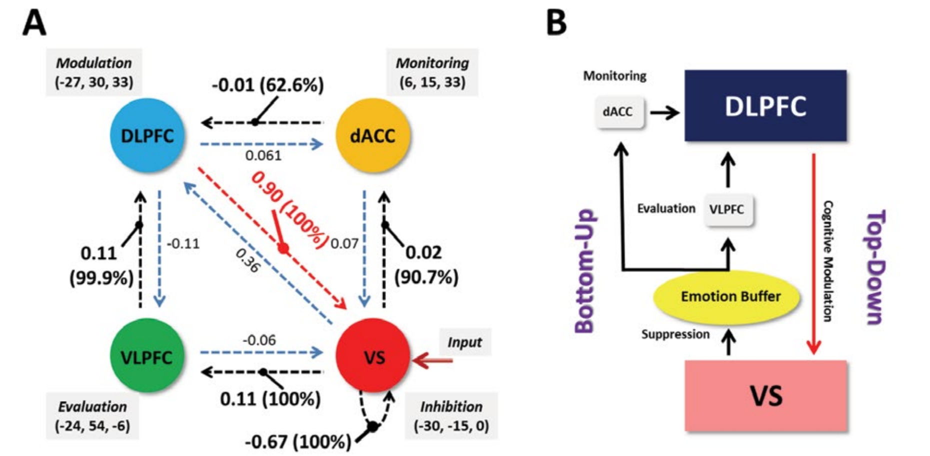

FIGURE 2. Dynamic models for self-regulating aversive emotions. (A) The optimal dynamic causal model depicts the connections between the VS, dACC, DLPFC, and VLPFC. Bidirectional endogenous connections (the fixed connections) were identified between each pair of nodes, except between the dACC and VLPFC. Cognitive functions and Montreal Neurological Institute (MNI) coordinates are shown for each region. For each modulatory effect, both the connection strength (which indicates the frequency of exertion) and posterior probability (%) (which represents the conditional probability given the observed data) are shown. **(B)** A dual regulatory model is proposed for the regulation of emotion. Bottom-up regulation involves an indirect pathway that is initiated by the VS to the DLPFC via both the VLPFC and dACC. Top-down regulation involves modulation imposed by the DLPFC on the VS directly.

overriding emotion and initial inhibition, respectively (*4, 12*). The DLPFC has been reported to be related to higher order (or "cold") regulatory processes, which are reliant on only attention and memory, and are free of affective processing (*13*). Note that these processes are quite possibly utilized spontaneously during the emotional self-regulation.

Self-regulation models for aversive emotion

Based on the shifts in brain activity across perception, inhibition, and modulation to control emotion and the optimal dynamic causal model described above, we have proposed that a frontostriatal circuit underlies a dual regulation model for emotional self-recovery (Figure 2B), in which both bottom-up and top-down regulation are involved. Bottom-up regulation initially attenuates emotions with negative valence (such as that induced by aversive stimuli) via the VS serving as an "emotion buffer" that enables the brain to endure the emotions by exerting a certain level of inhibition, until the emotions are defused over time. For intense emotions that exceed the magnitude that the VS can bear, the VS will recruit help from the DLPFC by transmitting signals about the intense emotions along indirect pathways via the VLPFC and dACC. This enables a top-down cognitive regulation by the DLPFC that directly modulates the VS (*4*).

Conclusion

Taken together, our data demonstrate that the brain recruits cognitive regulation during emotional self-recovery to decrease emotional-related discomfort after receiving aversive stimuli. Furthermore, our findings suggest that both VS-centric bottom-up and DLPFC-centric top-down regulation are recruited for self-regulating emotions with negative valence. The DLPFC exerts a modulatory effect on the VS only when the VS fails to suppress the induced emotions by self-inhibition. The underlying neuronal responses of this dual regulatory model may be attributed to the interaction between glutamatergic excitation and GABAergic inhibition [gamma-aminobutyric acid (GABA)]. We plan to further investigate the dynamic causal connectivity of brain regions in patients with MDD, and investigate whether their emotional abnormalities are related to impaired top-down regulation, impaired bottom-up regulation, or both.

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Recognizing emotions based on multimodal neurophysiological signals

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In the era of big data, the ability to computationally assess human emotions based on neurophysiological signals, such as brain signals, respiration, and heart rate, is now a possibility. Emotion, sometimes referred to as affect or mood, is an internal experience sometimes caused by external events. Emotion manifests in expressions such as joy, grief, fright, anger, sympathy, and disappointment.

Emotion recognition is a hot topic in cognitive neuroscience and psychophysiology, and has become increasingly relevant to computing and information sciences. Recent neurological studies have emphasized the role of emotion in social interactions, cognition, and rational decision making (*1, 2*). Within the field of artificial intelligence (AI), a new interdisciplinary area called "affective computing" (AC) has emerged. The goal of AC is to empower computer systems to recognize, comprehend, and respond appropriately to human emotions for the sake of natural human–computer interactions (HCIs) (*3*).

More practically, emotion recognition could help in detecting mood-related mental health problems such as depression, which is highly linked to suicide (*4*). The World Health Organization (WHO) estimates that by 2020, major depression will be the second leading cause of disability in the world, just behind ischemic heart disease (*5*). Although physiological and neuroimaging data have become increasingly available, psychiatrists urgently need better tools to utilize the information for diagnosing and prognosing depression in its earliest stages, when there is the highest potential for effective treatment. To address this, machine learning techniques, which can learn from and make predictions using data, may be key for mining reliable diagnostic and prognostic information from these data (*6, 7*).

In the field of education, the Massive Open Online Courses (MOOC) platform has been widely adopted around the globe. However, a major challenge has been how effectively the teachers or the platform can track the level at which a student is paying attention. Neuroscience and psychology research has shown that cognitive processes, such as attention and long-term memorization, are tightly linked to emotions (*1*). If a student gazes at the computer screen at length without displaying signs of interactive pleasure, it is likely that a mood of antipathy has emerged, which can result in low learning efficiency. AC can provide the ability to assess the emotional states of learners in an online environment based on analysis of signals from various sensory apparatuses, and teaching strategies can be automatically adapted to accommodate transitions in emotion, as they occur (*8*).

AC has been adopted for promoting the information retrieval (IR) experience, which underlies applications such as web search engines. Researchers have observed that positive emotions often reflect a user's satisfaction with search results (*9*) and interest in certain information (*10*). Negative emotions, on the other hand, occur more often with a user's dissatisfaction with search results and search strategies (*9*). Capturing the emotional states of users while they are seeking information through search engines can be used as feedback to adjust the search engines' retrieval strategies and to better predict the topical relevance of information being presented to users (*11, 12*).

Most emotion recognition approaches are based on the James-Lange theory, which claims there is a strong correlation between emotions and physiological arousal (*13*). However, to date most studies have concentrated on detecting emotions from a single modality of sensory data. Now, with recent advances in sensing technologies, synchronized detection of neurophysiological responses from different modalities can be acquired. These include measurements of temperature, respiration, electrical conductance of the skin, and electrical activity of the brain and skeletal muscles. Integrating these measurements with advanced machine learning techniques opens up opportunities to develop effective methods for recognizing human emotion.

In previous research, emotion recognition based on multimodal data typically concentrated on the feature-fusion method (which combines features from multiple modalities together directly) or decision-fusion method (which uses a majority vote or a weighted sum of decisions from multiple classifiers for each data modality) (*14, 15*). In these studies, the correlations across different neuro-physiological data modalities have not been effectively exploited. Our published work has shown that the idea of a multimodal deep learning approach is applicable and effective in recognizing emotional states from multiple channels of neurophysiological signals (*16*). In this article, we describe a multimodal fusion framework whereby deep learning techniques can be used to acquire representations across different data modalities, as opposed to just one, and to classify the emotional state of subjects. Specifically, we apply and evaluate our method on a widely used and publicly available benchmarking dataset, namely "A Dataset for Emotion Analysis using Physiological Signals," or DEAP (*17*).

Multimodal deep learning framework

Deep learning is a popular research branch of machine learning, which is inspired by progress in neuroscience and based on studies on information processing and the communication mechanisms of the underlying neural systems. Its hierarchical neural network-based learning architecture encompasses several layers of representations or "nodes," where the values of higher-level nodes are defined based on lower-level ones. Multimodal deep learning aims to gain joint features at an abstract level, by utilizing several pathways of deep learning from correlated data modalities. More recently, deep learning techniques have been successfully applied to feature learning in various pattern recognition tasks (*18*) and multimodal learning applications (*19, 20*).

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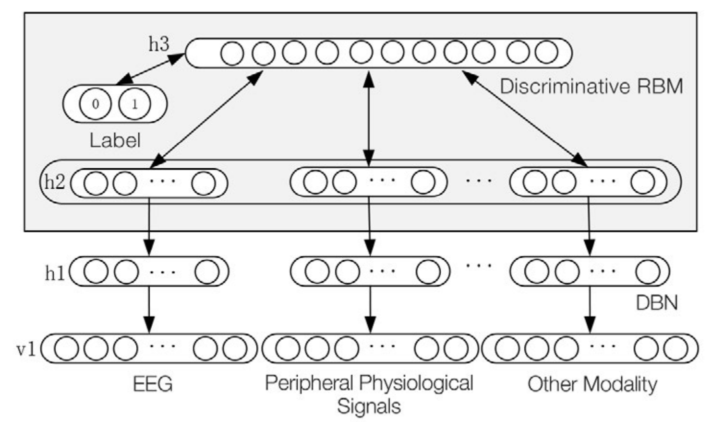

FIGURE 1. Deep learning framework for multimodal data.

In our work, we adopted multiple pathways of deep belief networks (DBNs), each of which is built for one data modality. A DBN is a type of deep learning model composed of several stacked restricted Boltzmann machines (RBMs), which are artificial neural networks that consist of two layers of input and output nodes. By stacking several RBMs together, a DBN is able to approximate any mathematical function for data transformation and representation. Usually, the lower RBM's output is regarded as the input of the upper one and it does not allow connections between nodes in the same layer. Each connection is assigned a weight parameter, and its value is decided and adjusted by several rounds of model training by utilizing sample data that is fed through the input layer.

Our multimodal deep learning framework is shown in Figure 1. Each DBN consists of two stacked RBMs, and v1 represents the input layer into which manually extracted features of electroencephalograms (EEGs) and peripheral physiological signals were fed. Further, h1 and h2 are output layers that can be used to extract higher-level abstract representations. Then a discriminative RBM (DRBM), a special kind of RBM acting as a classifier, is put over the combination of h2-layer representations for learning a shared representation in h3 and fulfilling emotion recognition tasks by the label layer, where each node represents one emotional state.

Empirical evaluation

The framework we describe has been validated on the publicly available DEAP dataset, which was collected through an experimental paradigm designed to elicit different emotions from the subjects through exposure to specifically selected music videos. The subjects' EEG signals, as well as other types of peripheral physiological signals, were continuously recorded while the music video was being viewed. Examples of these peripheral signals include the electrical activity of muscles [electromyogram (EMG)] and eye movement [electrooculogram (EOG)], galvanic skin response (GSR), respiration, and skin temperature. DEAP also provides data from subjects' self-assessment of their emotions, rated according to Russell's valence-arousal scale (*21*). By utilizing these rating values, we divided the samples into two emotional classes (i.e., positive and negative emotional states) as most studies have done for validating emotion recognition performance (17).

Feature extraction is important to machine learning tasks. In addition to the widely used linear features, we opted to extract a variety of nonlinear features (e.g., correlation dimension and Shannon entropy) from neurophysiological signals. We compared the recognition performance of our multimodal deep learning method with a commonly used traditional classification approach. We first applied the k-Nearest Neighbor (kNN) classifier to the features of EEGs. We then applied the same classifier to the combined features of peripheral physiological signals, and to the combined features of EEG and peripheral physiological signals. Through experimental comparisons, we have found that the use of the deep learning approach shown in Figure 1 to analyze multimodal neurophysiological signals can achieve better recognition of emotions than the traditional kNN classifier based on the use of different modalities individually or in combination.

In this article we have summarized how it is possible to recognize emotion using a deep learning approach based on multiple neurophysiological signals. In the future, emotion-related modalities not limited to neurophysiological signals (e.g., speech and functional magnetic resonance imaging) could also be added into the framework as shown in Figure 1. Going forward, it will be interesting to investigate the kind of neurophysiological signals that most strongly contribute to emotion recognition.

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Applying nontraditional approaches of electrophysiological data analysis to decision-making research

Dandan Zhang[1,†], Ruolei Gu[1,2,†], Pengfei Xu[1], Wenbo Luo[3], Yue-jia Luo[1,4*]

Synchronous firing of populations of neurons, which is an important source of brain electrical activity, contributes significantly to the neurobiological basis of human cognitive processing (*1*). Electroencephalography (EEG) captures this mechanism by measuring voltage fluctuations that result from the summation of the simultaneous activity of millions of neurons (*2*). The EEG signals being recorded contain information arising from the activation of scattered brain regions, which may be located either near or far from the cerebral surface. EEG predominantly measures the activity of cortical pyramidal neurons, because the geometrically parallel organization of these cells ensures that their synchronous firing can be easily detected via electrodes placed on the subject's head (*3*). It has been suggested that scalp EEG amplitudes elicited by the onset (or offset) of a sensory or a cognitive event (i.e., event-related EEG) can be detected as distinct from spontaneous or background EEG signals (*4*). This methodology has proven to be a valuable tool for cognitive neuroscientists, including those interested in human decision making (Figure 1A). The process of decision making can be broken down into several steps, including situation perception, option evaluation, action selection, and learning from outcome (*5*). The temporal overlap between the different stages of decision making provides huge difficulties for investigating the separate neural mechanisms underlying each stage. The EEG can help address this problem because it enables high temporal resolution (*6*).

As pointed out by Makeig et al., traditional event-related EEG data processing consists of two approaches, namely, a time-domain approach using event-related potentials (ERPs) that focuses on temporal features of the data, and a frequency-domain approach using spectrum analysis that focuses on a spectrum of frequencies or energies of the data. Neither of these fully represents

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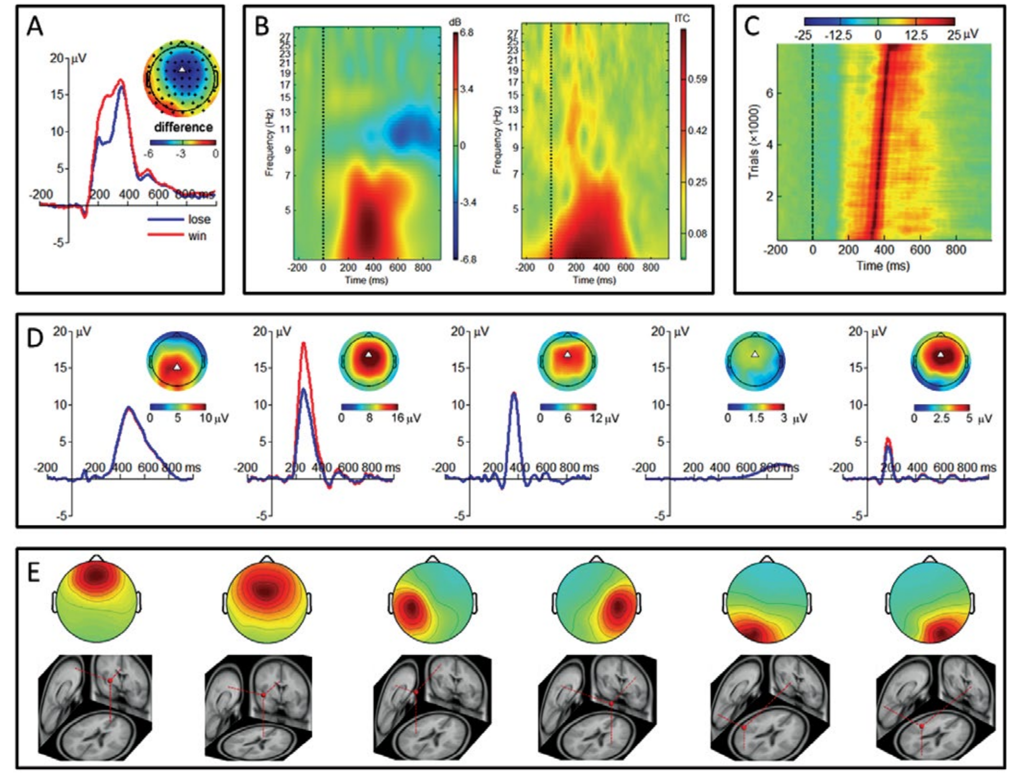

FIGURE 1. Examples of advanced electroencephalography (EEG) processing techniques. Participants took part in a monetary gambling game and the outcome feedback-elicited EEG data were analyzed. Refer to (*9*) and (*14*) for detailed experimental designs. **(A)** A traditional method for event-related EEGs, event-related potential (ERP) analysis. **(B)** A time-frequency analysis of EEG. Left panel: the event-related spectral perturbation (ERSP). Right panel: the inter-trial coherence (ITC). **(C)** The single-trial display of the P3-latency sorted ERPs. **(D)** Principle component analysis (PCA) of the data from (*9*). **(E)** Independent component analysis (ICA) of the data from (*14*).

the neural dynamics of the brain, which have important implications for the underlying neurocognitive function (*1*). The drawbacks inherent in the classical methods have long been acknowledged (see below), and researchers have sought to explore novel techniques of data analysis in recent years. Below we discuss the pros and cons of these techniques and their applications in decision-making studies.

Dynamics of neural synchronicity

Electrophysiological activity in the human brain is highly oscillatory, which means that the firing patterns of neighboring neurons tend to be synchronized because of the feedback connections between them (*3*). The theoretical significance of neural oscillation lies in the fact that it is the neuroelectric basis of distinct cognitive activities such as perception, memory, and consciousness (*7*). Data recorded from any given electrode contains power/phase dynamics that define the characteristics of neural oscillation (*3*). To decipher this information, a time-frequency analysis is necessary, which depicts the temporal synchrony of oscillatory activity over multiple frequency bands (Figure 1B). This approach helps unravel neural oscillation patterns in both the time and frequency domains simultaneously that cannot be reflected by traditional methods (for example, traditional cross-frequency coupling only results in a single index that reflects the intensity of synchronization between two oscillations over the whole time span) (*3*).

It is worth noting that a single EEG oscillation can be involved in different cognitive processes, because the combination of neurons that make up oscillations can belong to spatially overlapping or segregated functional networks (*8*). Therefore, it would be questionable to infer a one-to-one mapping relationship between a cognitive function and an oscillation response. Take medial frontal theta rhythms as an example. Numerous studies have reported that oscillations within the theta band (4–7 Hz) are critical for decision making under uncertainty, possibly reflecting neurophysiological processes underlying the way the brain learns from the environment (*9–11*). Nevertheless, frontal theta rhythms are also activated in a wide range of other cognitive tasks such as error processing and conflict detection, and thus likely represent a general operating mechanism involved in action monitoring, rather than a specific decision-making component (*11*).

Decomposing EEG data

The use of both principle component analysis (PCA) and independent component analysis (ICA) in EEG data processing is also becoming popular. The PCA approach treats the ERP waveform as a combined effect of temporally irrelevant voltages presenting simultaneously in the brain, and tries to provide a set of latent components that may index physiologically distinct processes (*1, 9*) (Figure 1D). By applying temporospatial PCA to ERP data, Foti et al. revealed that the feedback-related negativity (FRN)—represented as a negative wave elicited by the outcome feedback from decision-making tasks in conventional ERPs (*12*)—is actually a positive deflection localizing in the striatum (*13*). PCA components of ERP data are temporally or spatially orthogonal (or uncorrelated), because PCA specifically makes each successive component account for as much as possible of the remaining activity that has been unaccounted for by previously determined components. Unlike PCA, the ICA method seeks to maximize independent sources of activity and results in temporally independent components with unconstrained spatial distribution (*1*). By applying ICA to the EEG data recorded in a monetary gambling game, we found that the fronto-central theta component, the source of which is located in the anterior cingulate cortex, was closely associated with future risk-taking behavior (*14*) (Figure 1E).

PCA and ICA techniques enhance the precision of source localization of EEG data (*15*). However, we should keep in mind that as a data-driven method, neither PCA nor ICA is guaranteed to yield neurophysiologically meaningful results (*16*). Additional anatomical and empirical evidence is highly recommended (*17*).

Single-trial ERPs

Traditional analysis of event-related EEG data recognizes amplitude or energy changes time-locked to a given event by averaging epochs over a period of time, assuming that peaks at the same latencies are near-identical at the single-trial level (*18*). This oversimplified approach leaves a lot of the cognitively relevant information in the temporal dimension of EEG activity undiscovered (*3*). In contrast, single-trial analysis offers an opportunity to directly investigate systematic variations between trials (Figure 1C). This method does a better job of discovering potential links between cognitive processes and neural dynamics compared with conventional averaging (*3*). For instance, our recent study revealed that the P3 amplitudes in response to outcome feedback predict subsequent stay/switch decisions on a trial-by-trial basis (*14*). Importantly, single-trial analysis in the time-frequency domain could be used to determine whether averaged ERP features are shaped by stimulus-evoked power perturbations or phase synchronization/desynchronization of ongoing oscillatory activity (*19*). Delorme et al. showed that phase synchronization of the lower band of theta rhythm contributes significantly to the far-frontal positive component that indicates the speed of upcoming motor responses (*18*). This finding helps explain the neural mechanisms of motor decision preparation.

In summary, when appropriately used, newly developed methods of EEG processing can uncover novel aspects of decision-making dynamics that traditional analyses cannot. Still, researchers should be aware of the methodological shortcomings of these techniques to avoid producing results that are flashy but scientifically vague.

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Behavioral and electrophysiological profiles reveal domain-specific conflict processing

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Cognitive control refers to the top-down control of cognitive processes based on higher-order representations, such as goals or plans. It serves an essential role in carrying out goal-directed behaviors, especially when situations present conflicting information. A person's ability to perform a cognitive task can be hampered when the task involves an incompatible association between a stimulus and a response—a phenomenon known as the stimulus-response compatibility (SRC) effect. For example, in the Stroop task, participants are asked to name the color of a word; however, the word itself is presented in an incongruent color (e.g., the word "red" is displayed in blue ink). This creates a stimulus-stimulus (S-S) conflict, which stems from an incongruency between the task-relevant information (the color of the word) and task-irrelevant features of the stimulus (the word itself) (*1*). In contrast, a stimulus-response (S-R) conflict arises when there is incongruency between the task-irrelevant stimulus and the required response. One such example is the Simon task, in which participants are asked to respond to a stimulus that is displayed at the opposite side of the location of a response button (e.g., pressing a button on the right in response to an item shown on the left) (*2*). In addition, a person's performance on the current trial is also modulated by whether or not there exists incongruency in the preceding trial. Response times tend to be shortened in incongruent trials but to be lengthened in congruent trials, when following an incongruent trial as compared to following a congruent trial (*3*). Therefore, the SRC effect, which is indexed by the performance difference between the incongruent and congruent trials, is usually reduced following trials using incongruent information as compared to those using congruent information—a phenomenon known as conflict adaptation (CA) (*4*). This is likely because the brain regions involved in conflict resolution have already been activated from being presented with a task involving incongruent information and may continue to facilitate conflict processing in the following trial. Researchers often use SRC and CA effects to examine the mechanisms and brain regions involved in cognitive control of conflict processing. However, it is still unknown whether detection and resolution of S-S and S-R conflicts recruit distinct mechanisms or rely on the same resources in the brain.

Two models have been proposed for cognitive control of conflict resolution within the brain. The conflict-monitoring model is considered to be domain-general, meaning that the brain does not differentiate between S-S and S-R conflicts, and posits that the two types of conflict are resolved via the same mechanism (*5*). Thus, the conflict-monitoring model predicts that when both types of conflicts are present, they will interfere with each other and produce nonadditive SRC effects. In addition, CA could occur for both types of conflict because the conflict-monitoring model presumes that both S-S and S-R conflicts share the same modular architecture of conflict resolution within brain networks for cognitive control. In contrast, the dimensional overlap model posits that conflicts in different SRC tasks can be categorized into different types or domains (e.g., S-S and S-R conflicts), based on the similarity (overlap) between any two dimensional sets of task relevant stimulus, task irrelevant stimulus, and response (*6*). Therefore, S-S and S-R conflicts would be of a different nature and resolved by distinct and domain-specific modules. Thus, this domain-specific model has been proposed to refine the conflict-monitoring model (*7*).

We have conducted several studies collecting behavioral and event-related potential (ERP) data that support the hypothesis that S-S and S-R conflicts are processed via distinct mechanisms. According to the dimensional overlap framework, processing S-S conflicts should occur at the stimulus-processing stage—earlier than that of S-R conflicts, which are processed when the response is produced. We therefore examined the N2 component of electroencephalograph readouts, for which the amplitude is thought to index the level of conflict processing. The data showed that the N2 component evoked by the S-S conflict peaked earlier than that elicited by the S-R conflict, which suggests that processing of S-S and S-R conflicts has distinct temporal dynamics (*8*). In a second experiment, we tested whether SRC effects resulting from S-S and S-R conflicts are additive, which would be expected if the resolution of S-S and S-R conflicts relies on independent mechanisms. Our behavioral studies combining the spatial Stroop task (S-S conflict) and Simon task (S-R conflict) showed that the SRC effects on reaction times and error rates were indeed additive when both types of conflict were present (*9*). Finally, if distinct modules of cognitive control are engaged when processing S-S and S-R conflicts, then CA effects should be observed only within the same type of conflict but not across different types of conflict. Our ERP studies have shown that significant CA effects on N2 amplitudes (i.e., a reduced SRC effect following an incongruent trial versus a congruent trial) were only

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present when two consecutive trials involved the same type of conflict (*10*).

Taken together, our findings from our behavioral and ERP experiments support a domain-specific model for cognitive control of conflict processing. However, though such modular organization for cognitive control may be more efficient and can account for domain-specific modulation of conflict processing, we would caution against overinterpreting the data and concluding that cognitive control should be divided into endless distinct and specialized modules. Evidence from both behavioral and neural pattern classification studies suggests that both domain-general and domain-specific modules exist in the brain (*11*). More empirical studies are needed to examine the principal factors, such as sensory modalities or task sets, that impact such modular organization of cognitive systems.

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Computational-based behavior analysis and peripheral psychophysiology

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Computational-based behavior analysis aims to automatically identify, characterize, model, and synthesize multimodal nonverbal behavior within both human–machine as well as machine-mediated human–human interaction. It uses state-of-the-art machine learning algorithms to track human nonverbal and verbal information, such as facial expressions, gestures, and posture, as well as what and how a person speaks. The emerging technology from this field of research is relevant for a wide range of interactive and social applications, including health care and education. The characterization and association of nonverbal behavior with underlying clinical conditions, such as depression or post-traumatic stress, could have significant benefits for treatments and the overall efficiency of the health care system.

Here we review our collaborative research efforts on advanced computational approaches to studying nonverbal and physiological signals related to psychological states. First, we discuss the computational behavioral analysis framework. Second, we discuss the cardiovascular physiological measures that are the basis of the biopsychosocial model of our research. Finally, we discuss our intended future work and the limitations of integrating computational analytical techniques with physiological sensors in order to infer psychological states.

By utilizing computerized, machine-learned behavior assessment approaches, we have identified a number of behavioral indicators of psychological distress. Such indicators include, but are not limited to, the average intensity or duration of smiles (*1*), increased response times in controlled interview studies (*2*), attenuation of expressions associated with social isolation (*3*), and changes in the voice quality of a speaker (*3–5*). These findings not only confirm prior findings in the psychology literature, which mostly rely on subjective assessments and manual annotations, but also contribute to a better scientific understanding of psychological states through the application of advanced computational methods. The automated assessment of a patient's nonverbal behavior could prove valuable for clinicians and provide them with additional objective assessments of a patient's state or development over time.

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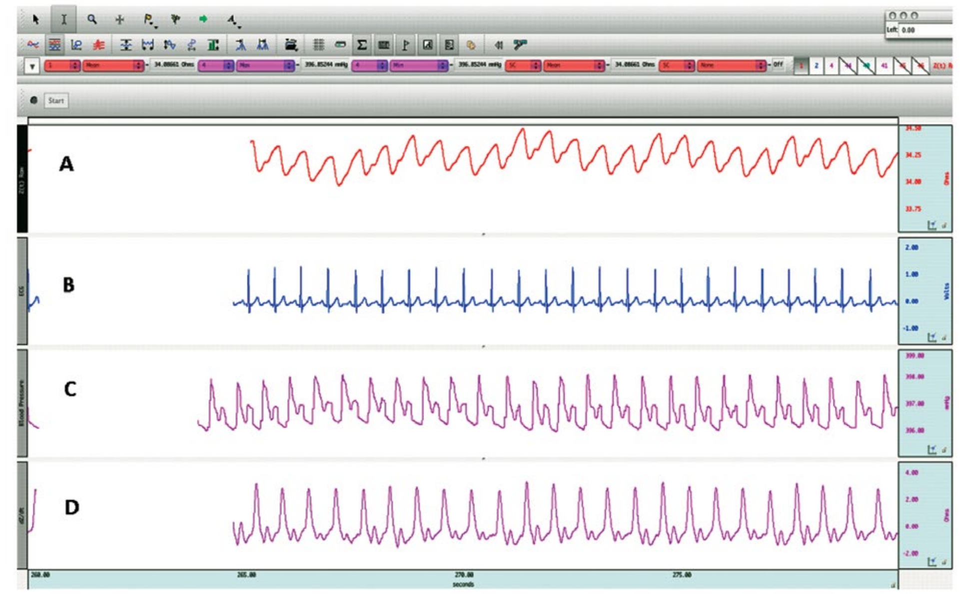

FIGURE 1. Sample continuous data stream of the multivariate cardiovascular physiology measures. (A) Impedance cardiograph. **(B)** Electrocardiogram. **(C)** Blood pressure graph. **(D)** *dZ/dt*, the derivative of the impedance cardiograph.

Within an educational context, computer-assisted training and assessments of a person's social skill proficiency and expertise can help to create individualized education scenarios, in particular for those with learning disabilities or social anxiety. Computer-assisted vocational training, for example, might be able to improve the chances that a young adult with autism spectrum disorder (ASD) can become a fully integrated member of society through experiential and guided preparation. Computationally based behavior analysis has already found its way into a number of application-oriented educational scenarios, including job interview training (*6*) and public speaking training (*7*, *8*), as well as science, technology, engineering, and mathematics (STEM)-oriented learning technologies (*9*).

This novel field of research is at the intersection of psychology, machine learning, multimodal sensor fusion, and pattern recognition, and is emerging as an essential field of investigation for computer scientists. Most recently, researchers have started to not only assess visual and acoustic behavior via unobtrusive and noninvasive sensors (i.e., cameras and microphones), but also track otherwise latent measures, such as a person's heart rate (*10*). This approach to assessing often inaccessible measures of a person's physiology could enable novel applications and provide a deeper understanding of the physiological processes underlying observable behavioral changes.

Psychologically grounded physiological measures

Most physiological approaches in computer science only use one type of physiological measure. Conversely, our research uses multiple psychologically grounded measures that reflect autonomic nervous system activity. For example, it is not uncommon for applied computer science researchers to measure a single peripheral physiological measurement, such as heart rate variability (HRV) (*11*) or electrodermal activity (EDA) (*12*), because they are assumed to be indicative of cognitive workload and/or stress. However, changes in HRV and EDA measures have been correlated with several different psychological states and processes, e.g., HRV can vary depending on cognitive workload and on how a risky choice is framed during the decision-making process (*13*, *14*).

Relying on single measures can mask important processes because of the one-to-many mapping between a single physiological measure and the numerous psychological processes to which it can be correlated. Conversely, according to the biopsychosocial model (BPS) (*15*) of challenge and threat, physiological measures of cardiovascular responses can be used to determine specific patterns that represent the two motivational states of challenge and threat. A person will perceive a situation as a challenge if they determine that the available resources outweigh what is needed to complete a task. Whereas, one perceives a threat if instead the evaluated resources do not meet the demands to carry out a task, or if there is uncertainty.

The same neural and endocrine processes affect cardiovascular responses during both a perceived challenge and threat, including increased heart rate (HR) and increased ventricular contractility (VC). However, cardiac output (CO) and total peripheral resistance (TPR) differ depending upon the motivational state. The neuroendocrine underpinnings (*16*) of cardiovascular responses involve the sympathetic-adrenal-medullary (SAM) and hypothalamic pituitary-adrenal-cortical (HPA) axis. Both states involve the activation of the SAM axis, while only the threat state involves both of the axes. A challenge state results in decreased TPR and an increase in CO, whereas a threat state leads to little or no change or a decrease in CO and little or no change or an increase in TPR (*17*). We infer CO, TPR, and VC by relating different points on the multivariate cardiovascular physiological data stream (Figure 1).

Social cues affect cardiovascular responses

Our research has applied the BPS model to understand how social interactions with a virtual human affect cardiovascular responses (*18*). We designed a scenario (game) in which participants negotiated with a virtual human partner over multiple issues regarding the sale of a mobile phone. Our motivation in using a virtual human and this particular interpersonal task was to increase the ecological validity of the experiment, while also maintaining tight experimental control of social cue manipulation. Virtual humans were able to make emotional facial expressions and behave either competitively or more cooperatively during the negotiation. The results showed the same patterns of cardiovascular measures as the BPS model of a psychological state of threat when there was discordance between the behavior and expressed emotion of the virtual human. A corresponding eye tracking analyses during this task further suggested that the participants experienced uncertainty because of the discordance, which is characteristic of a threat state. Specifically, participants in the discordant conditions looked at the virtual human's face more, most likely to sample information that might help them reconcile the discordance between the behavior and facial expressions.

Throughout the task, individual events during the game were synchronized with the cardiovascular physiology data stream. These events would take place at variable intervals because of the interactive nature of the task, but the average frequency was between 5 and 10 seconds. Traditionally, we have analyzed the physiological measures at every minute using ensemble averaging, which is the mean of a signal as a function of a microstate of that signal, e.g., a heartbeat. We then related the time points between the *dZ/dt* and the electrocardiogram on the ensembled waveform (a composite waveform for a specific time window). However, we anticipate moving to a more fine-grained analytical approach in which we relate events in the game to a window corresponding to the near-real time cardiovascular data stream. Moreover, we are currently engineering solutions to synchronize multimodal data from the computational behavior analysis framework with the corresponding time course in both the virtual game environments and physiological data streams. For example, a preliminary analysis indicates some interesting relationships between the voice quality measures of the computational behavior analysis and the BPS cardiovascular physiology measures (*19*). One applied goal in this line of work is to detect states of relative challenge or threat from the cardiovascular data in near-real time, so as to design an interactive virtual human that is responsive to the user's motivational state.

Certain limitations must be overcome in order to further understand the dynamics behind real-time changes in an individual's cardiovascular state and the concomitant psychological states. Practically, many of the sensing hardware setups are not robust enough to detect movement artifacts. Therefore, the current application for this approach involves tasks in which users are seated. Scientifically, much can be gained by understanding the variability of humans' physiological responses to the same stimulus (*20*). For example, two different individuals might have different cardiovascular responses as a result of how they evaluate perceived resources relative to perceived task demands. A future goal will be to understand the characteristics that predict how an individual will respond to different psychological stressors.

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Applications

Theories and models derived from computational psychophysiology studies can provide a foundation for translating research into new applications and interventions.

How the ancient art of acupuncture works: Neuroimaging studies shed light on brain activity

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In 1971, James Reston's story "Now, Let Me Tell You about My Appendectomy in Peking" appeared on the front page of *The New York Times*. The description of his treatment single-handedly ignited Americans' curiosity about China and began America's decades-long relationship with acupuncture *(1)*. Acupuncture—an ancient healing modality and still quite a mysterious technique originating in traditional Chinese medicine—is the insertion of needles into, and the subsequent stimulation of, specific points (acupoints) on the body to facilitate healing. In 1997, a U.S. National Institutes of Health (NIH) panel issued a consensus that acupuncture is effective as a therapeutic intervention for specific conditions and can have fewer and less harmful side effects than drugs or surgery (*2*). More recently, a survey conducted by the World Federation of Acupuncture and Moxibustion Societies showed that acupuncture was being used in 183 countries in 2013 (*3*). Researchers have since been investigating the effects of acupuncture on the human brain using neuroimaging techniques, providing insight into the particular brain networks involved in the treatment's impact. Here we discuss some of these studies.

Temporospatial encoding of acupuncture's effects on the brain

Acupuncture needle manipulation stimulates multiple peripheral sensory receptors, which send signals to the brain mainly through the spinal ventrolateral funiculus. Early studies using functional magnetic resonance imaging (fMRI) aimed to establish a spatial map correlating acupuncture stimulation at peripheral acupoints with the corresponding functional activation in the cerebral cortex (*4*). These studies used fMRI to identify attenuation of blood oxygen level-dependent (BOLD) signals in the limbic/paralimbic, brainstem, and neocortical regions (*5*). The BOLD signal attenuation, compared to a "resting period" baseline, represents decreased regional neuronal activity that occurs while an external stimulus is processed. A large proportion of the acupuncture neuroimaging studies since 1998 have used this method of analysis, dubbed a "block" design (*6*). The block design is built on a stimulus-response model that assumes the BOLD signal will instantaneously return to baseline (prestimulus) level after stimulation (*6*). However, clinical reports have made it clear that acupuncture provides relief well after the actual procedure and even peaks long after the stimulation session is terminated (*6*). Our analysis from 2009 indicated that because of the sustained effects of acupuncture, the block design and its related analytical methods have actually biased the experimental results of brain responses to acupuncture (*7*), and thus the results cannot be used to explain the mechanism of acupuncture.

More recently, we have published findings that could shed light on the complex mechanisms by which peripheral acupuncture stimuli and central nervous system (CNS) neuronal dynamics interact as a function of time. Needle manipulation alone can evoke consistently increased signal changes across several different brain regions, as well as more complex and time-varied neural responses during the poststimulus phase. We infer from these findings that acupuncture creates a biphasic response consisting of an initial phase involving effects due to needle stimulation of deep tissue, with skin piercing and biochemical reactions to tissue damage, followed by a second phase comprising prolonged physiological effects for a period after the removal of the acupuncture needle (*8*).

Stimulating different acupoints to treat various clinical conditions is usually accompanied by multidimensional physiological and psychological responses, which are also regulated by the CNS (*9*). These responses suggest that the peripheral acupoint-brain interaction may involve the coordinated activity of large-scale brain networks. The CNS encodes the body's responses to peripheral stimulation at different acupoints that are then deciphered within a functionally specific brain network (*10*). Furthermore, the late, sustained response (the second phase described above) utilizes these brain networks to implement certain long-term functions (*10*). A key question, therefore, is: Do the interactions between these brain networks control the expression of brain responses to acupuncture stimulation, and if so, in what way is this accomplished? To investigate this possibility, our research group used a non-repeated event-related (NRER) paradigm (*11*), employing two visual acupoints (GB37 and BL60) and a nonvisual acupoint (KI8) in tandem with fMRI. We found that needle stimulation at each of these acupoints separately induced spatially converging brain responses, which overlapped at the posterior cingulate cortex and precuneus (PCC/pC) region. The PCC/pC region then interacted with a vision-specific functional network [i.e., the visual resting state network (RSN)] in different patterns, and could thus serve as an information hub to drive the intrinsic visual network and implement specific brain functions after different acupoint stimulations (*10*). In a broader sense, this type of functional connectivity can be thought of as the brain being organized as a metanetwork (a network of coupled networks). For example, one landmark observation identified a distributed network of associated regions, often referred to as the default mode network (DMN), which behaves as a functionally coupled system (*12*). In addition, a 2009 study indicated that specific areas of the DMN, especially the PCC/pC, are key components within the network and can be considered as putative "cortical hubs" (*13*).

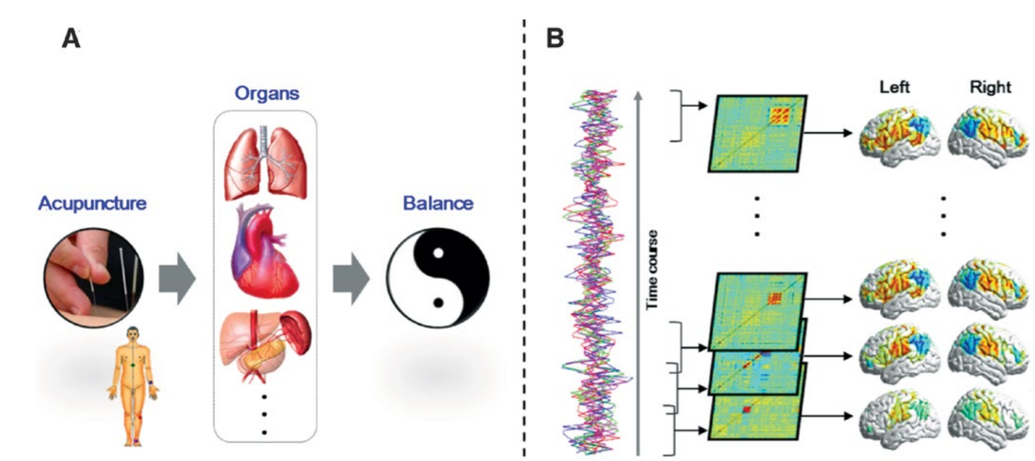

FIGURE 1. Encoding of acupuncture. (A) The theory of traditional Chinese medicine—which began about 3,000 years ago—suggests that the stimulation of the acupoints over the body's organs can generate the regulatory signals necessary to maintain the body's homeostasis and cure diseases. (B) Modern perspectives from neuroscience indicate that acupuncture treatments affect disease outcomes via changes in the brain. Neuroimaging techniques detect brain activity in response to external stimuli, which can be represented as a time-varied, dynamic brain network with various activation patterns. These different activation patterns are thought to represent acupuncture's specific effects.

Disease-specific neural correlates and acupuncture-targeted regulatory encoding in the brain

As one of the most widely used complementary and alternative medicines, acupuncture has shown promise for postoperative use and for lessening chemotherapy-induced nausea and vomiting and postoperative dental pain. Furthermore, acupuncture may be a beneficial adjunct or alternative treatment for drug addiction, stroke rehabilitation, asthma, and chronic pain, though the evidence for such benefits is less convincing than those reported for other uses (*2*). In 2006, Martin et al. reported that acupuncture significantly relieved the symptoms of fibromyalgia (*14*). Acupuncture has been shown to activate different types of afferent nerve fibers, and its effectiveness has been suggested to depend on individual symptoms and previous sensitization to acupuncture (*15*). Clinical reports further indicate that acupuncture can also modulate the body's homeostasis to produce treatment effects in patients *(9, 16, 17)*. Because these observations need further validation, quantitative brain measures may be used to provide an evidence-based rationale for the interactions of disease-specific neural correlates and acupuncture-targeted regulatory encoding in the brain.

Although peripherally applied acupuncture stimulation is mediated through multiple peripheral systems, the initiation of its therapeutic effect requires coordinated coactivation of multiple brain regions (*9*). Functional dyspepsia (FD), or indigestion, is the most common upper gastrointestinal symptom and is diagnosed when upper gastrointestinal endoscopy reveals no organic lesions that might explain the symptoms *(18)*. One recent study was designed to investigate acupuncture treatment in patients with FD (*19*). Seventy-two patients with FD were randomly assigned to receive either acupuncture or sham acupuncture treatment for four weeks. Ten patients in each group were randomly selected for positron emission tomography (PET) scanning before and after treatment. Compared with the sham acupuncture group, those receiving real acupuncture showed greater deactivation in the brainstem, anterior cingulate cortex, insula, thalamus, and hypothalamus, and these deactivations were associated with greater improvements in FD symptoms (*19*). Another study examined the efficacy of transcutaneous vagus nerve stimulation (tVNS) for one month in treating major depressive disorder, because the severity of depression has been significantly associated with functional connectivity changes between the DMN and several brain regions, such as the orbital prefrontal cortex, insula, and dorsal anterior cingulate cortex (*20*). This study suggests that tVNS-modulated treatment effects are not limited to a specific targeted brain region, but are associated with a wide range of brain networks contributing to emotion/affect regulation (see Figure 1).

Conclusions and future directions

It has long been the hope of both scientists and doctors to treat diseases using noninvasive techniques that activate self-regulating mechanisms without using drugs or surgery. One researcher's recent effort has focused

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on the use of a noninvasive neuromodulation technique called repetitive transcranial magnetic stimulation (rTMS) (*21*) to induce electrical currents in cortical neurons, which has achieved promising but limited success in the treatment of depression. The evidence presented in the present review demonstrates that peripheral acupuncture stimulation activates specific neural networks (*6*). These pathways give rise to the integration of external trigger signals, allowing the brain to initiate internal (self-regulating) mechanisms. Emerging computational models of brain networks provide some evidence-based rationale, as well as the first quantitative insights into the self-healing effects underlying the ancient art of acupuncture (*6*). These noninvasive brain imaging techniques hold the potential to reveal the pathways mediating the effects of acupuncture. Understanding these neural circuits and how they encode information is fundamental for determining how these treatments work.

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Improving working memory using EEG biofeedback

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Working memory (WM) refers to the ability to maintain and manipulate information over short periods of time in the context of concurrent processing or distractions (*1,2*). It is widely accepted that WM capacity is key for a wide range of higher-order cognitive functions (*3*), therefore the possibility of enhancing WM has stimulated a series of WM-training studies (*4-6*). Computerized WM training (CWMT), originally developed by Torkel Klingberg, has been widely employed for such research, in which subjects repeat WM tasks using a computer program that provides visual and verbal feedback and rewards based on the accuracy of every trial. Subjects who have practiced WM tasks using this type of feedback have been reported to have significantly higher improvements than controls (*5*). This form of repetitive WM practice is essentially behavioral feedback, which activates both the central executive and storage subcomponents of the related working memory of brain systems. Based on functional magnetic resonance imaging (fMRI) studies, researchers have attributed such WM improvements to long-lasting neuronal changes in WM task-specific areas of the brain. These changes are accompanied by alterations in common neural networks that are not only related to WM but also many other cognitive functions, such as fluid intelligence (*7*). Functional magnetic resonance imaging (fMRI) studies have provided further evidence suggesting that WM training induces plasticity that alters both WM-related neural networks and those related to other cognitive functions (*8*).

However, most, if not all, of these studies employed WM training using behavioral feedback in which subjects practice a task, but without use of the neurofeedback technology (NF). The purpose of NF technology is to help the brain function more efficiently based on approaches that induce autoregulation of specific brain regions using real-time data depicting fluctuations in brain activity. Studies have shown that WM capacity can be enhanced by NF training. In NF training, the subject's brain activity related to a WM task is observed and quantified and then shown back to the individual along with either a "reward" when the brain has changed its activity to a more appropriate pattern, or no "reward" if the goal is not met–thus the brain is trained to function more efficiently. This gradual learning process can induce enhanced activity in WM-related areas of the cortex and neural networks (5, 9). In one such example, Zhang et al. employed real-time functional magnetic resonance imaging (rtfMRI) to guide subjects' training. The fMRI signal recorded from the subjects' left dorsolateral prefrontal cortex (DLPFC) was transformed into visual feedback in the form of a graduated thermometer. The subjects then learned to improve their WM performance using a cognitive strategy in which they recited self-generated digit/letter sequences subvocally in reverse order. Subjects adjusted the sequences' content, length, difficulty, and recitation speed to increase the number of bars in the thermometer as high as possible, reflecting upregulated activation in the DLPFC (*9*).

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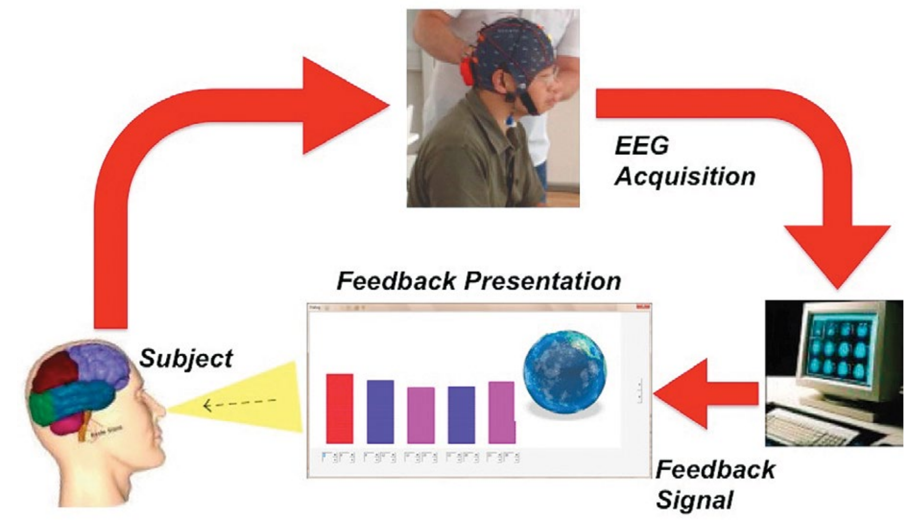

FIGURE 1. Scheme of EEG biofeedback.

Electroencephalography (EEG) is the most widely used type of NF signal, therefore the term NF is often referring to EEG biofeedback. EEGs can be used as feedback to teach self-regulation of brain function, i.e., the subject is taught to modulate excitatory and inhibitory EEG patterns using feedback of their brain activity (EEG signals) (Figure 1). EEG biofeedback is now used in treatments for a variety of neurological disorders and as a means for improving cognitive performance (*10*). Although NF training has been promising, additional research is needed to help improve the technology. For example, it is still unclear as to which features of an EEG are most effective for WM training and whether behavioral-based feedback or EEG-based biofeedback training is more efficient (less time consuming) for enhancing WM. Therefore, we designed a study to test both of these questions and discuss the results below.

EEG feedback features for improving WM

To investigate which EEG components can contribute the most to WM capacity, we designed a study to identify the moment-to-moment EEG spectrum features that represent various levels of WM (*11*). We recruited 17 healthy, right-handed student subjects (7 female, 20-23 years old) from Beijing Normal University, and asked the subjects to perform "2-back" (WM) tasks and control [frontal cortex (FC)] tasks. In the 2-back task, the subjects were shown a sequence of visual stimuli and then asked to judge whether a particular stimulus was identical to the one displayed two positions prior in the sequence.

During the experiments, a BioSemi ActiveTwo EEG acquisition system with 64 electrode channels was used to continuously record the subjects' EEG data. We estimated the power spectra of each of the 64 EEG channels to be 0.5 milliseconds. The power of the EEG rhythms, such as theta (4–7Hz), alpha (8–12Hz), sensorimotor rhythm (SMR) (12–15Hz), low beta (13–20Hz), and high beta (20–30Hz), is shown in Figure 2. Delta (0.1–3Hz) was not included here due to susceptibility to eye blink and eye movement. As shown in Figure 2 (left), we compared the average of the subjects' scalp maps during WM and FC tasks and found that the anterior-parietal region showed the largest differences in activation under the two conditions. Figure 2 (right) shows a comparison of EEG power, in which we observed that the power of the theta rhythms was larger in the WM trials than in the FC trials, whereas we observed the reverse for the alpha rhythms. We confirmed that the effects on both the theta and the alpha rhythms were statistically significant (*11*).

EEG biofeedback effects during WM training

To determine the effects of EEG biofeedback during WM tasks, we conducted a study in which we recruited 48 female student subjects (20–23 years old) and divided them randomly into 4 groups: the neurofeedback (NF)-training group (5 female, 7 male); the behavioral-training group (6 female, 6 male); the sham neurofeedback-training group (5 female, 7 male); and the no-training group (7 female, 5 male) (*11*).

Figure 3 outlines the experimental scheme. All of the subjects, except for those in the no-training group, attended one of the three types of training procedures. Each subject began their session with a pretest and ended with a posttest, in which they performed the 2-back WM tasks and their accuracy and response times were measured (*11*).

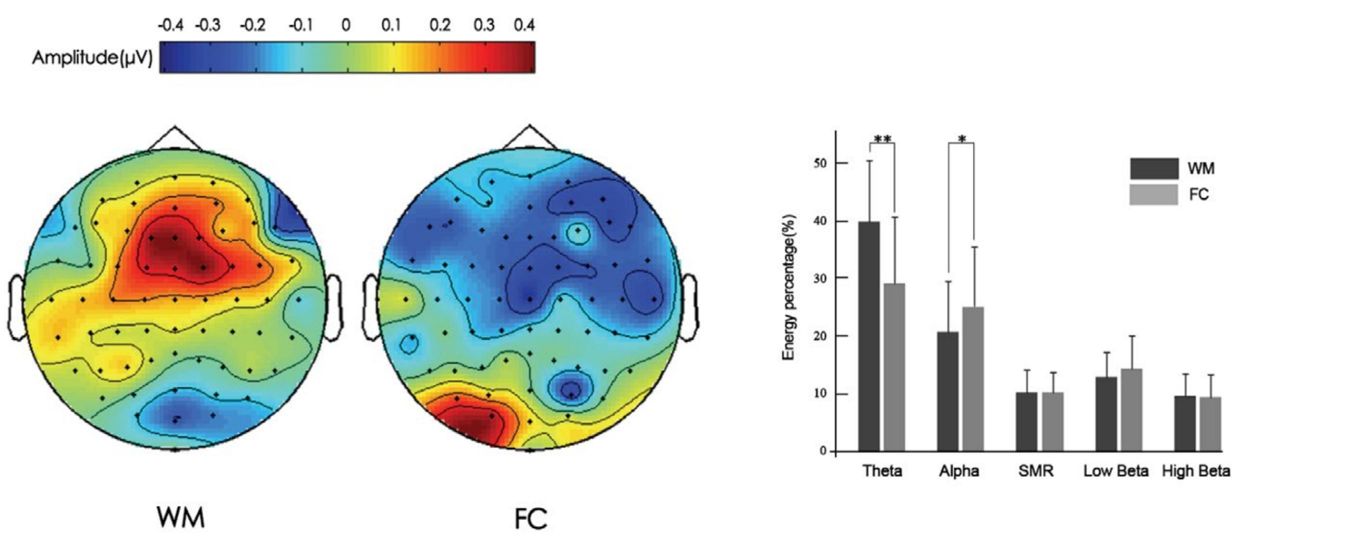

FIGURE 2. Comparison of EEG power spectra under working memory (WM) and control [frontal cortex (FC)] tasks. (Left) Scalp map for WM and FC tasks respectively. The activation regions during the WM task were mainly located in the anterior-parietal areas. (Right) Power percentage of EEG rhythms from grand average event-related potential (ERP) across 17 subjects and across electrodes in the anterior-parietal areas. Asterisks indicate significant differences between two task conditions. ***P*<.01, **P*<.05.

In the NF training group, the EEG signals related to the WM tasks were transformed into visual feedback—a rotating sphere with a graduated thermometer on the computer screen that was presented to subjects once every 500 milliseconds. Subjects were instructed to use a cognitive strategy to persistently increase the level in the thermometer or rotation speed of the sphere as much as possible. In the sham NF-training group, subjects completed the same experimental procedure and received the same instructions as the NF training group, except that they were provided with sham NF signals, which were not from their own EEG rhythms but rather from a mixture of noise and other subjects' signals. The magnitude and variability of the sham EEG signals were similar to those of the real signals. In the behavioral-training group, subjects attended the CWMT training, performing the WM (2-back) tasks using a computer program developed for this study. In the no-training group, subjects also attended the pretest and posttest, which was similarly separated by a 5-day interval; however, subjects were not trained in between the two testing sessions. This group served as a control to assess the effects of the repetitive performance of the same WM tasks in pretests and posttests.

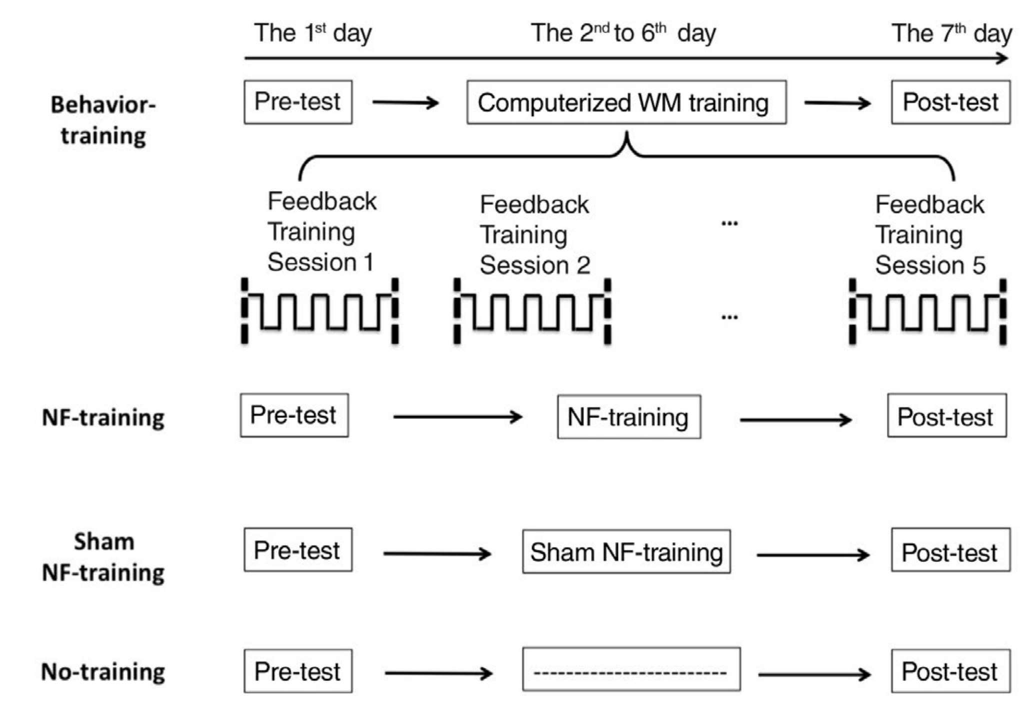

FIGURE 3. Experimental procedure for NF training and control groups.

We assessed the change in WM performance by measuring the accuracy and time of responses during the 2-back tasks for the pretests and posttests. A one-way analysis of variance (ANOVA) determined that the each of the groups' pretest performances were equivalent [accuracy: $F(3, 44)<0.184$, $P>0.906$; response time: $F(3, 44)<1.131$, $P>0.347$]. A pairwise comparison between the pretest and posttest results showed increased accuracy (an accuracy gain) for each of the groups; however, the effect was significant only in the NF-training, behavior-training, and no-training groups. The largest effect was in the NF-training group, followed by the behavioral-training group. This gain was significantly smaller for the sham-NF and no-training groups compared with both the NF-training and the behavioral-training groups. The accuracy gain that we observed between the different groups indicates that NF training and behavioral training are both superior to sham NF training or no training at all. However, it should be noted that behavioral exercises took more time to train subjects (five training sessions) and showed a slightly larger accuracy gain compared with NF training (one training session) (*11*).

Summary

The goal of our study was to elucidate the effects of NF during WM training. Our data demonstrated that young healthy adults can improve WM by training (evident by our subjects' increased response accuracy and decreased response time in the 2-back task). Future research will be needed to ascertain the neurological mechanisms underlying WM training.

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Computational modeling and application of steady-state visual evoked potentials in brain-computer interfaces

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A brain-computer interface (BCI) is a nonmuscular communication channel between the brain and a computer or external electronic device. Brain signals are directly translated into commands to control output devices so that locked-in patients—those incapable of moving or communicating verbally due to a medical condition such as paralysis—can interact with their environments. The brain signals used for BCIs can be generated by exogenous stimuli. The steady-state visual evoked potential (SSVEP) is one of the most commonly used brain signals in BCI studies. This is because the SSVEP-based BCI has several advantages, including a noninvasive nature, easy setup, and fast communication speeds (*1*). To improve the performance of the existing SSVEP-based BCI systems, we have created a computational model of SSVEP that we have used to develop guidelines for a BCI system design. Below, we discuss this model and present the high-speed BCI speller as an example of a successfully developed SSVEP-based BCI system.

SSVEP-based BCIs

SSVEPs are the electrical signals with which the brain responds to periodic visual stimuli. As shown in Figure 1A, when a subject receives a light stimulus, the luminance of which is modulated with a sinusoidal wave, SSVEPs—which exhibit a fundamental frequency component that is the same as the stimulus frequency and its harmonic—can be recorded over the occipital region on the scalp. SSVEPs have been widely used in BCI and cognitive neuroscience studies (*2*). Figure 1B shows a diagram of an SSVEP-based BCI speller. The system has 40 characters (or "targets"), which flicker simultaneously, but at different frequencies. When the user looks at a specific letter, the BCI system can recognize the fixated target by detecting the frequency of SSVEPs using a target identification method. In general, BCI performance can be evaluated using the information transfer rate (ITR), which describes how fast the target can be correctly recognized. ITRs of current

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SSVEP-based BCIs are typically less than 60 bits/min (*1*).

Computational model of SSVEP

A computational model of SSVEP is a mathematical formula describing the relationship between the visual stimuli and brain responses (Figure 2A). Computational modeling of SSVEPs is advantageous for developing target identification methods for SSVEP-based BCIs (*3*). Currently, there is a lack of computational models of SSVEPs for the specific purpose of designing a BCI. Therefore, we wanted to explore the potential for creating an efficient computational model to improve the performance of SSVEP-based BCIs.

We have proposed a computational model of SSVEPs that jointly considers the incoming stimulus signal and the resulting SSVEP responses (Figure 2B). Given a stimulus frequency, f_0, and an initial phase, φ_0, the stimulus signal can be described as follows:

$$x(t) = \sin(2\pi f_0 t + \varphi_0) \quad 0 \le t \le T$$

where *T* is the stimulus duration. The scalp-recorded EEG responses to the stimulus consist of SSVEPs, spontaneous EEG signals, and other noise (such as muscle artifacts and power line interference). We use the following model to describe SSVEPs recorded on the scalp:

$$y(t) = \sum_{k=1}^{N_H} a_k \cdot \sin\left[2\pi k f_0 \left(t - \tau_{AL}\right) + \varphi_k\right] + n(t) \qquad \tau_{AL} \le t \le T + \tau_{VP}$$

The evoked SSVEP signals consist of multiple sinusoidal components at the stimulation frequency and its harmonic frequencies. The number of harmonics N_H can be determined by the stimulus frequency and the upper-bound frequency of the responses (*4*). In our recent study, SSVEP harmonics were clearly observed within the frequency range that showed an upper-bound frequency around 90Hz (*5*). τ_{AL} is the visual delay between the stimulus and the SSVEP response (*6*). τ_{VP} is the duration for which a response persists following a stimulus. The amplitude and phase of each harmonic component are specified by α_k and ϕ_k, respectively. Generally, the amplitude of the harmonics decreases when the frequency of the harmonics increases. The phase for each harmonic component can be considered as a constant. However, the relationship between the stimulus phases and harmonic phases still remains unknown due to a lack of information about how the SSVEP harmonics are generated. For simplicity, other nonevoked signals are considered as noise and simplified as *n*(*t*) in the model. Here we only focus on modeling the evoked SSVEP signals.

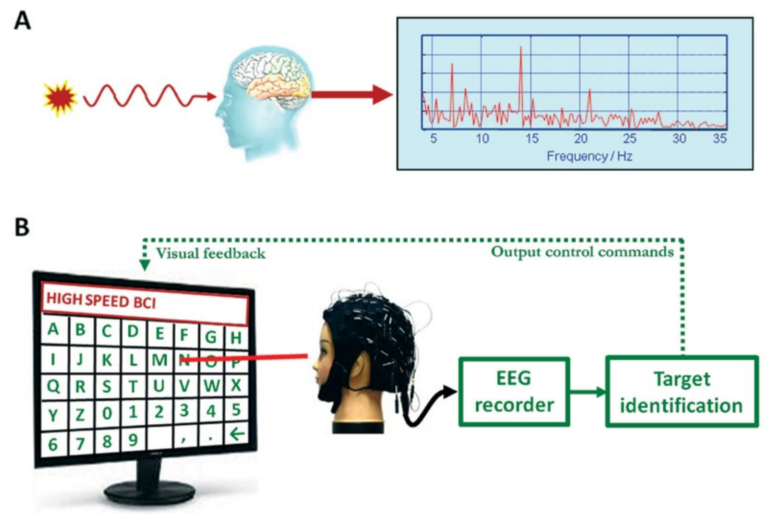


FIGURE 1. A steady-state visual evoked potential (SSVEP)-based brain-computer interface (BCI). (A) Example of SSVEP recordings in response to periodic visual stimuli. Fundamental and harmonic frequency components make up the SSVEP spectrum. **(B)** System diagram of an SSVEP-based BCI speller. Subjects focus on one letter at a time; each letter flickers at different frequencies. Once the specific frequency component is identified via the electroencephalogram (EEG) recorder, the corresponding letter appears on the screen.

Categorizing SSVEP modulation

The proposed computational model describes SSVEPs as a set of sinusoidal signals with specific frequencies and phases. Parameters in the model can be used to track how different cognitive tasks affect SSVEP. Typically, BCI and cognitive studies that use SSVEPs change only one parameter (e.g., frequency, phase, or amplitude) at a time. Recently, methods that can simultaneously modulate multiple parameters (e.g., frequency and phase together) have been proposed for BCI studies (*7*). The approaches for modulating SSVEPs can be categorized into three groups (see Figure 3):

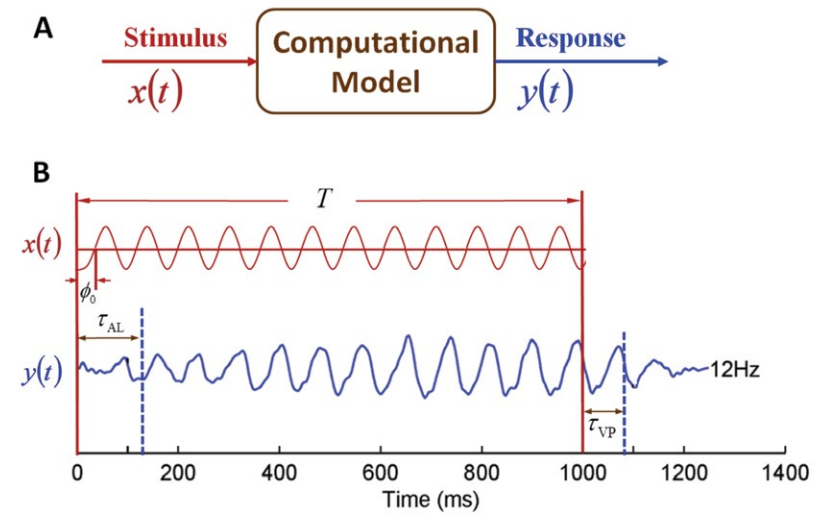
Frequency tracking

Frequency tracking is the most well-known characteristic of SSVEPs (*4*). SSVEPs exhibit the same frequency as the flickering stimuli. The widely used frequency tagging technique (i.e., multiple visual targets are tagged with different flickering frequencies, see Figure 3A) was developed based on this characteristic. The direction of the gaze or attention can be determined based on the frequency of SSVEPs. Frequency tracking is the most popular method for implementing SSVEP-based BCIs (*2*). The proposed computational model of SSVEP indicates that, in addition to the fundamental component, the harmonic components can also provide distinct information for frequency tracking.

Phase tracking

The initial phase of SSVEP can reflect the visual delay

FIGURE 2. Computational model of the steady-state visual evoked potential (SSVEP). **(A)** A computational model of SSVEP is a mathematical formula describing the relationship between visual stimuli and brain responses. *x*(*t*) is the stimulus signal and *y*(*t*) is the SSVEP response. **(B)** An example of a periodic visual stimulus (red line) and the resulting SSVEP (blue line) at 12Hz. *T* is the stimualtion duration. ϕ_0 is the initial phase of the stimulus signal. τ_{AL} is the visual delay between the stimulus and the SSVEP response. τ_{VP} is the duration for which a response persists following a stimulus.



between the stimulus and the SSVEP response in the visual pathway (*6*). A stable visual delay found in our recent study (*7*) suggests that phase tracking of SSVEPs is feasible and practical. A phase-tagging technique in which multiple visual targets are tagged with different phases at the same frequency (see Figure 3B) can be developed. It was noted that the phases of the harmonic SSVEP components could also be used for phase tracking. In recent BCI studies, the combination of frequency tracking and phase tracking was shown to be more efficient than either one alone (*7*). However, since the phase values of SSVEPs vary over time, phase tracking requires precise synchronization between the stimulus signals and the resulting SSVEPs.

Attention tracking

In addition to frequency tracking and phase tracking, attention tracking is another approach that employs SSVEP modulation. Overt attention (i.e., attending to the target by moving the eyes) and covert attention (i.e., mentally attending to the target without moving the eyes, see Figure 3C) impact SSVEPs in different ways (*8*). Specifically, one study of visual attention has shown that both the amplitude and phase of SSVEPs are modulated by covert attention (*9*). Therefore, attention tracking can be performed by measuring the amplitude and phase of SSVEPs. Attention tracking has been applied in BCI research to implement independent SSVEP-based BCIs that do not require eye movements to operate the system (*2*).

Guidance for design and implementation of SSVEP-based BCIs

Information transfer from stimulus to SSVEPs

To design BCI models, the relationship between the stimulus and SSVEP responses must be taken into account. Further, the SSVEP model proposed above emphasizes that the transferability of information from the stimulus to SSVEPs is an important principle to consider when designing an SSVEP-based BCI. The stable visual delay in the visual pathway ensures that the properties of the stimulus signals are carried through to the resulting SSVEP responses. For example, two stimuli with the same frequency and a 180-degree phase difference can result in two SSVEP signals that are negatively correlated (i.e., with a correlation coefficient of –1). Therefore, optimization of the stimulus signals can be used as a proxy for optimization of BCI performance. In this case, advanced target coding technologies such as multiple access (MA) methods in telecommunications, which allow multiple data streams to share the same communication channel, can be applied to improve the performance of SSVEP-based BCIs (*1*).

Framework for design and implementation of SSVEP-based BCIs

Based on our computational model of SSVEP, we have further proposed a general framework for the design and implementation of an SSVEP-based BCI. The framework, which can provide a highly efficient roadmap for the design of an SSVEP-based BCI, consists of three major procedures: benchmark dataset collection, offline system design, and online system implementation. Theoretically, the ability to ascertain SSVEPs directly from the stimulus data enables a system to be designed without real SSVEP data. However, due to the potential interference of SSVEP harmonics, assessing BCI performance using real SSVEP data will likely be more accurate. Our recent studies have shown comparable performance in offline and online BCI experiments (*5*, *7*). Therefore, simulating an offline BCI system with a benchmark SSVEP dataset is a simple and efficient way to design an SSVEP-based BCI. Certain characteristics of the stimulation signals (such as frequency, phase, and stimulation duration) can be simulated without the need for new data collection. Furthermore, within this framework, the stimulus coding and target identification methods can be tested jointly to achieve optimal BCI performance and, once optimized in the offline system design, they can be implemented in an online BCI system. This process can significantly facilitate the design of SSVEP-based BCIs.

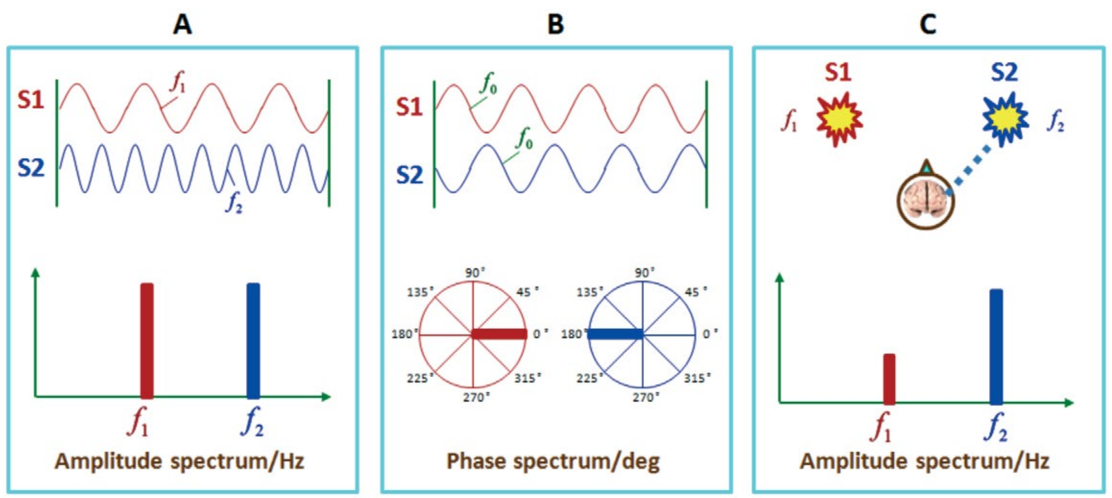


FIGURE 3. Approaches to modulate steady-state visual evoked potentials (SSVEPs). (A) Frequency tracking: Multiple targets are tagged with different flickering frequencies. (B) Phase tracking: Multiple targets are tagged with different phases at the same frequency. (C) Attention tracking: Multiple targets correspond to different attending locations or features. For example, attending to the right-side stimulus (S2) can lead to enhanced amplitude of SSVEPs at f_2.

The stimulus coding and target identification methods play important roles in optimizing the performance of SSVEP-based BCIs. Advanced stimulus coding methods (e.g., mixed frequency and phase coding) can significantly improve the coding efficiency (*7*). Target identification methods typically consist of signal processing and machine learning algorithms that can be applied to extract frequency and phase information of SSVEP. Under the computational model described above, selections of frequency band and time window are crucial for feature extraction (*5*). In addition, SSVEP training data can be used to improve target identification using machine learning techniques (*7*). Furthermore, information of SSVEPs from previous sessions and other subjects can be used to facilitate the training procedure in BCI operation (*10*). Another important factor affecting BCI performance is user attention. During BCI operation, visual attention needs to be maintained at a high level so that SSVEP parameters are stable across multiple trials.

Example application of high-speed BCI speller

We recently developed a high-speed BCI speller based on the system framework described above (*5*). The 40-character speller (see Figure 1B) used a frequency-coding diagram (frequency range: 8–15.8Hz; frequency interval: 0.2Hz). The three major procedures in system design and implementation were as follows: First, a benchmark SSVEP dataset was collected from 12 subjects in an offline BCI experiment. Second, the dataset was used for offline system design. The proposed computational model of SSVEPs suggested that the harmonic SSVEP components could provide valuable information for use in frequency detection. A filter bank canonical correlation analysis approach was developed to extract independent features from the fundamental and harmonic SSVEP components. The parameters of the filter bank and the classifier were optimized through evaluating offline BCI performance using the benchmark dataset. At the same time, the stimulus duration was optimized toward the highest ITR. Third, an online BCI speller, using the same parameters obtained from the offline system design, was implemented using a different group of 10 subjects. The online speller demonstrated an average ITR of 151 bits/min, to our knowledge one of the highest ITRs reported in BCIs. This example application demonstrates the efficacy of the proposed computational model of SSVEP in improving the performance of SSVEP-based BCIs.

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Using a scale-free method to convert brain activity into music

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Music can create experiences that can be shared by humans. Emotional expression and communication through music are strongly linked to health and well-being (*1, 2*). For many years, musicologists and scientists have attempted to uncover the relationship between music and the human experience. In recent years, musicians have been considered as an outstanding model for studying the operations of the human brain and in particular, the effect of music on brain functions (*3–6*). We carried out an inverse study of sorts, in which we recorded brain activity and converted the data into music. In 2009, we proposed a scale-free method (*7*) to translate electroencephalogram (EEG) data into music. The translation is based on the scale-free properties followed by both music and EEGs. Thereafter, we developed a series of scale-free methods for converting brainwaves (EEG recordings) into music (called "brainwave music") that represents different states of brain activity, such as eyes open and eyes closed for healthy people, and the moment of seizure onset for patients with epilepsy (*8–10*).

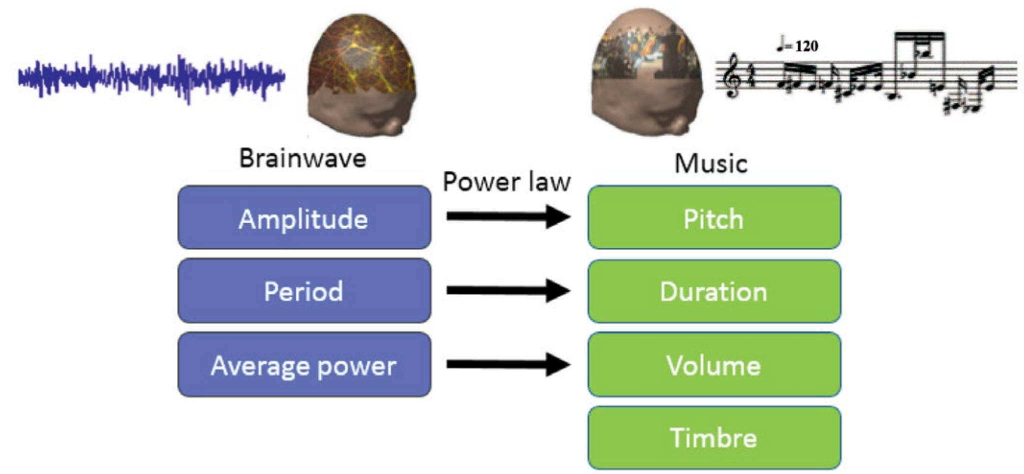

FIGURE 1. Paradigm used for translating electroencephalogram (EEG) data into music (*7*). The amplitude, waveform period, and average power are mapped to pitch, duration, and volume, respectively. The piano was chosen for the timbre. The mappings from amplitude to pitch are based on the scale-free law (power law).

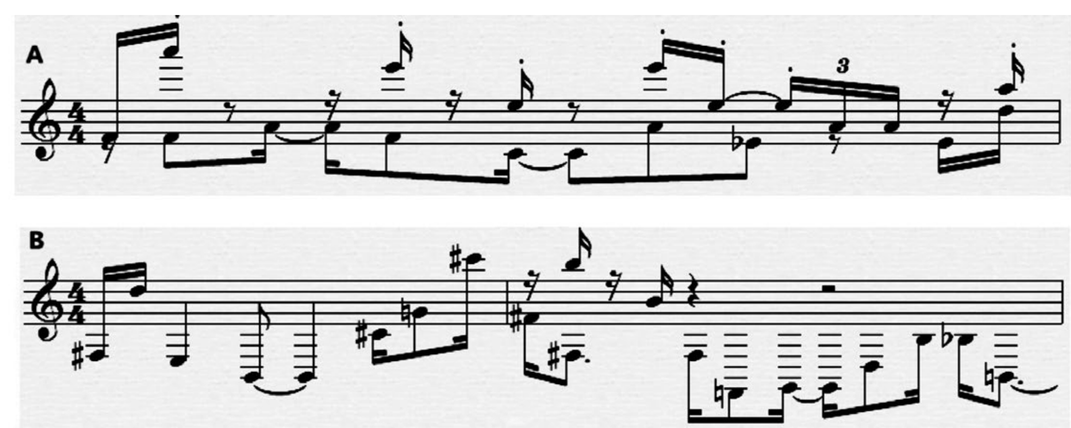

FIGURE 2. The score of a piece of music translated from the brain signals of (A) the female patient with Alzheimer's disease and (B) the healthy 5-year-old child.

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Recently, we evaluated brainwave music for two subjects: a healthy, 5-year-old child, and an 80-year-old female patient with Alzheimer's disease. We collected their EEG data using an electrode cap with 64 silver/silver chloride electrodes, connected using the established

10–20 system of electrode placement, and digitized the recording using a sampling rate of 500 Hz. The impedance for all electrodes was kept below 5kΩ and all the data were band-pass filtered (0.01–100 Hz) online using software from Brain Products GmbH (Starnberg, Germany; www.brainproducts.com). The recorded EEG data was translated offline to reference at infinity with Reference Electrode Standardization Technique (REST) software (http://www.neuro.uestc.edu.cn/rest/) (*11*). Participants gave informed consent before the experiment was conducted, in accordance with the established guidelines of the Ethics Committee of the School of Life Science and Technology at the University of Electronic Science and Technology of China.

We translated the brainwaves (EEGs) into music for both subjects using the method shown in Figure 1. We were surprised that the music created from the two subjects showed similar tempo and rhythm, and both recordings could be described as "peaceful" (Figure 2). Considering that this brainwave music can reflect a person's state of mind (*8–10*), we suggest that the elderly female subject and the child were possibly sharing similar intrinsic states at the moment of the recordings. This aligns with the ancient Chinese saying that "an old man may experience the same state of mind as a child," a state that music may elicit since it can affect human feelings.

In summary, scale-free brainwave music, a musical representation of brainwave activity, may provide a new way to peer inside the "heart" of the brain, or provide a new emotional brain-computer interface, as described in our previously published work (*7–10*). However, to find evidence to further support the idea that music may enable "an old man to experience the same state of mind as a child," additional research must be performed with a larger number of subjects. Overall, brainwave music may help us better understand some of the basic mechanisms within the brain and may be applicable for monitoring brain states, for use as an emotional brain-computer interface, or as a method of clinical rehabilitation (such as music therapy). However, additional work is needed to fully elucidate its underpinnings.

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Estimating biosignals using the human voice

Eduardo Coutinho and Björn Schuller*

Computational paralinguistics (CP) is a relatively new area of research that provides new methods, tools, and techniques to automatically recognize the states, traits, and qualities embedded in the nonsemantic aspects of human speech (*1*). In recent years, CP has reached a level of maturity that has permitted the development of a myriad of applications in everyday life, such as the automatic estimation of a speaker's age, gender, height, emotional state, cognitive load, personality traits, likability, intelligibility, and medical condition (*2*). Here, we provide an overview of one particular application of CP that offers new solutions for health care—the recognition of physiological parameters (biosignals) from the voice alone.

Unintrusive and pervasive monitoring

Currently, there are a variety of portable medical devices enabling patients to actively monitor the relevant factors contributing to their diagnosis and treatments. These devices are particularly important when frequent monitoring (daily or several times a day) is required for the adequate treatment and detection of symptoms, especially for patients with limited mobility and difficulties accessing medical facilities. Further, these technologies help address the shortage of qualified medical staff needed to adequately monitor patients, which can lead to delays in obtaining appropriate feedback and treatment.

The technologies currently available include those that measure heart rate, blood volume pressure, body temperature, respiration rate, and other physiological parameters. Such devices can be quite expensive and complicated for older patients and those with limited mobility, and often inconvenient for everyday use. Ideally, monitoring biosignals should be unobtrusive, not require additional electronic devices, and require minimal effort from the patient. Most importantly, monitoring should be easy to perform in emergency situations.

Computers or mobile phones are thus an obvious choice due to their abundance and their computational power, which is sufficient to acquire and analyze biosignals (*3–5*). If such devices are to be used, the signal being measured must be one that can be recorded without the need for additional equipment. Audio and video signals fit these criteria, as both have been previously used to estimate a variety of biosignals. For instance, video analysis of the skin can detect subtle color shifts triggered by physiological changes (such as cardiac rhythm or blood flow) (*6–8*). In the case of the human voice, physiological changes are detectable through vocalizations because both the larynx (where the vocal cords are located) and the pharynx (above the larynx) are controlled by the autonomic nervous system, which regulates blood pressure, heart rate, and perspiration (*9–12*).

Voice-based biosignal estimation presents a major advantage over video-based sensing, because audio acquisition is less limiting than video in that it does not need to be directed toward or be in contact with a patient's skin, and it can be used in a wider range of conditions (for instance, in the dark when video cannot be captured). This is of particular relevance in crisis situations, when additional sensors or the ideal conditions for adequate video analysis are not available. In such cases, by simply asking for medical assistance, vital information about the patient could be automatically collected and used to inform diagnosis and treatment.

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Recording condition	Recording device	Model type	Pulse level (HP/LP) UA (%)	Heart rate (HR) CC	Heart rate (HR) MAE (BPM)	Skin conductance (SC) CC	Skin conductance (SC) MAE (μMhO)
Sustained vowels	Headset	IS	83.1	0.809	8.4	0.978	84.4
		MS	79.6	0.770	10.6	0.891	265.3
	Ambient	IS	82.7	0.861	8.1	0.960	88.2
		MS	76.0	0.574	11.7	0.633	311.2
Breathing periods	Headset	IS	84.1	0.722	10.7	0.908	153.7
		MS	78.6	0.629	13.1	0.632	469.7
	Ambient	IS	81.9	0.718	10.6	0.905	165.3
		MS	72.9	0.521	14.8	0.483	570.8

TABLE 1. Results for the automatic regression of heart rate (HR), skin conductance (SC), and classification of pulse level (HP: high pulse; LP: low pulse). IS: individual speakers; MS: multiple speakers; UA: unweighted accuracy; CC: Pearson's linear correlation coefficient; MAE: mean absolute error. Table adapted from (*13*).

Voice-based physiological monitoring

In a recent and comprehensive attempt to estimate biosignals from the voice alone (*13*), we evaluated the estimation of two biosignals—heart rate (HR) and skin conductance (SC)—and the classification of pulse level (high pulse/low pulse; HP/LP) using acoustic features extracted from audio recordings. We designed an empirical study to collect subjects' HR and SC from 19 subjects (4 female; 15 male). In addition, we obtained audio recordings of breathing sounds and from the repeated pronunciation of the sustained vowel "a." The recordings were collected in two pulse-level states: a "neutral" state (characterized by a low pulse), and a high-pulse state, which was induced by asking subjects to run up and down six flights of stairs (three stories) and down a hallway immediately prior to the recording. In order to evaluate the influence of the sound recording conditions, audio recordings were obtained with two different devices: a high-quality sound recorder ("ambient") and a common, commercially available headset ("headset"). The full database consists of 1,420 audio recordings (and concomitant HR and SC recordings).

The audio recordings were analyzed using the openSMILE (Speech and Music Interpretation by Large Space Extraction) software toolkit (*14*), which was used to extract a large set of acoustic descriptors. These descriptors included 4,368 acoustic features comprising a variety of energy-, spectral-, and voice-related information, which was used to develop computational models that predict SC, HR, and pulse level using state-of-the-art machine learning regression (to determine the exact value of SC and HR) and classification techniques (to determine pulse level, either high or low). These computational models were created for individual speakers (IS) and multiple speakers (MS), i.e., using the recordings from all speakers to generate a model that can be applicable to any speaker rather than a specific speaker. The models' performances in the regression tasks were estimated using Pearson's linear correlation coefficient (CC) and the mean absolute error (MAE). For the classification of pulse levels, the performance was estimated using the unweighted accuracy [UA, i.e., the unweighted arithmetic mean of the number of correctly identified pulse levels in each condition (HP or LP)]. A summary of the results is shown in Table 1.

Next, we evaluated whether voice recordings could be used to identify pulse level and estimate SC and HR values. The results demonstrated that one's pulse level could be correctly identified with an accuracy as high as 84.1% of the IS model (ambient microphone audio recordings of breathing). Furthermore, HR and SC regression analysis showed that the best linear correlation coefficients were 0.861 [MAE of 8.1 beats per minute (BPM); IS model using the sustained vowels audio recordings obtained with an ambient microphone] and 0.978 [MAE of 84.4 micromhos (μMhO); IS model using the sustained vowels audio recordings obtained with a headset microphone)], respectively. We drew three main conclusions from the results. First, common microphones are a viable option for estimating biosignals from the voice, as the performance was comparable for both microphone types. Second, both types of recording conditions—sustained vowels and breathing sounds—led to similar classifications of the subjects' pulse level, although the use of sustained vowels was slightly better than breathing sounds for the regression experiments (*13*). In another study, we evaluated which acoustic features would be best suited for estimating biosignals. The results showed that with an optimized set of 150 acoustic features, a subject's pulse level could be accurately determined, with a UA of 91.4% and correlation coefficients of 0.876 for SC and 0.838 for HR (but only when using 100 acoustic features for the analysis, not 150) (*15*).

The dataset used in our work—the Munich BioVoice corpus (MBC)—has been made publicly available (*15*) and was used in the Interspeech 2014 Computational Paralinguistics Challenge (*2*). Competing teams were asked to classify HP/LP based on freely chosen features extracted from voice recordings of text that was read after exercise or under resting conditions. The winning team achieved an accuracy of 75.3% (*16*).

Conclusions and perspectives

Taken together, our studies have shown that audio recordings of a person's breathing, pronunciation of sustained vowels, and reading of text can be used to predict biosignals. Gathering such information from voice recordings has a lot of potential use for technologies that require noninvasive, passive collection methods. For instance, a mobile phone could be used to continuously or periodically record a subject's voice (with or without speech) without the need for user intervention. This would require little or no effort from the user and be well suited to patients with limited mobility or in emergency situations when user intervention is not possible.

However, the use of audio recordings to estimate biosignals is still in its infancy and has a lot of room for improvement. For example, the data from this technology is still less accurate than what can be obtained by using dedicated medical equipment, and more research is needed to improve its quality. Furthermore, the technology would gain from research on which acoustic and vocal features are optimal to use, from exploration of more powerful modeling paradigms, from the calibration of models based on individual differences in physiological activity, and from the acquisition of larger data sets for refining speaker-independent models. Finally, this type of research would benefit from more attention from the speech community and from the application of state-of-the-art machine learning techniques.

In summary, our studies have found that audio-based recognition has the potential to be used as a software application on mobile phones and computers for remote monitoring of HR and SC. One advantage of using such audio recordings is that analyses could be performed in an atemporal fashion, e.g., using past recordings to investigate a patient's history and their condition's evolution over the period that preceded diagnosis and treatment. If the technology is further improved, it could be used for passive, noncontact monitoring of patients, which would require minimum attendance by its user and improve the quality of life for many people.

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Ecological validity: Predicting psychological profiles using Internet behavior

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The validity of psychological studies depends on the quality of the behavioral, physiological, and biological data collection. Traditionally, such data has been collected through laboratory experiments, whereby experimental parameters are rigorously controlled, yet require intrusive and artificial conditions (*1*). In contrast, the "ecological" discipline of psychological research maintains that such data are subject to inaccuracies, and proposes to collect data in real-world settings.

In the past, acquiring data in "real life" has been difficult and ineffective. However, rapid developments in information technology have brought about profound changes in data collection. The data revolution now enables collection of real-life data efficiently in several complementary ways. First, Web 2.0 technologies, such as social networking sites, blogs, and other types of social media have achieved global popularity and use. Users' personal profiles, self-expression, and daily communication can be recorded automatically (*2*). Second, the popularity of mobile devices, such as smartphones and tablets, makes it possible to integrate data with the location and time signatures of users (*3*). Through installed apps, mobile devices can record a high level of detail about individuals' behavior across different settings and situations encompassing their daily lives. Third, wearable devices, such as smart glasses, watches, and bracelets, are now the subject of constant innovation and have been increasingly accepted by consumers. These devices perform daily monitoring and recording of behavioral and physiological data, such as body movements, heart rate, body temperature, and even neural activity, making it possible to collect real-life data for any given individual. Thus psychological data collection is no longer limited to particular situations in a laboratory setting.

Since such Internet-mediated data collection is not built on well-designed experiments in the laboratory, it brings new challenges in processing large and unstructured data.

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To address the problem, new data processing techniques, such as feature extraction and machine learning, have been introduced. Using such techniques, we have systematically examined the feasibility of identifying and predicting the psychological profiles of individuals based on real-life data acquired from social media, smartphones, and wearable devices. We have further expanded our analyses from the individual to the population level to further test the feasibility of acquiring dynamic psychological profiles of the broader public.

Predicting individual profiles using social media behaviors

We conducted research using one of the most popular Chinese social media platforms, Sina Weibo, which is similar to Twitter. We built computational models for predicting users' personalities (*4*), mental health status (*5, 6*), and subjective well-being (*5, 7*) by acquiring and analyzing data on their Weibo behaviors. We recruited active Weibo users, based on their total and average everyday number of Weibo posts. With their consent, we then downloaded their Weibo posts and digital records of web-based activities and measured the following psychological features: their Big-Five personality traits [the personality structure composed of five dimensions, measured by the Big Five Inventory (BFI)] (*8*); depression and anxiety [by the depression and anxiety subscale of Symptom Checklist 90 (SCL-90)]; suicide probability [by Suicide Probability Scale (SPS)]; and subjective well-being [by the Positive and Negative Affect Schedule (PANAS) and the Scales of Psychological Well-Being (PWB)]. The sample size was between 444 (for depression and anxiety) (*5*) and 1,785 (for subjective well-being) (*7*).

We extracted four categories of features from the Weibo data to build computational models: (a) User profile and settings, including demographic information (such as age and gender) and account settings (such as username and privacy settings); (b) Weibo usage parameters, such as the number of individuals denoted as "followers" or "following," the time period between updates, and the number of original or forwarded posts; (c) Weibo linguistic expression features, which are extracted using the Simplified Chinese version of LIWC (Linguistic Inquiry and Word Count) (*9*); and (d) deep learning features. Features a, b, and c—features which are both static and dynamic when sampled in a time series—contain a rich body of information about users' mental profiles, which can be used for training prediction models. Meanwhile, they can also be put into deep learning models (a set of machine learning models for high-level abstraction of data) to construct deep learning feature matrices. Such features can also be used for training prediction models. After feature extraction, methods such as stepwise regression can be employed for feature selection.

To differentiate between groups with higher and lower scores on various personality traits or on the risk of suicide, we used algorithms such as support vector machine (SVM), simple logistic regression (SLR), and Random

Forest (RF) to build classification models. For predicting continuous variables, such as scores on personality and subjective well-being, we built regression models such as pace regression, multivariate adaptive regression splines (MARS), and support vector regression (SVR). The predictive accuracy was fairly good, particularly for classification tasks. For example, the accuracy of distributing Weibo users into either high- or low-score groups for different personality types ranged from 84% to 92% through SVM (*4*). In addition, through SLR and RF, our model retrieved over 70% of the Weibo users labeled high-risk with overall suicide probability or with each of the four subscales of SPS (*6*). In terms of the performance for predicting continuous variables, the correlation coefficients between the predicted scores, which were achieved through pace regression, MARS or SVR, and questionnaire scores, generally reached a medium to strong level (0.48–0.60) (*4, 7*). We also implemented our strategy using data acquired from Renren, another well-known social networking site that is similar to Facebook and widely used by Chinese students, and found the accuracy of predicting the individuals' Big-Five personality traits were comparable with the Weibo data (*10*).

Predicting individual profiles using smartphone behaviors

To predict users' mental profiles based on their behaviors on mobile devices, we employed an Android app called MobileSens, which records mobile behaviors and uploads the data to our server. Using this data, we conducted studies to predict psychological profiles for the Big Five personality traits, and for depression, interaction anxiousness, loneliness, and subjective well-being (*11, 12*). Three categories of behavioral features were extracted from original usage logs to train computational models. Those features included the frequency of use of (1) basic smartphone functions, such as dialing, texting, and GPS; (2) the most popular social apps, such as QQ, WeChat, and Sina Weibo; and (3) different categories of apps, such as communication, games, and health. We used a stepwise regression for feature selection and pace regression for training models. For agreeableness, extraversion, openness, subjective well-being, depression, and loneliness, we observed a moderate correlation (0.30–0.48) between predicted scores and questionnaire scores; and the correlation coefficients were higher for females than males for nearly all of the measured psychological indices.

Predicting individual profiles using body movements

Smart bands have become a popular wearable device. Most contain a built-in three-axis acceleration sensor, which can precisely record the movements of the body part where it was worn, usually the wrist. There is evidence that an individual's emotional state can be reflected in one's own gait (*13*), therefore body movement data acquired from the acceleration sensor of a smart band can potentially be used to monitor the user's emotional state. We conducted a series of studies analyzing body movement data from Kinect 3D cameras, smartphones with built-in acceleration sensors attached to the wrist and ankle, and smart bracelets. Participants' body movements were recorded by the three devices while walking under conditions that induced positive or negative emotional effects. We built computational models to classify emotional states as positive or negative using the features extracted from the body movement data. Our preliminary results indicate that the predictive accuracy of the models was above 70%.

Predicting public profiles using social media behaviors

Social media provides an efficient way to detect public attitudes and thoughts because of its access to a large number of users. Understanding such trends is a potentially potent, albeit controversial, tool for defining public policy. Traditionally, conducting a questionnaire survey or interviews with a large number of respondents has been the preferred way of measuring public attitudes. However, public opinion polling is time consuming and costly, and it cannot monitor changes in public attitudes in real time. In contrast, information gained from studying social media can more directly and powerfully reflect public attitudes.

Whereas direct statistics on social media parameters are already in place to profile changes in public attitudes (*14*), we have refined this concept with more elegant computational approaches. Using the techniques we previously used to predict individuals' psychological profiles, we have developed methods to perceive public social attitudes through a large sample of Weibo behaviors (*15*). In this study, Weibo users from targeted regions were recruited and asked to complete a social attitude questionnaire about social stability in modern China (*16*). We performed the extraction and selection of Weibo features using the same methods as the individual mental profile predictions. We used algorithms such as multitask learning and incremental regression to train the prediction models. Based on this analysis, the average predictive accuracy for each aspect of social attitude was approximately 85%. Since Weibo behavior records are traceable, we can further divide Weibo data into time slices to acquire longitudinal data. More importantly, since Weibo data is continuously updated, it is feasible to track trends in public social attitudes in real time. Thus our trained model can be used for a larger segment of Weibo users to obtain profiles for an even larger proportion of the population. Such predictions could be an important reference for indicating the public social attitudes in the real world.

In summary, our work has shown the potential of using information technology and computational methods—such as feature extraction and machine learning—for obtaining and processing large quantities of real-life data from social media, mobile devices, and wearable devices. This Internet-mediated data can be used to predict the psychological profiles of individuals and the public.

Many challenges exist, such as improving the accuracy of the predictions, ensuring that the sample of users represents the larger population, and maintaining the privacy of users. Nonetheless, our approach can bring about significant benefits—namely, building a system of psychological information with better ecological validity that can meet the needs of real-world applications.

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国家重点基础研究发展计划

Depression risk prediction: Research and development using multimodal biological and psychological information

Program description
The National Basic Research Program of China (973 Program) focuses on innovative theories and technologies for the risk prediction of depression and rapid intervention. It incorporates the latest advances in psychology, information science, cognitive science, and biomedical engineering. This project explores not only state-of-the-art biosensor, multimodal data mining, and modeling technologies, but also investigates evolutionary mechanisms correlating biological and psychological traits with depression. Further, we are developing prototype systems to verify the veracity and efficacy of the research findings.

Participating institutions
- Lanzhou University (Principal Investigator)
- Institute of Electronics, Chinese Academy of Sciences
- Institute of Psychology, Chinese Academy of Sciences
- Capital Medical University
- Beijing University of Technology
- Huazhong University of Science and Technology
- Tianjin University
- Shenzhen University

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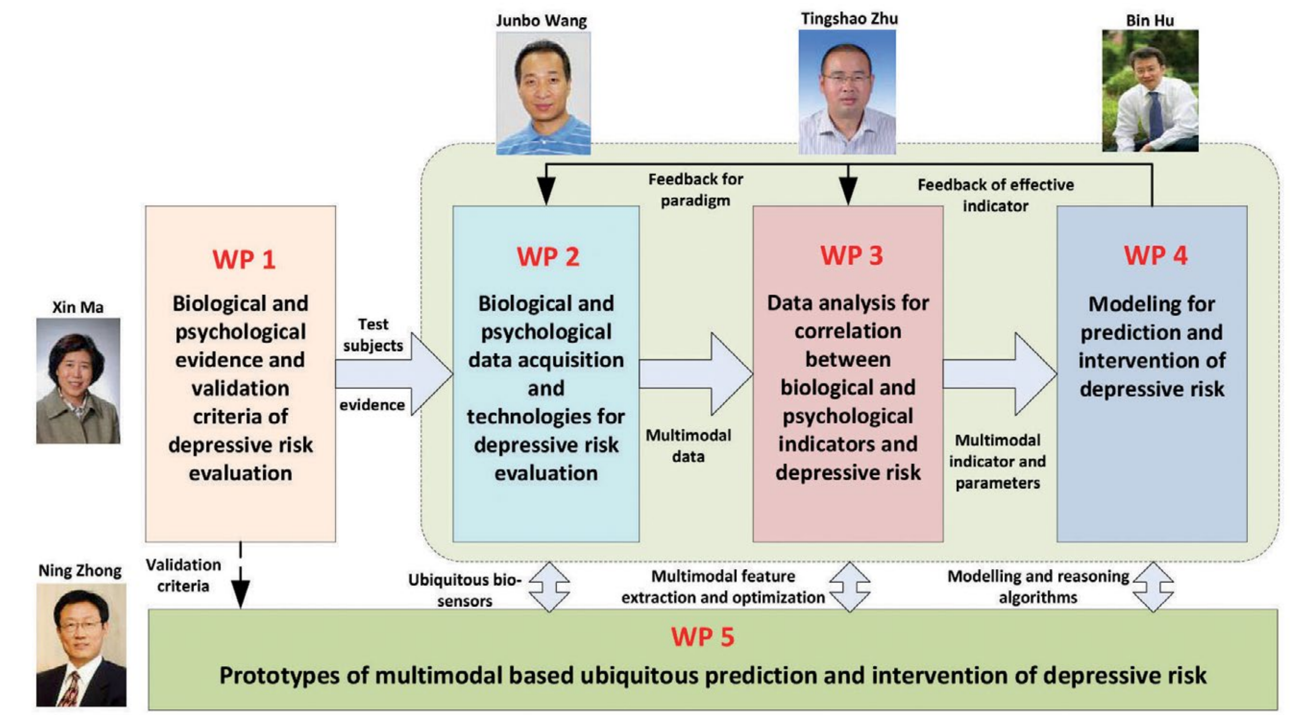

This diagram shows the National Basic Research Program's five work packages (WP), how they are related, and the WP leaders.