REVIEW PAPER

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A review on EEG-based methods for screening and diagnosing alcohol use disorder

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Abstract

The screening test for alcohol use disorder (AUD) patients has been of subjective nature and could be misleading in particular cases such as a misreporting the actual quantity of alcohol intake. Although the neuroimaging modality such as electroencephalography (EEG) has shown promising research results in achieving objectivity during the screening and diagnosis of AUD patients. However, the translation of these findings for clinical applications has been largely under-studied and hence less clear. This study advocates the use of EEG as a diagnostic and screening tool for AUD patients that may help the clinicians during clinical decision making. In this context, a comprehensive review on EEG-based methods is provided including related electrophysiological techniques reported in the literature. More specifically, the EEG abnormalities associated with the conditions of AUD patients are summarized. The aim is to explore the potentials of objective techniques involving quantities/features derived from resting EEG, event-related potentials or event-related oscillations data.

Keywords Alcohol use disorder · EEG · REEG · ERP · ERO · Alcoholics screening · P300 intensities · Coherence · Phase delay

Introduction

Drinking Problems that become severe are termed as alcohol use disorder (AUD) (APA 2013). Alcohol consumption less than 48 g per day or 144 g per week is categorized as safe (Parsons and Nixon 1998). In contrast, more intake than the mentioned quantity is categorized as unsafe or heavy drinking. Eventually, chronic heavy drinking leads to AUD including both alcohol abuse (AA) and alcohol dependence (AD) (a severe form of AA). According to the Diagnostic and Statistical Manual of Mental Disorders V (DSM V), people with alcohol abuse keep drinking despite social and personal problems (APA

2013). On the other hand, people with alcohol dependence not only fulfill the criteria of alcohol abuse, but also have increasing tolerance and withdrawal symptoms once abandoned drinking, also termed as alcoholics (Moss et al. 2007). The cumulative toxic effects and heavy consumption of alcohol may lead to medical, neurological, psychiatric and social problems.

Although both the screening and assessment of AUD patients are effective policies to reduce associated harmful effects; however, these policies are of subjective nature and heavily dependent on self-assessment questionnaires. The self-reporting renders the screening procedures subjective and may have many challenges such as involving patient's dishonesty. In addition, most AUD patients are found unable to measure individual drinking quantities and are less candid about their consumption (Popham and Schmidt 1981; Solomon et al. 1980; Watson et al. 1984). It may lead to misjudgments regarding the actual alcohol intake and treatment administration unless verified by objective measures such as reliable markers of alcohol consumption or evidence provided by neuroimaging technologies (Solomon et al. 1980). Hence, to improve the screening and

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assessment accuracy and ultimately to improve the treatment efficiency, it is necessary to combine self-report tests with these objective techniques.

Neurological data have been analyzed to extract useful information for the successful screening and assessment of alcoholic conditions. For example, the frontal atrophy and white matter damages caused by chronic heavy drinking are discovered by Magnetic Resonance Images (MRI). In addition, Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) have been used to detect the changes at neurotransmitter level (Ritsner 2009). In practice, the modalities can provide in vivo information and encourage investigations of new options for behavioral intervention or pharmacological modification to reduce alcohol craving and the risk of relapse (Heinz et al. 2009). With respect to other modalities, electroencephalography (EEG) has been preferred by researchers for AUD treatment due to its low cost, non-invasiveness, high temporal resolution ($\sim$ 1 ms), portability, and convenience. Hence, in this review paper, the EEG-based studies are discussed.

In literature, EEG-based methods have been proposed to analyze AUD related problems such as deficiency in attention (Saletu-Zyhlarz et al. 2004), imbalance of neurotransmitter system (Rangaswamy et al. 2002) and recovery of mental state in individuals prohibited from drinking. Those evidences may be used to facilitate drug discovery, optimization and candidate compound selection. In addition, EEG can help clinicians understand better the alterations in brain activities during AUD as well as medication effects on structural and functional recovery (Parvaz et al. 2011). To summarize, EEG could offer three potential means to improve treatment efficiency (NIAAA 2012):

- Combined with other self-report tools (CAGE, MINI) during screening to identify individuals with alcohol-related problems and who are at risk (Miller et al. 2006);
- Identifying the subset of abstainers (alcoholics who stop using alcohol after detoxification) at highest risk for relapse (Bauer 2001; Winterer et al. 1998);
- Evaluating new medications or behavioral interventions by providing outcome measures to determine if the interventions are having desirable effect (treatment outcome prediction).

In this paper, various EEG-based methods to perform the AUD screening and assessments are reviewed including their key findings and important research gaps. In addition, the related state-of-the art approaches are discussed to explore their potentials for future research in the area including resting-electroencephalography (REEG), event-related potential (ERP) and event-related oscillation (ERO).

The rest of the paper is organized as follows. The "Resting EEG (REEG)" section discusses REEG-based studies that are based on electrophysiological measures such as changes in amplitudes and power of different frequency bands and their behavior after detoxification or long-time treatment. In addition, the paper emphasizes the EEG coherence, phase delay and synchronization likelihood as promising electrophysiological measures for further research involving AUD patients. Moreover, the "Event related potential (ERP)" section discusses the ERP component, i.e., P300. More specifically, the P300-based methods are evaluated and compared with each other to show deficits in cognitive processes of AUD patients. The "Event related osscilations (ERO)" section discusses the findings involving the ERO, for example the P300 can be decomposed into different frequency components which have already shown some progress in the study of alcoholism recovery after long time treatment. In short, the paper discusses the known effects of AUD on EEG signal in each subsection along with related EEG methods. Lastly, in "EEG as utilities for alcoholics treatment" section, the studies discussing AUD identification and relapse prediction are highlighted with an intention to show their potential for clinical practice for AUD treatment. In addition, their limitations are also presented.

Resting EEG (REEG)

Resting EEG (REEG) data involved electrophysiological recordings during a state of rest, e.g., eyes closed (EC) and eye open (EO) conditions without being involved in any experimental activity (e.g., an odd-ball task). The REEG data are of composite nature and may be decomposed into frequency bands such as delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz) and gamma (> 30 Hz). The frequency bands carry different kind of physiological information and have been associated with the brain activities. For example, the delta and theta bands are manifested during information encoding in order to create new memory (Klimesch 1999); alpha band indicates the information retrieval from memory and attention (Klimesch 1999); the beta and gamma bands are associated with perception (Sedley and Cunningham 2013), learning (de Souza et al. 2013) and attention (Barry et al. 2010). The alpha band may be further divided into two or more sub-bands, e.g., low alpha (8–10 Hz); high alpha (10–12 Hz) (Rangaswamy et al. 2002; Saletu-Zyhlarz et al. 2004; Winterer et al. 1998). As alpha activity expresses normal functioning of the brain, beta band is considered as excitatory while slow bands including delta and theta may be

interpreted as inhibitory (Saletu-Zyhlarz et al. 2004). There is a speculation that the gamma band is modulated by theta band and also shows the action of inhibitory interneurons by a mechanism of nesting of gamma rhythms within theta rhythms (Nyhus and Curran 2010).

Studies based on REEG data have identified differences of neuronal activities between alcoholics and control subjects involving different brain regions (Campanella et al. 2009; Parvaz et al. 2011; Porjesz et al. 2005). As an example, techniques such as spectral power analysis combined with Statistical Probability Maps (SPM) may illustrate the difference in the power distribution of various brain regions (Saletu-Zyhlarz et al. 2004). As shown in Fig. 1, the SPM are brain topographic maps that describe differences between two sets of EEG variables based on statistical tests. The statistical results are used to generate maps with color codes. Figure 1 shows topographic maps based on absolute (AP) and relative power (RP) computed using the Welch periodogram method (Welch 1947). In this study, the SPMs were constructed according to the procedure mentioned elsewhere (Duffy et al. 1981; Saletu et al. 1987).

The relative power is the percentage of power computed for one band (e.g., delta) with the total power computed for all EEG frequency bands (e.g., delta, theta, alpha, beta, and gamma). In the figure, SPM highlight not only the differences between mean values of each group but also the variability within each group. The figure shows bird's eye view of the human scalp, nose at the top and 19 dots corresponding to 19 scalp electrode positions. The differences of activations (quantified by the statistical test) are color coded such as the red and orange colors represent significant increases of EEG power observed in AUD patients as compared with control subjects. The blue and cyan colors represent significant decreases of power found in AUD patients as compared with control subjects. In the absences of significant differences, the white color is used. In Fig. 1 (left side), AUD patients show a decrease in theta and high gamma RP and an increase in the other bands as compared with controls. In Fig. 1 (right side), the changes were not significant overall, but they were mostly distributed in some regions such as occipital or left parietal.

EEG spectral power changes

The statistical differences of spectral power between alcoholics and control groups have been linked with different pathologies involving the AUD patients. For example, the higher theta power has been reported in alcoholics when compared with control subjects (Bauer 2001; de Bruin et al. 2004, 2006; Rangaswamy et al. 2003; Winterer et al. 1998). This abnormal increase might reflect the reduction or blocking the ability to encode new information (Klimesch 1999). Similarly, by performing comparison under EC condition, Rangaswamy et al. (2003) found an increase of theta power at all scalp loci, prominent at central and parietal in males and at the parietal for females. In addition, the significant changes in theta power was considered to be associated with cortical atrophy (Coutin-Churchman et al. 2006; Saletu-Zyhlarz et al. 2004).

Alpha band is predominant REEG rhythm observed during relaxed alert state. Decrement in alpha band of alcoholics, especially in the occipital region, is indicative of deficiency in information retrieval from memory and attention (Saletu-Zyhlarz et al. 2004). Alpha band can also be analyzed in time domain and is categorized based on voltage (microvolts squared per octave). For example, low-voltage alpha (LVA) ($< 10\ \mu V$) is observed more in alcoholics than controls by Ehlers and Phillips (2007; Ehlers et al. 2004). However, the observed difference was not significant.

In the studies of alcoholism, power of beta band is more popular than the power of gamma band. For example, elevated beta band power was observed in AD patients in
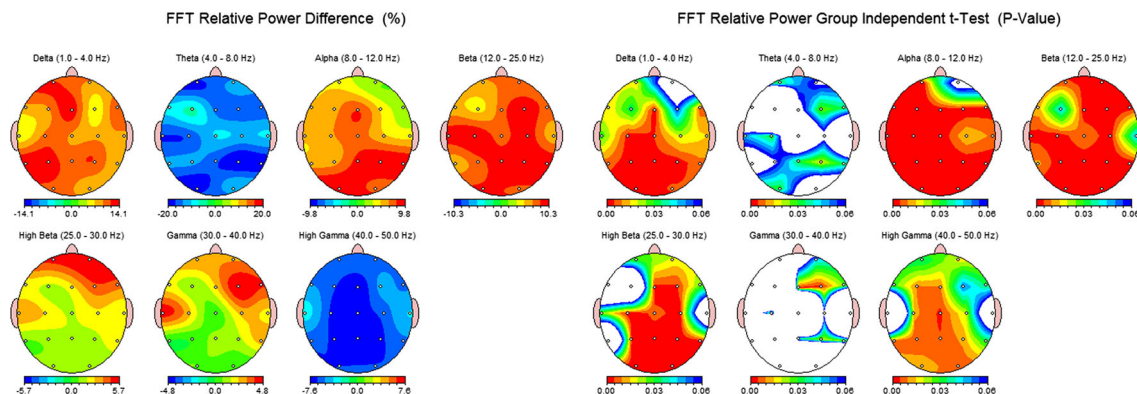
Fig. 1 Differences between AUD patients and controls in EO state. Inter-group differences are depicted in relative power (RP) measures (left) and significant independent *t* test (p-value) measures (right)

the whole brain. In addition, it was studied to be not influenced by age and other clinical variables like recentness and quantity of drinking (Coutin-Churchman et al. 2006; Rangaswamy et al. 2002; Saletu-Zyhlarz et al. 2004). However, gender influences beta power, i.e., more manifested in male as compared with female alcoholics. The alteration of beta band power was explained as an electrophysiological index of excitation-inhibition homeostasis in the cortex (Rangaswamy et al. 2002). Beta power was also utilized to perform the relapse prediction for detoxified patients and compared their spectral power with controls (Bauer 2001). The classification and analysis results showed a significant increase in beta power of relapse-prone patients as compared with abstinence-prone patients and controls. However, it was also found that these changes might be related to medication (especially benzodiazepine), sensoperceptual alterations (hallucinations, illusions), clinical seizures and family history of alcoholics. These factors can alter beta power and affect the classification accuracy (Coutin-Churchman et al. 2006).

As compared with alcoholics, the detoxified patients showed similar spectral power changes as summarized in Table 1. The changes are also different between relapse-prone and abstaining patients. By evaluating detoxified patients enrolled in residential treatment programs, Saletu-Zyhlarz et al. (2004) showed an increase in delta and theta power in relapsing patients and found no difference in abstaining patients as compared with controls after 6 months follow-up. In alpha band, the changes are reversed with the decrease of relative power in relapsing patients and increase of relative power in abstaining patients (Bauer 2001; Saletu-Zyhlarz et al. 2004). In beta band, the changes showed consistency between relapsing and abstaining patients with an increase of absolute power and relative power in both groups. It was more significant in relapsing group. However, these changes have not been analyzed or explained clearly if they are the signs of recovery or they are the effects of medication and withdrawal symptoms caused by the detoxification.

EEG coherence, phase delay and synchronization likelihood

The EEG-based quantities/features such as power spectral density provide information regarding a specific brain region. For example, the absolute or relative power shows the brain activity at a EEG sensor location. In contrary, EEG measures such as the inter-hemispheric coherence, phase delay and synchronization likelihood are used to explore functional influences among different brain regions involving more than one EEG sensor locations. The computation of coherence considers relationship of brain electrical activities between two different brain areas and provides their coupling information. While coherence and power spectrum represent relationship of different brain activities due to the changes in volume conduction of EEG signal. The phase delay expresses direction of the connection which is computed by measuring directional flow between 2 EEG electrodes at different scalp locations.

Tcheslavski and Gonen (2012) highlighted significant reduction of EEG power, coherence and phase synchronization in alcoholics as compared with controls. Integration of coherences, phase delays and spectral powers may reveal more about the alterations in brain activities during alcohol addiction. In addition, higher coherence in first degree male relative (parents, full siblings, or children) of alcoholics was found in the frontal and cento-parietal than in controls without a family history of AUD (Michael et al. 1993). This coherence abnormality observed in relatives of alcoholics might have proved the heritable risk of alcohol abuse.

The coherence estimation is more suitable for stationary data with linear relationships. In case of non-stationary REEG data, coherence may not detect rapidly changing interdependencies (Stam and Van Dijk 2002). Improvements such as incorporation of nonlinear dynamical systems have been proposed to analyze synchronization between two interacted chaotic systems. One method is to use synchronization likelihood (SL), which is a measure of

Table 1 Spectral power alterations in alcoholics and detoxified patients as compared with controls

Frequency band	Subjects	Phenomenon
Theta and delta	Detoxified patients	Decrease power, especially more significant in delta band
	Alcoholics	Decrease power in frontal
Alpha	Detoxified patients	Decrease power in relapsing patients and increase power in abstaining patients
	Alcoholics	Decrease power and show lower voltage but not significant
Beta	Detoxified patients	Increase power in all scalp loci, more significant in relapsing patients and fast-beta
	Alcoholics	Increase power of slow beta in central and parietal, increase fast beta in frontal
Gamma	No confirmation about the alteration of gamma band in alcoholics	

generalized synchronization between 2 dynamic systems (de Bruin et al. 2004). The time-based EEG data has to be transformed into a state-space model to compute SL. de Bruin et al. (2004) stated that heavy drinkers exhibit increased theta synchronization as compared with light drinkers during EC condition. The augmented theta synchronization in heavy drinkers resembled an increase in theta coherence in AUD patients versus controls. This similar effect from both heavy drinkers and alcoholics implied pure effects of alcohol intake on synchronization of brain activity, while minimizing confounding influence of genetic factors related to AD. These differences also showed that coherence, phase delay and SL could be potential features for identification of people with AUD.

EEG-based machine learning methods for AUD patients

More recently, various REEG-based machine learning (ML) methods have been proposed to automate the screening and diagnosis of AUD patients (Acharya et al. 2014; Faust et al. 2013a; Guntaka and Tcheslavski 2013; Mumtaz et al. 2016, 2017; Yazdani and Setarehdan 2007). The methods are based on automatic detection of alcoholism-related changes in the EEG signals. In addition, the methods involved combination of signal processing techniques such as wavelet, nonlinear dynamics, and chaos theory and pattern recognition and classification techniques. The advancements in signal processing techniques allowed the researchers to compute EEG-based features that could be utilized for automatic identification of AUD patient's specific EEG patterns.

Summary

Table 2 summarizes EEG changes commonly reported in the AUD patients. These EEG changes might be useful as a guiding tool for further research studies, e.g., the increases of theta power as indicator for alcoholics, and increase of beta power as an overall assessment for alcoholics and relative problems. Increase of beta power was primary characteristic feature found in alcoholics and high-risk subjects. However, it was associated with benzodiazepines intake (Bauer 2001) that were mainly used for alcohol detoxification. Therefore, beta power needs to be considered when used for alcohol treatment evaluation. In contrary, theta and delta bands were found significantly increased in alcoholics than reported in controls. In addition, these bands were not affected by medication or found in people with family history of alcohol abuse. However, the findings based on alpha and gamma bands are not matured and yet considered as active research areas that warrants further investigations.

In addition, techniques including chaos theory may reveal more information about alcoholics because of inherent complexity and nonlinearity of REEG data. To improve further understanding, the REEG data analysis can utilize its nonlinear characteristics by integrating chaos analysis with traditional time–frequency methods. This can also pave a way for discovering discriminants between people with AUD and controls. The findings in detoxified patients including relapsing and abstaining patients (Bauer 2001; Saletu-Zyhlarz et al. 2004) also provide utility for predicting patients with high risk of relapse. However, the results need to be verified to observe the effects of medication on beta power of alcoholics. Despite rapid progress on alcohol addiction, few reports and studies focused on alcohol treatment utilizing REEG. Future research can focus on integration of features such as spectral power, coherence, phase delay etc. In addition, the features can be data mined based on novel classification algorithms to achieve better accuracy, sensitivity and specificity in addition to automating the whole process during screening and treatment prediction.

Event related potential (ERP)

Segments of electrophysiological data recorded during a cognitive activity time locked with an experimental stimuli (e.g., sensory, motoric, or cognitive events) are grand averaged, termed as event-related potentials (ERPs). Unlike REEG data, the variations of ERP components in alcoholic's exhibit reduced P300 (P3) amplitudes and larger latencies as compared with controls. These abnormalities of alcoholics could be analyzed by (1) evaluating and comparing ERP components in various brain regions between alcoholics and controls, and (2) examining the effects of different stimuli types, socio-demographic data, and family history and drinking habits on ERP components.

One method to extract P300 is to average only epochs without eye artifacts and pick the largest positive peak in the latency window from 250 to 450 ms after stimulation (peak detection). Using this method, Suresh et al. (2003) highlighted the finding that lower P300 amplitude observed in alcoholics in both gender for auditory oddball task, but found more significant in male patients. Wan et al. (2010) applied P3 as predictor in discrimination function (a statistical analysis to predict a categorical dependent variable) (Fisher 1936) for those patients who did complete treatment (abstainers) and achieved 63.9% of prediction rate. The result indicated that there might be difference in P3 between relapsers and abstainers.

In Go/No-Go paradigm, the target stimulus occurs more frequently than non-target stimulus. In a study using the

Table 2 Overview of REEG studies on alcohol addiction

Methods		Findings
Features	Participants	
Spectral power	191 detoxified patients and 240 controls (Coutin-Churchman et al. 2006)	Significant correlation between decreased power of slow bands and cortical atrophy in detoxified patients
		Increased power in beta band correlated with medication, clinical seizures and family history of AUD
	22 detoxified patients and 58 controls (Saletu-Zyhlarz et al. 2004)	Decrease delta and slow alpha power, increase beta power in alcoholics compared with controls
		6 months abstainers showed an increase of slow band and fast beta, a decrease in fast alpha and slow beta
	307 alcoholics and 307 controls (Rangaswamy et al. 2002, 2003)	Increased theta power at all scalp locations, prominent at the central and parietal in male, and at the parietal in female in alcoholics as compared with controls
		Increased low beta (12–20 Hz) power in the whole brain, but most prominent in the central and parietal, increased high beta (20–30 Hz) power in frontal
		The increase of beta power was more prominent in male alcoholics than female
	People with family history of AD including 108 Hispanic and 269 non-Hispanic (Ehlers et al. 2004)	Low voltage alpha in alcoholics
		Alpha amplitude may be associated with ethnic variation, but not drinking status, family history of AD, or other disorders
		Female with family history of AD were found to have higher slow alpha (8–9 Hz) and beta power than male
	61 alcoholics and 176 controls (Ehlers and Phillips 2007)	AD was associated with LVA in occipital areas and in men only
		No association between alpha amplitude and family history of AD
	48 relapsers, 59 abstainers and 22 controls (Bauer 2001)	Achieve accuracy with 61% sensitivity, 85% specificity, 75% positive predictive and 74% negative predictive respectively using logistic regression
Coherence and phase delay	77 alcoholics and 45 controls (Tcheslavski and Gonen 2012)	Spectral power and coherence of slow bands in alcoholics are lower than in controls
		Phase synchrony of alcoholics also reduced in α_2 (10–12 Hz) and β_1 (12–20 Hz) frequency at central region
Synchronization likelihood (SL)	11 heavy drinkers and 11 light drinkers (de Bruin et al. 2004)	The increases in theta and gamma synchronization that of heavy drinkers might indicate damages in hippocampal–neocortical connectivity
	18 light, 33 moderate and 34 heavy drinkers (de Bruin et al. 2006)	Low synchronization of alpha and slow-beta in left hemisphere in heavy drinkers
		Lower synchronization of fast-beta band in moderate and heavy male drinkers

same P3 extraction method with Go/No-Go paradigm, Kamarajan et al. (2005) showed lower amplitude of P3 components in alcoholics to both target (Go) stimuli and non-target (NoGo) stimuli as compared with controls, and there was less difference between these two stimuli in alcoholics. P3 has shown its ability for identify the chronic alcoholics. However, way back to 1985, it was suggested that low P3 voltages might not be reversible, or might recover slowly after long abstinent periods (Porjesz and Begleiter 1985). In addition, the results have been confirmed in the study of Alcoholics Anonymous members (fellowship of people who share their experiments and

support each other to overcome their alcohol related problems and recover from alcohol addiction). The study showed that alcoholics still manifest low P3 amplitudes after extremely prolonged abstinent (3–10 years) (Porjesz and Begleiter 1985). The finding means that P3 cannot be used as assessment tool for alcohol addiction treatment because there is not much difference in P3 component between relapsers and abstainers even after a long-time treatment (3–10 years). However, it was suggested that the low voltages of P3 in alcoholics could be an indicator for alcohol addiction screening. Kamarajan et al. (2006) also suggested that the amplitude of P3 might be considered as

an endophenotype for genetic studies (biochemical markers that reveal about individual inherited risk of alcohol abuse).

Some improvements have been achieved in alcoholic treatment prediction by analyzing P3a. Marinkovic et al. (2001) reported the decrease in both P3a and P3b as compared to baseline following a low dose of alcohol (0.4 g of alcohol per kg of body weight), and also more significant decrease were shown in P3a than P3b. The result suggested P3a as a potential screening tool for alcoholics. On the other hand, Anderson et al. (2011) examined P3a amplitude as a predictor in the discriminant function for treatment success for substance dependence. They claimed that P3a amplitude was a robust predictor of AD treatment, and even more accurate than P3b and other AD measurements.

However, there are significant issues with the artifact rejection process. Firstly, it is fundamental difficult to apply for early components because these components are relatively small as compared with the P300 and easily affected by artifacts. In this case, the artifact rejection is a relatively crude process because it eliminates large number of trials with artifact from the EEG averages. Secondly, it is difficult for alcoholics to control eye blinking and movements, hence resulted into EEG data with more artifacts than usual. In addition, interval of stimulus is around 1500 ms or we have two stimuli for every 3 s. However, the frequency of eye-blink is about 20 times per minute or blinking occurs every 3 s (Iwasaki et al. 2005). In conclusion, the number of stimulus is only twice of the blinks and it means that half of trials will be eliminated and lead a great loss of information and an unrepresentative sample of trials due to bypass artifacted trials. Moreover, some of the experiment models themselves such as visual stimulus required the participants to keep their eyes open for a long time (> 5 min) that will make them tired and blink more frequently, especially for AUD patients. Under these eye-blinking conditions, the artifact correction techniques (techniques that do the subtraction of the voltages due to eye blinking and eye movement from recorded signal to recover original signal) are alternative solution that is more suitable to recover those small components. By using artifact correction to retrieve early components, Marco et al. (2005) reported about the deficit in auditory sensory gating (neurological processes of filtering out redundant or unnecessary auditory stimuli in the brain from all possible auditory stimuli) reflected by P50 component in abstainers. Curtin and Fairchild (2003) also indicated the relationship between alcohol and cognitive function from the N450 reduction and negative slow wave (NSW) associate with behavioral impairment resulted from failure in cognitive control function during alcohol consumption. More investigation about the impairments of early ERP components may help to reveal the deficiency observed in cognitive processing of alcoholics.

The conventional method of averaging and peak detection could lead to misinterpretation of ERP components. To minimize this, single trial analysis methods have been proposed for the identification of ERP components. Pfefferbaum et al. (1991) applied Woody filter techniques to analyze single trial ERP and found that the frequency of P3 generation to startling stimuli was the same in both alcoholics and controls but with smaller amplitude in alcoholics when analyzing the blink responses. This difference was considered to reflect the abnormality of automatic processes in alcoholics. They also found that family history of drinking might be the primary determinant of small P3 amplitude, and more prominent than the time and amount of alcohol exposure.

In another approach, Crego et al. (2009) has proposed principal component analysis (PCA) as a promising technique for acquiring ERP components and reducing their dimensions for multichannel EEG recordings. In their study, N2 component was found to be significantly larger during binge drinking than found in control group. In addition, P3 also exhibited deficits in working memory function during binge drinking in frontal, central and parietal regions.

Summary

Table 3 summarizes key findings commonly reported in the literature involving the discrimination of AUD patients and healthy controls. For example, the findings such as less P300 peak amplitude and longer latency of the ERP components (especially P3a and P3b) are commonly reported. The lower amplitude, in general, is more significant and more consistent than the longer delay of peak latency. However, the changes in P3 components seem to be irreversible after long time abstinent. Thus, the P300 amplitude is suggested to be taken as a screening tool or to provide endophenotype for genetics studies. Other ERP components need more investigation for their ability of classification and prediction in clinical treatment. Novel techniques in artifact correction and component extraction can help reveal more information in small components and the nature of these neurocognitive deficits in alcoholics.

There are several limitations with the conventional method of averaging and peak detection that can lead to misinterpretation of ERP components. To minimize the misinterpretation by using averaging method and understand deeper about cognitive mechanism of alcoholics, many single trial analysis methods have been proposed for the identification of ERP components, e.g., Woody Filter technique, PCA and ICA.

Table 3 Overview about ERP studies on alcohol addiction

Methods		Findings
ERP extraction	Participants	
Averaging and peak-detection	393 alcoholics and 170 controls (Costa et al. 2000)	Significant decrement of P300 amplitude in alcoholics and antisocial personality disorder patients (APSD) at anterior region (significant among subjects age < 30 for APSD)
	27 alcoholics and 27 controls (Hada et al. 2000)	Smaller P3a amplitudes in anterior region correspondent to the rare non-targets in alcoholics without any difference in peak latency
	71 abstainers and 159 controls (Suresh et al. 2003)	Significant decrease of P3 amplitudes in the whole brain of abstainers
		Smaller P3 amplitudes in women with family history of AD
	12 controls, 12 alcoholics, 12 depressed and 12 alcoholic-depressed (Maurage et al. 2008)	Alcoholics showed more delayed P3b (longer reaction time) than controls for the Emotional facial expression (EFE) discrimination tasks
	17 detoxified patients and 17 controls (Marco et al. 2005)	Deficit in P50 auditory in abstainers which related to deficit in sensory gating
		Partial P50 recovered after abstinence period
	51 abstainers and 24 controls (Glenn et al. 1993)	Predicting relapsers/abstainer status using N2L, P3A and N1A indicated low accuracy (63%)
	44 detoxified patients (Anderson et al. 2011)	Significantly reduced P3 amplitude in patients who did not complete the treatment could provide 63.9% accuracy classified for alcoholics
	48 alcohol user and placebo (Curtin and Fairchild 2003)	Reduced N450 and NSW associate with failure in cognitive control function and lead to behavioral impairments
	30 alcoholics and 30 controls (Kamarajan et al. 2005)	Significantly lower P3 amplitudes in alcoholics. Less difference between the NoGo and Go conditions in alcoholics. Less anteriorization of CSD polarity in alcoholics during NoGo processing
	78 abstainers and 58 controls (Pandey et al. 2012)	Significantly reduced N2 peak amplitudes and current density in alcoholics. Controls showed significantly larger NoGo than Go N2 amplitudes
Woody filter	27 alcoholics and 32 male controls (Pfefferbaum et al. 1991)	Alcoholics generated a P3 as often as controls but with smaller amplitude. Family history of drinking, rather than the time and amount of alcohol exposure appears to be the primary determinant of small P3 amplitude
PCA	42 heavy drinkers and 53 controls (Crego et al. 2009)	In matching conditions, the N2 component was significantly larger in the heavy drinker than in controls in central and parietal regions. P3 also exhibited the deficit in working memory function in binge drinking in the frontal, central and parietal regions

Event related osscilations (ERO)

Event related oscillations (ERO) are electrophysiological data recorded during performance of a cognitive activity. Both ERO and REEG data share similar frequency bands; however, their interpretations are different. For example, faster frequencies (alpha, beta and gamma) observed during ERO recordings show synchronization of local neurons, whereas slower frequencies (delta and theta) correspond to long distance synchronizations. EROs are categorized into either evoked (phase-locked to the stimulus during trial) or induced oscillations (non-phase-locked to the stimulus during trial). Quantified in time–frequency domain, the induced activities can reflect either decrease or an increase in power (relative to the pre-stimulus period) termed as event-related desynchronization (ERD) or event-related synchronization (ERS), respectively (Andrew and Fein 2010b). Like REEG analyses, studies involving EROs

also analyze alterations in the brain activities based on power of various frequency bands located in different brain regions with three terms: event-related evoked power ERO_{EVK}, induced or non-phase locked power ERO_{NPL} (including ERS power and ERD power) and event-related total power ERO_{TOT} (sum of ERO_{EVK} and ERO_{NPL}). All these powers are analyzed using time–frequency presentation such as spectrogram to obtain the differences between alcoholics and controls which will be discussed in the next subsection.

Studies involving ERO P300 components

Based on power of different frequency bands, many studies have found that the P300 components primarily involved the oscillations of theta and delta bands (Andrew and Fein 2010b; Jones et al. 2006; Kamarajan et al. 2004, 2006; Krause et al. 2002; Rangaswamy and Porjesz 2008). Jones

et al. (2006) indicated that frontally focused theta band activity (4–5 Hz) and posterior distributed delta band activity constitute the P300 component. They also found that alcoholics showed significant deficits in evoked delta and total theta power which contributed the most power to P300 waveform. The findings provided the reason of lower P300 amplitude by the deficits in ERO power. According to these studies, the theta oscillations formed N200 and early part of the P300 component, while delta oscillations formed main part of the P300 component. Moreover, these powers were also found significantly lessened among alcoholics as compared with controls when responding to the visual stimuli (Gilmore and Fein 2012; Rangaswamy and Porjesz 2008) and Go/NoGo paradigm (Kamarajan et al. 2004, 2006). ERO_{TOT} and ERO_{EVK} provide an alternative representation of the group difference but less effective than P3b amplitude (Andrew and Fein 2010a). In addition, Andrew and Fein (2010a) suggested that theta ERO_{NPL} might provide discriminatory information for alcoholics.

The recovery from alcoholic condition is a slow process and usually takes approximately 3 months (Addolorato et al. 1998). Therefore, process involving EEG can be scheduled into 2 stages to compare with the results from laboratory test (Andrew and Fein 2010a, b; Gilmore and Fein 2012): (1) Short-Term Abstinent Alcoholic (STAA) is defined as 3–6 months abstinent patients; and (2) Long-Term Abstinent Alcoholic (LTAA) is defined as 6–12 months abstinent patients. By studying ERO_{NPL} during the recovery of alcoholics, it was found that the LTAA showed a larger theta ERS power to the target stimulus than controls. The same finding was achieved in both STAA and LTAA (Gilmore and Fein 2012). In addition, the magnitude of enhancement in STAA was greater than in LTAA. Therefore, the induced theta ERS may be an indicator of brain function recovery for alcohol addiction treatment. Besides that, delta ERO_{EVK}, delta and theta ERO_{TOT} were also found to be significantly lower in LTAA as compared with controls. This finding could provide an alternative and comparable representation of P3b amplitude reduction for assessing recovery progress or relapse prediction. The changes in ERO power of slow bands were reported not only in alcoholics but also in those who are at high risk of AUD. Rangaswamy et al. (2007) found a decrease of theta ERO_{TOT} and delta ERO_{EVK} for visual target stimuli in the offspring of high risk alcohol addiction. This finding might be used for detecting the inherited risk of alcohol abuse.

Regarding the induced theta ERS power, it was found to be associated with working memory and attention processes (Krause et al. 2000). Hence, greater theta ERS in STAA and LTAA suggested that alcoholics had to pay more attention and greater working memory to perform target detection during oddball task. The greater theta ERS in STAA relative to LTAA may indicate compensatory mechanisms in alcoholics to overcome working memory and attention deficits. However, there may be a limitation for an increase of induced theta ERS power that can cause breakdown of compensatory mechanism as task demands increase. Therefore, induced theta ERS of alcoholics need more investigation under heavy task (condition that requires heavy memory load) to examine how the task demands could affect the differences between alcoholics and controls.

Other ERO studies

Alcohol consumption was also observed to affect slow oscillations. By examining the effects of alcohol on EEG during an auditory memory task, Krause et al. (2002) have discovered significant effects in theta and alpha frequency bands. The administration of alcohol caused a decrease of early-appearance of ERS responses during auditory encoding and increased the later-appearing ERD responses during retrieval. This indicated that alcohol had disorganizing effects on brain electric oscillatory systems in both theta and lower alpha frequency range during cognitive processing. However, the study did not investigate more about the correlation between long-time effect of alcohol consumption and alteration of slow oscillations. By studying alcohol dependence related alterations, Tcheslavski and Gonen (2012) concluded that a decrease of average EEG power in alcoholics were significantly observed in left central and right cento-parietal regions for delta oscillation; in left frontal-central, central, parietal, right temporal, and right temporal-parietal regions for theta oscillation; in left frontal-central and right parietal and occipital regions for slow alpha oscillation; and in right occipital region for fast alpha and slow beta oscillations.

Besides delta and theta oscillation, gamma ERO was also found to be affected under visual stimuli in alcoholics. Rangaswamy et al. (2007) and Padmanabhapillai et al. (2006) highlighted gamma ERO as a strong marker for AD screening. In their studies, the responding suppression of gamma band activity to target stimuli observed in the frontal region of alcoholics were associated with cognitive processes (Padmanabhapillai et al. 2006). Moreover, evoked gamma oscillation during visual perception and alteration in gamma power could be used as screening tool for alcoholics. However, this application required more investigation (Andrew and Fein 2010a).

Summary

In conclusion, most of the ERO studies applied the traditional trials averaging methods to acquire ERP and ERO

waveform components, also described in Table 4. These methods have similar limitations of overlapping between different trials as discussed in ERP section ("Event related potential (ERP)"). To overcome it, Jones et al. (2006) suggested to use dynamic time–frequency windows defined during single trial at single electrode per study participant. It helped to minimize misinterpretation of averaging method.

Alcohol addiction studies based on ERO involving time–frequency analysis revealed new findings about cognitive processes of alcoholics. These findings might provide better understanding on the deficits in alcoholics. The studies in ERO were mainly focusing on evoked delta, gamma induced and total theta power. Evoked delta and theta powers were suggested to contribute the most power in P300 signal. The significant decrease of evoked delta and theta power proved to be more significant than P300 to reflect the deficits observed during decision processes in alcoholics in response to stimulus. The finding might help to improve clinical screening and diagnose for alcohol

addiction treatment. Future research can concentrate more on the use of dynamic time–frequency and may analyse other frequency bands to achieve better accuracy and understand more about the cognitive processes of alcohol addiction patients.

EEG as utilities for alcoholics treatment

EEG may be utilized for screening AUD patients, relapse prediction and evaluation of medication effects. As summarized in Table 5, despite the rapid development in physiological studies of alcoholic brains, few reports discuss about application of EEG for early relapse detection and medication evaluation. However, their accuracy is not enough to be applied during clinical practice. Besides that, in the review articles and materials about clinical and neuropsychiatric application for alcohol addiction treatment (Ritsner 2009; Tavakoli et al. 2011), EEG was not

Table 4 Overview Of ERO studies on alcohol addiction

Methods		Findings
ERO extraction	Participants	
Trial averaging	20 alcohol use (Krause et al. 2002)	Significantly decreased EEG theta ERS (centre and anterior) during encoding and decreased lower alpha ERD during retrieval (centre and posterior)
	58 alcoholics and 29 controls (Kamarajan et al. 2004)	Significant reduction in delta and theta power during NoGo trials in frontal → deficient inhibitory control and information-processing mechanism
	50 people with family history of alcoholics and 50 controls (Kamarajan et al. 2006)	Significant reduction in delta and theta and alpha 1 (8–9 Hz) power during No-Go trials
		This reduction was prominent at the frontal region
	77 detoxified patients and 45 controls (Tcheslavski and Gonen 2012)	Reduce power in frontal region for low EEG frequency, and more occipital in higher frequency
	122 alcoholics and 77 controls (Padmanabhapillai et al. 2006)	Significant reduction of the early evoked gamma band response in the frontal region during target stimulus processing
	100 alcoholics and 100 controls (Jones et al. 2006)	Significant lower P300 (compared with N100, N200, P200) amplitudes in alcoholics (compared with controls)
		Alcoholic were significantly less ERO power in the posterior delta ERO_{EVK} (forming P3) and frontally theta ERO_{TOT} (early P3) bands but not in the alpha band
	48 low risk and 98 high risk subjects (Rangaswamy et al. 2007)	The theta and delta post-stimulus oscillations are remarkably reduced in adolescent offspring of alcoholics
		The P300 amplitudes are reduced not as strong as seen for the oscillations
	48 LTAAs and 48 NACs (Andrew and Fein 2010a)	The LTAA showed significantly lower evoked Delta ERO power and total delta and theta ERO power. It provided an alternative and comparable representation of the reduced P3b amplitude in LTAA
	48 LTAAs and 48 NACs (Andrew and Fein 2010b)	Significantly larger theta ERS to the target stimulus in LTAAs. Induce theta power measures are more powerful and independent group discriminators than the P3b amplitude
	43 LTAAs, 31 STAAs and 72 controls (Gilmore and Fein 2012)	Theta ERS was larger in both STAA and LTAA compared with controls and the magnitude of this enhancement was greater in STAA than in LTAA

Table 5 Related studies about EEG application and their limitations

Objective	Features	Algorithm	References	Results (%)
Predicting relapse	Spectral power	Logistic Regression	Bauer (2001)	75
	Spectral power with Hjorth's features	Discriminant Analysis and ANN	Winterer et al. (1998)	83–85
	P300	Discriminant Function Analysis	Wan et al. (2010)	63.9
Screening alcoholics	Spectral power and coherence	Locally Weight Regression	Guntaka and Tcheslavski (2013)	66.45
	ERP's components	ANN	Lopes et al. (2004)	71
	ERP's components	Learning Vector Quantization	Lopes et al. (2005)	80
	Gamma Visual Evoked Potential (VEP) power	Least square Support Vector Machine (SVM)	Shooshtari and Setarehdan (2010)	82.98
	Raw EEG in F4 and P8	Hidden Markov Model	Zhong and Ghosh (2002)	90.50
	Gamma VEP	MLP – BP with Elliptic filter	Kanna et al. (2005)	91
	Approximate Entropy (ApEn), Sample Entropy (SampEn), Largest Lyapunov Exponent (LLE), (high order spectra) HOS	SVM	Acharya et al. (2012)	91.70
	HOS	Fuzzy Sugeno Classifier	Faust et al. (2013b)	92.40
	ERP's components	Random Forest	Kuncheva and Rodríguez (2013)	94.50
	Multi gamma band VEP	MLP	Rangaswamy et al. (2007)	94.55
	Yule Walker coefficient	Artificial NN	Ek et al. (2013)	95.00
	Wavelet Relative Power	K-nearest Neighbor	Faust et al. (2013a, b)	95.80
	Horizontal Visibility Graph Entropy	K-nearest Neighbor	Zhu et al. (2014)	95.80
	Gamma VEP	PCA	Ong et al. (2005)	95.83
	Gamma VEP	MLP	Palaniappan et al. (2002)	96.10
	Gamma VEP	LDA	Palaniappan (2005)	97.40
	Gamma VEP	KNN	Palaniappan (2006)	98.71
	Spectral power using Haar wavelet	Multilayer Perceptron Network (MLP)	Kousarrizi et al. (2009)	98.83
	Spectral Entropy	Probabilistic Neural Network	Padmanabhapillai et al. (2006)	99.00
	VEP energy in occipital	KNN OR Support Vector Data Description	Zúquete et al. (2010)	99.20
	Mean and variance of signals	Bayes with KNN and PCA (claim to classify AA)	Yazdani and Setarehdan (2007)	100
Classify epileptic and alcoholic	Recurrence Quantification Analysis (RQA)	Gaussian mixture model (GMM)	Ng et al. (2012)	98.6

mentioned in primary health care. In addition, few studies have applied EEG for AUD treatment.

For relapse prediction, there are few studies using spectral power and nonlinear features, e.g., extracting Hjorth features from REEG. Unfortunately, their accuracy is not efficient enough for clinical practice because of either low sensitivity (Bauer 2001) or low specificity (Winterer et al. 1998). ERP techniques have not shown any evidence about the recovery of detoxified patients. One of ERP components, P300 is not suitable for relapse prediction because it was confirmed to not recover after long time treatment. Wan et al. (2010) have tried to apply P300 for relapse prediction and the result has shown no discrimination between relapsing and abstaining patients with accuracy of 63.9%. On the other hands, derivatives of P300 using ERO techniques such as evoke delta, induce theta ERS and evoke gamma power might act as alternative marker for AUD detection.

Regarding AUD screening, various studies have utilized different electrophysiological features and classification algorithms with high accuracy (> 90%) for the classification between alcoholics and controls. These results once more confirm about the difference between AUD and controls, and provide evidence about EEG capability for AUD screening in clinical practice. However, there is no discussion or analysis about the features and algorithms used in most of those studies.

Organic changes in the brain were observed during alcoholism which leads to seizure like epileptic cases. Ng et al. (2012) has implemented an automatic method to differentiate epileptic, controls and alcoholics using EEG with accuracy of 98.6%. However, the validity of data is doubtful because the study has utilized datasets from different sources with different experiment designs (oddball visual stimulus vs. eye closed resting), equipment (64 channels vs. 128 channels) and references systems (Cz vs. common average reference) without any indication about the synchronization between two datasets. Moreover, the dataset of alcoholism in the study contained not only alcoholics but also control subjects (Zhang et al. 1997). In general, there is also a lack of standard procedures to categorize study populations during clinical evaluation. In addition, factors such as sociodemographic characteristics and family drinking history need to be considered and controlled.

Discussion and conclusion

In this paper, a comprehensive review of the contributions made by EEG based techniques for AUD and its related challenges are discussed. The aim is to highlight key findings that could guide future research in this context.

Studies based on neuroimaging techniques have proved their efficiency for AUD screening including alcohol consumption and its related problems. However, these techniques are not popular in clinical practice because physicians have little knowledge of current researches as applied to clinical practice (Miller et al. 2004). Furthermore, the existing EEG methods receive little attention as most of the EEG studies are not efficient enough and robust to be considered clinical effective. This is because of the methodological differences among different studies. In addition, the small sample sizes employed by these methods pose limitation to generalize their findings.

About EEG methodology, there are numerous methodological differences in AUD studies. The differences are based on various experimental paradigms, extracted features, and data processing methods used across studies. Despite of these differences, common points are focused on the neurophysiological variations in alcoholics. The deficit in frontal lobe activities of the brain has been well documented including the decrease of slow band power in REEG (Coutin-Churchman et al. 2006; de Bruin et al. 2006; Rangaswamy et al. 2003; Saletu-Zyhlarz et al. 2004), the smaller amplitude and more latency P300 responses (Costa et al. 2000; Marinkovic et al. 2001; Suresh et al. 2003) and decrease power of slow band oscillation (Jones et al. 2006; Kamarajan et al. 2006; Krause et al. 2002; Tcheslavski and Gonen 2012).

The EEG-based spectral power and coherence show their ability in analyzing and discriminating AUD patients from controls. Spectral power shows overall differences between AUD patients and controls but not significant at every EEG electrodes. Using spectral power would help to explain the alteration of brain activities of AUD patients. In comparison with absolute power, the relative power shows more discrimination between the two groups. Especially, theta power has proved its potential by outperform the other frequency bands with a remarkable power decrease in AUD. Despite few inconsistent results such as (Rangaswamy et al. 2003), more recently, studies have proved the decrease in theta power observed in alcoholics while comparing with control subjects. The changes of theta power in alcoholics were also reported in literature as a consistent indication for alcoholics screening. In addition, power of gamma band shows significant differences between AUD patients and controls. However, its potential has not received adequate attention. On the other hand, the coherence displays the associations between different brain regions and their variation under the effect of alcohol in AUD people. The changes in coherence also synchronized with changes in spectral power, or more specifically in relative power with the decrease in theta bands and the increase in higher frequency bands. However, like the discussion in "EEG coherence, phase delay and

synchronization likelihood" section, the changes seemed to be more prominent with the decrease in theta band. Besides that, the diminished EEG coherence is more significant in long range connections.

Besides the novelty as compared with self-report tests, the unpopularity of other AUD screening tools such as EEG also included the challenge in translating preclinical or discovery phase into clinically useful biomarkers. In addition, studies involving biomedical research are expensive, time-consuming, confounded with requisite human samples and lack of analytical standardization (Freeman and Vrana 2010). On the contrary, self-reports have been developed earlier than the other methods and they are also easier, cheaper and faster to apply (only use questionnaire). This might explain why there are many studies using the existence dataset instead of designing and conducting their own experiments.

However, there are few limitations associated with the studies about alcoholics screening described in Table 5:

- The studies listed in the Table 5 used common dataset from the study of Zhang et al. (1997). Due to common datasets, between studies comparisons were easier and saved useful time. On the other hand, it will reduce the variety of dataset and the generalization of the results. Ehlers et al. (2004) have mentioned in their study (Ehlers et al. 2004) about the presence of ethnic stratification that different ethnics might exhibit in different ways under the effects of alcohol. More specifically, the association between EEG distribution and alcohol dependence varies, and it also depends on individual's ethnic heritage. Therefore, it is necessary to study usefulness of EEG in screening for alcoholics on different dataset from different kinds of participants.
- The dataset might contain only detoxified alcohol dependent patients. The dataset was described in the study of Zhang et al. (1997) to do classification for participants using SSAGA (Semi-Structured Assessment for the Genetics of Alcoholism) which was indicated to be high reliability for alcohol dependence but not for alcohol abuse (Bucholz et al. 1994). Another proof was that the participants were hospitalized for 30 days of detoxification. However, there are few studies mistaken the participants in dataset with alcohol abusers and social drinkers. In conclusion, no such study exists about AUD screening using EEG and further studies including screening for people with alcohol abuse and high risk of alcohol abuse are needed.

The progress in AUD study using EEG has provided new methods for studying the recovery of AUD patients. The new EEG phenomenon (evoked theta, evoked delta, induced theta ERS, gamma oscillation) of EROs may be a candidate for assessing treatment progress. So far, there is still no study about the association between a deficit in gamma band and the duration of abstinence and its ability for discriminating between relapsers and abstainers.

It appears that REEG and ERP components provide potential mechanism for classifying AUD patients and identifying people with high risk of AUD. Now classification algorithms and combination of various features are recommended that can discriminate between AUD patients and controls. The EEG analysis methods using nonlinear characteristics and non-stationary of REEG and new methods of extracting and analyzing ERP component may provide more features for studying alcohol addiction.

In the future, EEG study on alcohol addiction may focus on the recovery of alcoholics after detoxification. It will help to develop biomarkers for evaluating the treatment efficiency and to understand more alternations of the brain while recovering. EEG signals can also be analysed using novel features to capture various aspects of brain activities in people with AUD. Therefore, better understanding and results may be achieved.

In conclusion, the studies presented in this review have shown their potentials only as research tools. There is a need to put effort to translate their key findings into clinical practice. It needs further combined efforts from researchers from clinical and technology side.

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