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Low voltage alpha EEG phenotype is associated with reduced amplitudes of alpha event-related oscillations, increased cortical phase synchrony, and a low level of response to alcohol

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ABSTRACT

Low voltage EEG (LVEEG) is a heritable phenotype that differs depending on ancestral heritage, yet its impact on brain networks and cognition remain relatively unexplored. In this study we assessed energy and task related phase locking of event-related oscillation (EROs), behavioral responses, measures of IQ and personality, and expected responses to alcohol in a large sample of individuals with LVEEG compared to those with higher voltage variants. Participants (n = 762) were recruited from a Native American community and completed a diagnostic interview, the Quick Test, the Subjective High Assessment Scale Expectation Version (SHAS-E) and the Maudsley Personality Inventory. Clinical and spectral analyzed EEGs were collected for determination of the presence of a LVEEG variant. EROs were generated using a facial expression recognition task. Participants with LVEEG (n = 451) were significantly more likely to be older, married and have higher degrees of Native American heritage but did not differ in gender, income or education. Individuals with LVEEG were also found to have decreased energy in their alpha EROs, increased phase locking between stimulus trials, and increased phase-locking between cortical brain areas. No significant differences in the cognitive tests, personality variables or alcohol dependence or anxiety diagnoses were found, however, individuals with LVEEG did report a larger number of drinks ever consumed in a 24-h period and a less intense expected response to alcohol. These data suggest that alpha power in the resting EEG is highly associated with energy and cortical connectivity measures generated by event-related stimuli, as well as potentially increased risk for alcohol use.

1. Introduction

EEG alpha oscillations are the single most salient feature of the waking electroencephalogram (EEG); they are most prominently seen in the resting state EEG in the occipital areas when the eyes are closed. Resting state alpha oscillations have historically been viewed as an "idling" rhythm associated with relaxation or non-focused attention that are reduced in amplitude during cognitive or sensorimotor stimulation or replaced by slower waves during drowsiness (for a recent review see Basar, 2012; Bazanova and Vernon, 2013; Niedermeyer and Lopes da Silva, 1999). Changes in the amplitude and phase of alpha oscillations in the EEG can also be measured during task conditions and the synchronization or enhancement of ongoing EEG alpha oscillations by a time locked cognitive and/or sensory process is termed an event-related oscillation (ERO) (Basar et al., 2000, 2001a; Begleiter and Porjesz, 2006; Roach and Mathalon, 2008). Event-related oscillations in the alpha frequency range have been attributed to a number of cognitive processes (Basar, 2012; Basar et al., 1997, 2001b; Klimesch et al., 1994, 1997, 2007) and individual differences in alpha oscillations have also been associated with neuropsychiatric disorders (see Basar and Guntekin, 2013).

Over the last decade a prevailing theory has emerged that has viewed alpha oscillations as an important top-down mechanism of neuronal inhibition that exerts control over the timing of neuronal discharges in nearby populations (see Klimesch, 2012; Klimesch et al., 2007) and thus may play a prominent role in the control of cortical excitability. In the past few years several studies have recorded both EEG alpha power and functional MRI, as well as EEG alpha power modulation of fMRI resting-state connectivity (see Scheeringa et al., 2012). It has been demonstrated that alpha power correlates with decreased activity in the dorsal attention system of superior frontal and intraparietal regions (Laufs et al., 2003; Mantini et al., 2007), and increased activity in the cognitive control/alerting network, comprised of the dorsal anterior cingulate cortex, frontal operculum/anterior insula and thalamus and that in this capacity it is important in maintaining sustained cognitive control and alertness (Dosenbach et al., 2007; Sadaghiani et al., 2010). Using a combination of EEG and event-related

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optical signal, it has also been demonstrated that suppression of posterior alpha is preceded by increased activity in the regions of the dorsal attention network and decreased activity in regions of the cingulo-opercular network (Mathewson et al., 2014).

Alpha oscillations have also been suggested to provide a basic mechanism subserving a number of cognitive processes including attentional, executive and contextual functions (see Palva and Palva, 2011). Most prominent have been studies that have evaluated EROs in the alpha frequency range to investigate working memory (see Guntekin and Basar, 2014). Basar and Stampfer (1985) first described the association between alpha activity and working memory. A series of studies have provided strong support for the idea that alpha power increases reflect: enhanced control of access to working memory (see Klimesch, 2012; Manza et al., 2014; Roux and Uhlhaas, 2014), the gating of task-irrelevant sensory information (Jensen and Mazaheri, 2010), and the clearing and updating of incoming information (Sadaghiani et al., 2010). Alpha oscillations have also been utilized to investigate responses to affective stimuli using the presentation of faces and facial expressions (see Balconi and Pozzoli, 2007, 2008; Guntekin and Basar, 2014, for review). In one study, it was demonstrated that alpha EROs were significantly higher following presentation of angry faces than following happy faces at posterior locations (Guntekin and Basar, 2007). Alpha responses to different facial expressions have even been demonstrated in a patient with cortical blindness (Del Zotto et al., 2013), suggesting that alpha oscillations may reflect unconscious process of facial expressions. While it is tempting to speculate on a specific role for alpha EROs in cognitive processing of sensory and emotional information, as well as working memory, it has also been suggested that it may not be possible to launch a specific hypothesis for alpha oscillations as they may serve a more general function in sensory, motor and memory functions than what has been suggested by some authors (Basar and Guntekin, 2012).

One of the important factors that is often not taken into consideration when theorizing about the functional significance of power in alpha oscillations is the fact that the amplitude of the alpha rhythm is a trait variable that varies greatly between individuals, and in some individuals it is virtually absent. This phenotype, called low voltage EEG (LVEEG), was first described by Adrian and Matthews (1934) based on visual inspection of the EEG. Early genetic studies also identified LVEEG as being highly heritable, suggested it might have an autosomal dominant mode of inheritance, and provided data in a few families for linkage to a marker on chromosome 20q (see Anokhin et al., 1992; Steinlein et al., 1992; Vogel, 1962, 1970, 2000). If alpha oscillations represent a powerful inhibitory mechanism subserving a host of important brain network operations then how is this accomplished in individuals who have little or no measurable alpha rhythm? It has been suggested that in individuals with LVEEG that alpha oscillations are not absent but rather there is insufficient synchronization of local cortical alpha rhythms for the signal to be recorded on the scalp (Anokhin et al., 1992). It has also been suggested that LVEEG is a result of weakened thalamo-cortical links leading to insufficient pacemaking activity of cortical neurons (Bazanova and Vernon, 2013; Vogel et al., 1979a,1979b). To date no studies have recorded EROs in the alpha frequency range or evaluated phase-locking or synchronization of EROs between cortical regions specifically in individuals identified with this EEG variant, as compared to those with higher amplitude variants, in order to determine if they have a relative deficiency of neuronal synchronization.

Although the psychological and cognitive characteristics of individuals with LVEEG have not been adequately explored some studies have found significant associations with another genetically regulated trait, the risk for alcoholism. For instance, in early studies, a cross-sectional association between having a relatively lower voltage EEG and alcohol dependence was found in primarily EuroAmerican populations (Arentsen and Sindrup, 1963; Coger et al., 1978; Jones and Holmes, 1976; Varga and Nagy, 1960). More recently it has been demonstrated that LVEEG records may be four times more common in some types of alcoholics, particularly those with anxiety, as compared to non-alcoholics (Enoch et al., 1995, 1999). The presence of a low voltage EEG has also been demonstrated to be associated with differing subjective responses to acute alcohol administration (Ehlers et al., 1999; Propping, 1980).

One reason that the LVEEG phenotype has been understudied is the fact that LVEEG is not highly prevalent in most populations (~4% in EuroAmerican populations, see Anokhin et al., 1992; Niedermeyer, 1987) so that large scale EEG screening would be required to obtain a relatively small number of cases. We have previously reported that LVEEG is more prevalent in an American Indian community sample than what has been documented in other select Asian or EuroAmerican populations (see Ehlers and Phillips, 2007; Ehlers et al., 1999). The prevalence of alcohol use disorders also differs among population groups. Although use of alcohol varies among tribes, as a whole, Native Americans suffer high rates of alcohol and drug dependence and higher alcohol-related death rates than any other U.S. ethnic group, and alcohol dependence rates up to five times that of the general U.S. population (Beals et al., 2005a, 2005b; Ehlers et al., 2004d, 2006; Kunitz, 2006; May, 1982; May and Smith, 1988; Robin et al., 1998; Shalala et al., 1999). The present report is part of a larger family study exploring risk factors for substance dependence in a community sample of American Indians (Ehlers et al., 2001a, 2001b, 2001c, 2001d, 2004a, 2008a; Gilder et al., 2004, 2006, 2007, 2009). The lifetime prevalence of substance dependence in this Indian population is high and genetic and environmental risk factors for substance dependence have been identified (Ehlers and Wilhelmsen, 2005, 2007; Ehlers et al., 2004a, 2006, 2007a, 2007b, 2007c, 2008b, 2008c, 2009, 2010a, 2010b, 2011, 2012; Gizer et al., 2011; Wall et al., 2003; Wilhelmsen and Ehlers, 2005). We have also demonstrated that LVEEG is highly prevalent in this population and that alpha EEG phenotypes are substantially heritable and are linked to specific areas of the genome also demonstrated to harbor genes associated with substance dependence (see Ehlers et al., 2010a, 2010b). We have additionally demonstrated that event related alpha oscillations elicited by a facial recognition task were significantly associated with externalizing diagnoses in this population (Criado et al., 2012). Using data from this unique population, several fundamental questions regarding the LVEEG phenotype were evaluated in the present study: (1) We assessed energy in event-related oscillations, in a range of frequencies, that were generated to a facial recognition task in those individuals with LVEEG compared to those with higher voltage variants; (2) We determined whether task-related phase locking of EROs were significantly different within scalp locations and between the frontal and posterior cortical networks in a range of frequencies in individuals with LVEEG; (3) We evaluated demographic characteristics, behavioral responses to the facial recognition task, IQ, and personality variables in those individuals with LVEEG and higher voltage variants; and (4) We tested for associations between anxiety disorders, alcohol dependence, the largest number of drinks ever consumed in a 24-h period, and expected level of response to alcohol in those individuals with LVEEG and higher voltage variants.

2. Methods

2.1. Experimental participants

Participants were recruited from eight geographically contiguous Indian reservations, as previously described (Ehlers et al., 2004d; Gilder et al., 2004). To be included in the study, participants had to be an Indian indigenous to the catchment area, between the age of 18 and 70 years, and be mobile enough to be transported from his or her home to The Scripps Research Institute (TSRI). Participants were excluded from electrophysiological analyses if they had a history of head trauma or were currently using medications that could bias the EEG recording. The protocol for the study was approved by the Institutional Review Board (IRB) of TSRI, and the Indian Health Council, a tribal