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Conflict-related medial frontal theta as an endophenotype for alcohol use disorder

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ABSTRACT

Diminished cognitive control in alcohol use disorder (AUD) is thought to be mediated by prefrontal cortex circuitry dysregulation. Research testing the relationship between AUD and specific cognitive control psychophysiological correlates, such as medial frontal (MF) theta-band EEG power, is scarce, and the etiology of this relationship is largely unknown. The current report tested relationship between pathological alcohol use through young adulthood and reduced conflict-related theta at age 29 in a large prospective population-based twin sample. Greater lifetime AUD symptomatology was associated with reduced MF theta power during response conflict, but not alpha-band visual attention processing. Follow-up analyses using cotwin control analysis and biometric modeling suggested that genetic influences, and not the consequences of sustained AUD symptomatology, explained the theta-AUD association. Results provide strong evidence that AUD is genetically related to diminished conflict-related MF theta, and advance MF theta as a promising electrophysiological correlate of AUD-related dysfunctional frontal circuitry.

1. Introduction

Theoretical models of alcohol use disorder (AUD) implicate impaired cognitive control as a crucial risk factor for, and consequence of, problematic alcohol use (Goldstein & Volkow, 2002; Iacono, Malone, & McGue, 2008; Zucker, Heitzeg, & Nigg, 2011). Various regions of the prefrontal and anterior cingulate cortex are involved in cognitive control processes (Cavanagh & Frank, 2014; Cohen, 2014a; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004; Ullsperger, Danielmeier, & Jocham, 2014). Converging evidence suggests the presence of AUD-related anomalies across multiple measures of the prefrontal cortex. These include reduced grey and white matter volume (Welch, Carson, & Lawrie, 2013), suboptimal neurocognitive performance (Lopez-Caneda, Holguin, Cadaveira, Corral, & Doallo, 2014; Smith, Mattick, Jamadar, & Iredale, 2014; Verdejo-Garcia, Lawrence, & Clark, 2008), and functional abnormalities during executive functioning tasks (Burwell, Malone, Bernat, & Iacono, 2014; Feil et al., 2010; Goldstein & Volkow, 2011; Harper, Malone, & Iacono, 2018; Kamarajan et al., 2004; Pandey et al., 2012). Strong empirical evidence suggests that cognitive control is potentially biophysically realized (in part) through rhythmic electroencephalographic (EEG) signals, such as medial frontal (MF) cortex theta-band (3–8 Hz) activity (Cavanagh & Frank, 2014; Cohen, 2014a). However, relatively few studies have investigated the relationship between AUD and electrophysiological prefrontal correlates of cognitive control. Because the majority of previous work examining AUD-related prefrontal correlates was conducted using case-control or observational research designs, it is unclear to what extent the observed brain-based anomalies reflect a heritable premorbid characteristic toward AUD or the potential consequences of alcohol symptomatology. This study was designed to parse out the genetic or exposure-related contributions underlying the association between AUD and electrophysiological correlates of cognitive control (e.g., MF theta).

Situations requiring cognitive control, such as response uncertainty/conflict, primarily involve activity from frontal brain structures, including the anterior cingulate and posterior medial frontal cortices (Miller & Cohen, 2001; Ridderinkhof, Ullsperger et al., 2004; Ullsperger et al., 2014). One of the most robust and replicable neurophysiological correlates of response conflict/uncertainty is enhanced theta-band EEG power over the medial frontal cortex (Cohen, 2014a). During cognitive control tasks, MF theta power likely reflects a reactive signal associated with conflict detection, performance monitoring, and attentional resistance to distractor interference (Cavanagh & Frank, 2014; Clayton, Yeung, & Kadosh, 2015; Nigbur, Ivanova, & Stuermer, 2011). MF theta is thought to function as a central “hub” of the frontal control circuit (2014a, Cavanagh & Frank, 2014; Cohen, 2011). In this role, theta is

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hypothesized to play a mechanistic part in signaling and recruiting dorsal prefrontal regions to exert increased control and behavioral adaptation on a trial-to-trial basis to help resolve conflict or response uncertainty (Cavanagh, Figueroa, Cohen, & Frank, 2012; Cohen & Cavanagh, 2011; Cohen & Donner, 2013).

The involvement of prefrontal cortex structures in the generation of conflict-related theta is substantiated by several lines of invasive and non-invasive neuroimaging research (Cavanagh & Frank, 2014; Cohen, 2014a). Source localization of scalp recorded EEG and magnetoencephalography (MEG) signals indicate that medial frontal cortex regions, including the anterior cingulate and pre-supplementary motor area, are likely generators of midfrontal theta during cognitive control (Cohen & Donner, 2013; Dippel, Muckschel, Ziemssen, & Beste, 2017; Hanslmayr et al., 2008; Makeig, Delorme et al., 2004; McDermott, Wiesman, Proskovec, Heinrichs-Graham, & Wilson, 2017; Tollner et al., 2017). Intracranial recordings in humans (Cohen, Ridderinkhof, Haupt, Elger, & Fell, 2008; Wang, Ulbert, Schomer, Marinkovic, & Halgren, 2005) and non-human primates (Tsujimoto, Shimazu, & Isomura, 2006; Phillips, Vinck, Everling, & Womelsdorf, 2014; Tsujimoto, Shimazu, Isomura, & Sasaki, 2010; Womelsdorf, Johnston, Vinck, & Everling, 2010), and EEG-informed fMRI (Debener et al., 2005) corroborate the involvement of medial frontal structures in control-related frontal theta generation.

In addition to theta, suppression of alpha-band (8–13 Hz) power over posterior/occipital cortices is also observed during cognitive control and response selection (Gonzalez-Villar & Carrillo-de-la-Pena, 2017; van Noordt, Desjardins, Gogo, Tekok-Kilic, & Segalowitz, 2017). Alpha suppression may reflect increased top-down selective attention toward task-relevant stimuli to improve stimulus processing in the associated sensory region (Clayton et al., 2015; Klimesch, Sauseng, & Hanslmayr, 2007; Thut, Nietzel, Brandt, & Pascual-Leone, 2006). This is because *increased* alpha power is hypothesized to reflect local cortical inhibition of task-irrelevant regions (Clayton et al., 2015). For example, during a visual cognitive control task, the presence of alpha power over the visual cortex could impair visual attentional allocation. Thus, a *decrease* or *suppression* of alpha in visual regions is thought to promote selective attentional processes to facilitate cognitive control and successful task performance (Gonzalez-Villar & Carrillo-de-la-Pena, 2017; van Noordt et al., 2017).

Given the importance of MF theta during cognitive control and response conflict, and work implicating diminished control-related neurocognitive processes in AUD (Dick et al., 2010; Feil et al., 2010; Harper et al., 2018; Kamarajan et al., 2004), diminished MF theta power may be a potential electrophysiological correlate or mechanism of alcohol-related cognitive control anomalies. Parieto-occipital alpha is also an important correlate of the cognitive control system, and has been shown to differ between alcoholics and controls during a go/nogo response inhibition task (Pandey et al., 2016). However, little is known about any relationship between alpha during cognitive control/response conflict and alcohol use, and so more work is necessary to better determine the association between AUD and alpha. Comparing how frontal theta and parieto-occipital alpha relate to AUD can help determine whether AUD is related to variations in several components of the cognitive control system (frontal theta and visual alpha), or is instead selectively associated with individual differences in frontal theta. The theta and alpha measures were chosen for study because of their prominent status in recent influential human and animal models of the cognitive control/response conflict system (Cavanagh & Frank, 2014; Clayton et al., 2015; Cohen, 2014a) as compared to other measures (e.g., parietal P3). Additionally, time-frequency measures, such as theta/alpha, can offer a richer investigation of event-related EEG dynamics compared to traditional event-related potential components (Donner & Siegel, 2011; Makeig, Debener, Onton, & Delorme, 2004; Siegel & Donner, 2010).

In traditional observational or case-control research designs, it is difficult to make strong causal inferences regarding the association between alcohol use and brain function. For example, some previous reports interpret group differences in theta between healthy controls and abstinent alcoholics to be reflective of alcohol exposure-related effects (Gilmore & Fein, 2012, 2013). It is plausible that the observed effect is not solely driven by any potential exposure-related effects, but instead reflects relative contributions from a) a common genetic vulnerability underlying both alcohol dependence *and* theta variations and b) alcohol exposure-related effects. Complicating this are several lines of research offering evidence for both the consequences of AUD symptomatology on the brain (Everitt & Robbins, 2005; Jacobus & Tapert, 2013; Kalivas & Volkow, 2005) and the premorbid genetic vulnerability towards both problematic drinking and prefrontal brain dysfunction (Iacono et al., 2008; Zucker et al., 2011).

Given that the major aim of the current study is to delineate the genetic and environmental contribution to AUD and midfrontal theta, quasi-experimental research designs/methods, such as twin studies, are needed to accomplish this goal (Vaidyanathan, Vrieze, & Iacono, 2015). The cotwin control (CTC) design (McGue, Osler, & Christensen, 2010), a type of natural experiment (Rutter, 2007), is a stringent test of the exposure-related effects of AUD on an outcome (e.g., theta). This is accomplished by comparing outcomes between twins who differ in degree of problematic alcohol use. Because monozygotic (MZ) twins fully share their genotype and rearing environment, any comparison between twins in a MZ pair accounts for *all* genetic/shared environmental effects that may potentially confound a causal alcohol effect. In this design, the brain dynamics of the lesser-using twin provide a close estimate of the expected brain dynamics of the heavier-using twin had s/he drank less. This is an analog to observing the counterfactual, or what an outcome would be if the individual did not have the same level of exposure (McGue et al., 2010; Rubin, 2007). If alcohol symptomatology has a deleterious exposure-related effect on conflict-related theta, the twin endorsing more AUD symptoms would be expected to exhibit reduced theta than the lesser-endorsing cotwin. In contrast, if familial factors account for reduced theta, both the heavier- and lesser-using twins should exhibit comparable theta power. A complementary statistical method to evaluate etiology is biometric modeling. This method separates the observed phenotypic association between two measures, such as AUD symptoms and theta, into genetic and environmental components. These components can be used to determine to what extent the observed correlation is due to the relative contributions of a heritable genetic vulnerability (endophenotypic relationship; Gottesman & Gould, 2003; Iacono, Malone, & Vrieze, 2017) and an environmental exposure-related consequence (AUD symptomatology). These two twin-based statistical methods can be used to make causal inferences regarding the etiological basis of any association between AUD and conflict-related theta or alpha power.

In a recent report (Harper, Malone, & Iacono, 2017), we investigated the association between adolescent alcohol use (a quantitative index of alcohol consumption/exposure) and adult conflict-related frontal theta in a large prospective twin sample. Results of that report indicated that greater drinking in adolescence (ages 11–17) was associated with reduced response conflict-related theta power in adulthood (age 29). The CTC design and biometric modeling offered evidence suggesting that the reduction in frontal theta was not a consequence of adolescent drinking, but was instead primarily due to common genetic factors underlying individual differences in both adolescent drinking and frontal theta activity (Harper et al., 2017a). This finding is consistent with two high-risk family studies linking familial risk of alcohol dependence and reduced theta during a monetary gambling task (Kamarajan et al., 2015) and a response inhibition task (Kamarajan et al., 2006). The results from Harper et al. (2017a) provided initial evidence that conflict-related midfrontal theta is a potential endophenotype for alcohol misuse.

The current report was designed as an extension of the previous analyses in Harper et al. (2017a) to evaluate, in the same prospective twin sample, the etiological effects of cumulative lifetime pathological alcohol use (i.e., AUD) past age 17 and up to age 29 on cognitive control-related theta dynamics. The vulnerability of the prefrontal cortex to the possible neurotoxic effects of drinking continues as the brain matures during early adulthood (Bennett & Baird, 2006). As