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Neurophysiological capacity in a working memory task differentiates dependent from nondependent heavy drinkers and controls

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ABSTRACT

Background: Determining the neurobehavioral profiles that differentiate heavy drinkers who are and are not alcohol dependent will inform treatment efforts. Working memory is linked to substance use disorders and can serve as a representation of the demand placed on the neurophysiology associated with cognitive control.
Methods: Behavior and brain activity (via fMRI) were recorded during an N-Back working memory task in controls (CTRL), nondependent heavy drinkers (A-ND) and dependent heavy drinkers (A-D). Typical and novel step-wise analyses examined profiles of working memory load and increasing task demand, respectively.
Results: Performance was significantly decreased in A-D during high working memory load (2-Back), compared to CTRL and A-ND. Analysis of brain activity during high load (0-Back vs. 2- Back) showed greater responses in the dorsal lateral and medial prefrontal cortices of A-D than CTRL, suggesting increased but failed compensation. The step-wise analysis revealed that the transition to Low Demand (0-Back to 1-Back) was associated with robust increases and decreases in cognitive control and default-mode brain regions, respectively, in A-D and A-ND but not CTRL. The transition to High Demand (1-Back to 2-Back) resulted in additional engagement of these networks in A-ND and CTRL, but not A-D.
Conclusion: Heavy drinkers engaged working memory neural networks at lower demand than controls. As demand increased, nondependent heavy drinkers maintained control performance but relied on additional neurophysiological resources, and dependent heavy drinkers did not display further resource engagement and had poorer performance. These results support targeting these brain areas for treatment interventions.

1. Introduction

Not all heavy drinkers develop alcohol use disorder, despite having similar alcohol use patterns. Identifying neurobehavioral patterns that differentiate heavy drinkers who develop alcohol use disorder from those who do not will provide valuable information about the individual differences associated with this disorder, thereby informing treatment efforts. A common approach used to characterize neurobehavioral abnormalities associated with mental health problems like alcohol use disorder is to compare individuals with a particular condition to controls using experimental tasks designed to measure specific neural processes and associated behavioral output within a neuroimaging environment. In this way, challenging brain activity and behavior during task performance can uncover deficiencies and/or compensatory mechanisms. In particular, the cognitive control of behavior and inter-connected processes such as working memory have been a research focus due to their essential roles in normal psychosocial functioning. For example, studies using working memory tasks and neuroimaging techniques have demonstrated working memory deficits are linked to altered brain activity in various mental health disorders including, but not limited to, schizophrenia (Jansma et al., 2004), pathological dissociation (Elzinga et al., 2007) and bipolar disorder (Cremaschi et al., 2013).

Abnormal working memory has also been identified as a critical concern in substance use disorders, having been demonstrated in individuals dependent on alcohol (Pitel et al., 2007) and various other classes of drugs including opioids (Vo et al., 2014), cannabinoids (Vo et al., 2014), stimulants (Albein-Urios et al., 2012; Duarte

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et al., 2012). That working memory deficits are found across problematic users of alcohol and other drugs is perhaps not surprising considering that impaired control over the use of these substances is a characteristic of substance use disorders and behavioral control relies, in part, on working memory (Hofmann et al., 2008). More specifically, control over the decision to use alcohol and other drugs requires working memory to integrate information related to previous consequences of substance use and current contingencies surrounding the decision to use (Weber and Johnson, 2009). Reduced working memory capacity in these individuals might be more easily overloaded during the evaluation of this information, resulting in impulsive, maladaptive substance use decisions in the present and for the future (Wesley and Bickel, 2014; Wesley et al., 2014). Indeed, several theories of impulsivity as a factor in drug abuse and in externalizing disorders, such as ADHD, posit a bi-directional relationship between working memory and inhibitory control (Barkley, 1997; Fillmore, 2003; Finn, 2002). Consistent with this idea, studies have shown that low working memory ability is associated with greater trait impulsivity (e.g., Gunn and Finn, 2013). Experimental manipulation of working memory load has revealed that increasing load to a capacity limit increases impulsive performance on a decision-making task (Hinson et al., 2003). Also, research on the acute effects of alcohol on inhibitory control showed that the disinhibiting effects of the drug are, in part, due to the alcohol-induced reductions in information processing capacity (Fillmore and Van Selst, 2002). Taken together, these lines of evidence provide corroborating evidence for the important link between working memory and under-controlled behavior.

A substantial amount of clinical research has characterized the neurocircuitry underlying cognitive control and working memory, as well as the network-level changes that occur as these processes are engaged. A recent meta-analysis (Niendam et al., 2012) of 193 functional magnetic resonance imaging (fMRI) studies indicated that the primary brain regions involved in the cognitive control of behavior included prefrontal cortex regions, such as the dorsal lateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC), as well as the superior and inferior parietal cortices (sPar), precuneus and precentral gyrus. In general, these areas are part of an integrated dorsal processing stream involved in overlapping cognitive functions (Wesley and Bickel, 2014) that is engaged in response to external demand. For example, engagement of the DLPFC, superior parietal cortices, ACC, striatum, thalamus and insula has been detected by fMRI during working memory tasks, in line with the performance requirements of those tasks, such as match mismatch detection and response inhibition (reviewed in Wilcox et al., 2014). By contrast, when external demand is not present and the brain is considered to be in the default mode of functioning, activity is greater in brain areas such as the ventral medial prefrontal cortex (vmPFC) and posterior cingulate cortex (PCC) (Raichle and Snyder, 2007; Wang and Li, 2013). As external demand is imposed, activity typically decreases in the default-mode network and increases in cognitive control networks, consistent with the heuristics of a free energy framework for biological systems (Friston, 2009, 2010; Friston et al., 2006).

Altered brain activity has been demonstrated using fMRI during the performance of working memory tasks in individuals with substance use disorders. By way of introduction to the present study, the following overview focuses on research in adults with alcohol use disorder that used N-Back type tasks, which are well-established working memory tasks that have been adapted for use in a neuroimaging environment. While performing a 2-Back spatial working memory task, individuals with alcohol use disorder displayed reduced bilateral DLPFC activation compared to control participants when performing the task at equivalent level (Pfefferbaum et al., 2001). In another study (Tapert et al., 2001), emerging adult (i.e., 18–25 years old) women with alcohol use disorder and matched controls completed a task in which they were instructed to respond when an abstract line drawing appeared in a location that had been previously occupied. Participants with alcohol use disorder were less accurate on the task and had less activity in the right superior and inferior parietal, right middle frontal, right postcentral and left superior frontal cortex compared to controls. In a study that used a non-spatial 2-Back task, reduced activity was observed in the bilateral frontal and pre-central cortex and left superior temporal and parietal cortices of individuals with alcohol use disorder compared to social drinkers (Park et al., 2011). Importantly, these impairments in working memory performance and altered activity in associated brain areas appear to be clinically significant. For example, individuals with alcohol use disorder who exhibited greater bilateral rostral and ventral lateral, prefrontal cortex activity given equivalent performance of a 2-Back task were more likely to remain abstinent through a 7 month post-treatment period (Charlet et al., 2014).

A limitation of prior studies that have evaluated working memory performance and associated brain activity in individuals with alcohol use disorder is that a control group with similar alcohol use history has not been included to differentiate between alcohol exposure and problematic behaviors. Furthermore, those studies have not considered dynamic changes in brain activity and/or recruitment of other regions as a step-wise function of neurophysiological demand. Understanding how brain function changes in response to increasing task demand, however, could provide new insights into the neural resources (or lack thereof) available to meet the external constraints placed on the cognitive control processes needed for successful abstinence and/or recovery. The present study sought to extend previous work by comparing working memory performance and associated brain activity in individuals who met criteria for alcohol use disorder (heavy drinkers who were dependent; A-D) to a group with a comparable alcohol use history (heavy drinkers who were nondependent; A-ND), as well as a group of individuals who reported non-problematic alcohol use (CTRL). Further, this study included zero- (0-Back), low- (1-Back) and high- (2-Back) working memory load conditions. In addition to typical analyses examining brain activity during low (0-Back vs. 1-Back) and high (0-Back vs. 2- Back) working memory load conditions, the current study used a step-wise transitional approach to determine the concurrent increases and decreases in brain activity associated with transitioning to neurophysiological states with low (1-Back > 0-Back and 1-Back < 0-Back) and high (2-Back > 1-Back and 2-Back < 1-Back) external demand on neurophysiological resources. In this way, we sought to identify potential differences in the neurophysiological capacity associated with a critical cognitive process in individuals who vary in their alcohol use history and expression of problem drinking behaviors. To the extent that neurobehavioral impairments are associated with alcohol dependence and not just heavy alcohol consumption, we predicted reduced performance and brain activity in heavy drinkers who were dependent relative to the nondependent heavy drinkers.

2. Methods

2.1. Participants

The Wake Forest School of Medicine Institutional Review Board approved the study protocol. Potential participants responded to local media advertisements by phone and an initial screen was performed to determine study eligibility. Individuals reporting illicit drug use, diseases of the central nervous system, head trauma, current use of psychotropic medications, or any condition that prohibited entry into an MRI scanner were ineligible. Individuals who passed this initial screening were invited to the laboratory for addi-