Psychiatry Research: Neuroimaging ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Associations between regional brain physiology and trait impulsivity, motor inhibition, and impaired control over drinking

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ARTICLE INFO

Article history:
Received 13 August 2014
Received in revised form
16 February 2015
Accepted 28 April 2015

Keywords:
Cerebral blood flow
fMRI
Inhibitory control
Stop task
Alcohol

ABSTRACT

Trait impulsivity and poor inhibitory control are well-established risk factors for alcohol misuse, yet little is known about the associated neurobiological endophenotypes. Here we examined correlations among brain physiology and self-reported trait impulsive behavior, impaired control over drinking, and a behavioral measure of response inhibition. A sample of healthy drinkers ($n=117$) completed a pulsed arterial spin labeling (PASL) scan to quantify resting regional cerebral blood flow (rCBF), as well as measures of self-reported impulsivity (Eysenck I_7 Impulsivity scale) and impaired control over drinking. A subset of subjects ($n=40$) performed a stop signal task during blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging to assess brain regions involved in response inhibition. Eysenck I_7 scores were inversely related to blood flow in the right precentral gyrus. Significant BOLD activation during response inhibition occurred in an overlapping right frontal motor/premotor region. Moreover, impaired control over drinking was associated with reduced BOLD response in the same region. These findings suggest that impulsive personality and impaired control over drinking are associated with brain physiology in areas implicated in response inhibition. This is consistent with the idea that difficulty controlling behavior is due in part to impairment in motor restraint systems.

1. Introduction

Impulsivity, which refers broadly to acting without thinking, is a widely accepted risk factor for alcohol abuse (Potenza and de Wit, 2010). Measuring impulsive personality traits encompasses several distinct conceptual and methodological factors. One such factor that has been repeatedly implicated in alcohol abuse is difficulty controlling or inhibiting inappropriate behavior. Such poor behavioral control can be assessed by both self-report personality inventories and behavioral laboratory measures. On personality inventories, greater self-reported difficulty controlling behavior or acting without forethought is associated with increased drug and alcohol use (Petry, 2001; Finn, 2002). Behavioral measures of inhibitory control include stop signal and go/no-go tasks, which measure the ability to inhibit prepotent or instigated motor behavior, such as a finger press. Poor response inhibition on these tasks has also been repeatedly linked with greater alcohol use and problems (Bjork et al., 2004; Nigg et al., 2006; Rubio et al., 2008).

One potential explanation for the increased risk of alcohol-related problems in impulsive individuals is a specific instance of impaired impulse control: impaired control over drinking. Impaired control refers to a decreased ability to limit or abstain from alcohol consumption despite persistent intentions to do so (Heather et al., 1993). Impaired control is a well-established feature of problematic alcohol use, with two DSM-V criteria for alcohol use disorders that reflect impaired control (i.e., drinking greater amounts than intended and inability to quit or control drinking; American Psychiatric Association, 2013). Moreover, impaired control is becoming increasingly recognized as a problem for young adult drinkers, as this is one of the first symptoms endorsed by those transitioning from social- to dependent-drinking (Leeman et al., 2012, 2014).

Impaired control and impulsivity/behavioral under-control are conceptually linked, in that impaired control refers to difficulty controlling the specific behavior of alcohol consumption. As such, it is reasonable to assume that individuals who have a general

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http://dx.doi.org/10.1016/j.pscychresns.2015.04.010
0925-4927/

difficulty controlling behavior or inhibiting inappropriate responses might also display impaired control over drinking. Indeed, initial studies show correlations between impaired control and both self-report and behavioral measures of inhibitory control (for review, see Leeman et al. (2012)). However, little is known about the neurobiological endophenotypes of trait impulsivity in general, and impaired control specifically. Understanding the neural correlates of impulsive traits and impaired control could have important implications for identifying individuals at risk for alcohol use disorders, and for developing treatments.

In a reasonably large sample of 117 healthy subjects who spanned a range of drinking, the current study examined anatomic regions in which measures of brain physiology were correlated with self-reported trait impulsive behavior in general, impaired control over drinking specifically, and a behavioral measure of motor response inhibition. Specifically, we identified regions where impulsive personality and impaired control correlated with resting cerebral blood flow. Additionally, we examined fMRI blood oxygenation level-dependent (BOLD) activation during a response inhibition (stop signal) task as a function of impaired control. Given previous evidence about brain areas involved in response inhibition (Congdon et al., 2010; Bari and Robbins, 2013; Rae et al., 2014), we expected trait impulsivity and impaired control to be associated with less activity in right frontal regions.

2. Methods

2.1. Subjects

The sample of 117 right-handed regular drinkers (98 men and 19 women), ranging from moderate to heavy, participated in one of three previous studies (functional magnetic resonance imaging or positron emission tomography) conducted at the Indiana University School of Medicine and the Indiana Alcohol Research Center. Subjects were recruited by community advertisements and provided informed consent as approved by the Indiana University Institutional Review Board. The study was carried out in accordance with the Declaration of Helsinki. Interested volunteers were first screened by phone and then completed an in-person interview to determine medical history and current and past drug and alcohol use. Exclusion criteria included self-reported neurological disorders (injury, disease) of cerebral origin, and any major DSM-IV Axis I psychiatric disorder (aside from alcohol abuse/dependence), including drug dependence. All participants had a zero breath alcohol content at the time of study. Six participants had a positive drug screen (marijuana/THC, $n=4$; opiates, $n=1$; TCA, $n=1$); consequently, the data were analyzed with and without these participants. No differences were observed, and results reported here are based on the entire sample.

2.2. Measures

2.2.1. Alcohol use measures

During the in-person interview, subjects were given the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994), a semi-structured interview that assesses the symptoms of an alcohol use disorder (AUD). The SSAGA was used to create a total AUD symptom count as outlined in the current DSM-V. Subjects also completed the Timeline Follow-back (TLFB; Sobell and Sobell, 1992), a self-reported retrospective timeline calendar of alcohol consumption, estimating the number of standard drinks consumed each day over the past 90 days. From this we calculated participants' average number of drinks per week and average number of drinks per drinking day. In addition, subjects completed the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1989), a 10-item self-report measure that assesses patterns of drinking, dependence, and alcohol-related problems. Scores on the AUDIT range from 0 (no alcohol-related problems) to 40 (most severe alcohol-related problems), with ≥ 8 being a commonly used threshold for hazardous drinking (Babor et al., 2001).

2.2.2. Impulsive personality

Impulsive personality was assessed using the Eysenck I_7 Impulsiveness Questionnaire (Eysenck et al., 1985). The impulsivity subscale consists of 19 yes/no questions related to acting on impulse (e.g. 'Do you often do and say things without stopping to think; Do you need to use a lot of self-control to keep out of trouble?'), with a total possible score range of 0–19. As originally reported by Eysenck et al. (1985) for adults aged 20–29, normative values are 7.9 (S.D.=4.1) for males and 9.0 (S.D.=4.2) for females.

2.2.3. Impaired control over drinking (IC)

Subjects were classified as having impaired (IC) or no impaired control (no-IC) over their drinking based on the following two DSM-V symptoms of alcohol dependence as derived from the SSAGA: (1) drinking in larger amounts, or for over a longer period than intended, and (2) persistent desire, or one or more unsuccessful efforts, to cut down or control drinking. Subjects endorsing one or both of these symptoms were grouped in the IC group, and subjects endorsing neither were grouped in the no-IC group.

2.2.4. Response inhibition

A subset of subjects ($n=40$, 39 of whom were included in Kareken et al. (2013))[1] performed a stop signal task during blood oxygenation level-dependent (BOLD) fMRI to assess brain activation during response inhibition. Task procedures are described in detail by Kareken et al. (2013). Briefly, participants responded as quickly as possible to Go signals (horizontal green arrows), but attempted to withhold their responses on trials in which a Stop signal (vertical red arrow) appeared subsequent to the Go signal. An adaptive staircase algorithm adjusted the delay between the Go and Stop signals to target a stop failure rate of 50%. Stop signal reaction time (SSRT), an estimate of the time needed to stop (withdraw) the Go response, was calculated by subtracting a subject's average stop-signal delay from that subject's xth percentile Go RT (correct trials only), where x corresponds to the stop failure rate (Band et al., 2003).

2.3. Procedure

Procedural details specific to the individual studies are reported elsewhere (Kareken et al., 2012, 2013; Oberlin et al., 2013). All subjects completed the self-report measures of alcohol consumption and impulsivity during their initial study sessions at the Indiana Clinical Research Center. Subjects then returned for either one (Kareken et al., 2012; Oberlin et al., 2013) or two (Kareken et al., 2013) magnetic resonance imaging (MRI) sessions. Detailed timelines of the specific MRI protocols for each of these studies are provided in Supplementary Fig. 1. All subjects completed a Pulsed Arterial Spin Labeling (PASL) scan to measure resting regional cerebral blood flow (rCBF) as part of the MRI protocol.

Those subjects participating in the stop signal functional MRI (fMRI) study were imaged under both intravenous alcohol and saline infusions in counter-balanced order (Kareken et al., 2013). Here we re-examined the BOLD fMRI data from these participants as a function of impaired control over drinking, but using data from the saline condition only. This permitted an examination of the overlap between regions where resting rCBF was associated with Eysenck I_7 and areas where impaired control over drinking affected BOLD activation during response inhibition. PASL scans from this stop signal study were obtained at baseline (i.e., before saline infusion).

2.4. Imaging

Subjects were imaged on a Siemens (Erlangen, Germany) 3 T Magnetom Trio-Tim scanner equipped with a 12-channel head coil array. A T_1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence was used to acquire high-resolution anatomical images ($1.0 \times 1.0 \times 1.2$ mm^3 voxels) for co-registration and normalization to the Montreal Neurological Institute (MNI) coordinate system.

PASL scans (5:45 min duration) measured rCBF (ml/100 g/min) using a one-compartment model (Wang et al., 2003), and were acquired using Q2TIPS pulse sequence (Luh et al., 1999) labeling scheme, as detailed in Wang et al. (2011) with a 64 label-control pair readout (single-shot gradient-echo echo planar imaging (EPI)); 18 ascending axial slices; matrix, 64×64; $3.75 \times 3.75 \times 6$ mm^3 voxels; GRAPPA acceleration factor 2; 3D prospective acquisition correction algorithm). During the PASL acquisition, subjects were instructed to relax with their eyes closed. To ensure that subjects remained awake and in a lightly attentive state throughout the scan, subjects were directed to press a button on a response box (Current Designs, Inc. Philadelphia, PA) when they heard a distinct tone (750 Hz, 750 ms long). This tone was played five times at a random time during 1-min intervals. As a criterion for inclusion, we required that participants respond to at least four of the five tones. Reaction time was not emphasized, and subjects were told that the tone and their response were solely to ensure that they were awake.

In the stop signal task subset, three BOLD contrast sensitive scans measured stop task responses (gradient-echo EPI 193 volumes; repetition time, 2000 ms; echo time, 29 ms; flip angle, 76°; 35 interleaved 3-mm-thick axial slices; matrix, 88×88; $2.5 \times 2.5 \times 3.0$ mm^3 voxels; GRAPPA acceleration factor 2; and 3D prospective acquisition correction algorithm).

[1] One subject was excluded from the Kareken et al. (2013) sample but included here given the subject's indeterminate status with regard to a family history of alcoholism; one subject included in the Kareken et al. (2013) article was excluded here given technical problems with the subject's PASL image data.

Please cite this article as: Weafer, J., et al., Associations between regional brain physiology and trait impulsivity, motor inhibition, and impaired control over drinking. Psychiatry Research: Neuroimaging (2015), http://dx.doi.org/10.1016/j.pscychresns.2015.04.010