Psychiatry Research: Neuroimaging 233 (2015) 125–130

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Decreased gray matter volume in inferior frontal gyrus is related to stop-signal task performance in alcohol-dependent patients

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ARTICLE INFO

Article history:
Received 6 August 2014
Received in revised form
18 February 2015
Accepted 13 May 2015
Available online 21 May 2015

Keywords:
Addiction
Alcohol
Inferior frontal gyrus
Gray matter volume
Response inhibition
Stop-signal task

ABSTRACT

Impairment in inhibitory control has been proposed to contribute to habitual alcohol use, abuse and eventually dependence. Moreover, alcohol-dependent (AD) patients have shown a loss of gray matter volume (GMV) in the brain, specifically in prefrontal regions associated with executive functions, including response inhibition. To date, no study has evaluated whether this prefrontal GMV reduction is related to response inhibition in alcohol dependence. To address this issue, we acquired high-resolution T1-weighted magnetic resonance mages from recently detoxified AD patients ($n=22$) and healthy controls (HC; $n=21$). Differences in local GMV between groups were assessed by means of voxel-based morphometry (VBM). Moreover, within the AD group, mean local GMV reductions were extracted and correlated with behavioral performance on the stop-signal task. We found a significantly decrease in GMV in the left inferior frontal gyrus (IFG) in AD patients compared with HC subjects. Further, mean local GMV in this area correlated positively with reaction times on go trials during the stop-signal task in AD patients. Our findings suggest that GMV losses in the IFG in AD patients are related to faster go responses on the stop-signal task.

1. Introduction

Alcohol dependence is characterized by impulsive drinking despite awareness of negative consequences. A central factor that may contribute to excessive drinking is an impaired ability to inhibit habitual behavior, which could be a risk factor for impulsive drinking, a consequence of the toxic effects of alcohol, or both (Goldstein and Volkow, 2011). Indeed, alcohol abuse and dependence have been shown to be associated with difficulties in inhibitory control (for a review, see Sullivan and Pfefferbaum, 2005). This impaired inhibitory control in alcohol-dependent (AD) patients very likely contributes to poor treatment outcome and relapse (Tuithof et al., 2014).

Functional neuroimaging studies have identified a key involvement of the frontal cortex in inhibitory control, often measured with stop-signal and go/no-go tasks (Goldstein and Volkow, 2011; Levy and Wagner, 2011). During stop or no-go trials, participants have to inhibit prepared responses. Functional imaging studies in healthy subjects have shown that the inferior frontal gyrus (IFG) is active during response inhibition (e.g., Garavan et al., 1999; Levy and Wagner, 2011; Swick et al., 2011; Gan et al., 2014; for a review, see Chambers et al., 2009). Moreover, mild alcohol intoxication seems to decrease levels of activation in the right IFG (Gan et al., 2014). In AD patients, decreased prefrontal activation during response inhibition has been found, suggesting impairments in inhibitory control (Li et al., 2009).

Studies of brain structure are in alignment with the above findings on activation. First, Aron et al. (2003) demonstrated that patients with lesions in the right IFG had longer stop-signal reaction times (SSRTs), i.e., relatively poor response inhibition, compared with healthy controls, and larger IFG lesions were related to poorer response inhibition in these patients. Second, patients with lesions in the left IFG demonstrated more failures to inhibit responses on a go/no-go task,

Abbreviations: AD patients, alcohol-dependent patients; AUDIT, Alcohol Use Disorder Identification Test; DARTEL, diffeomorphic anatomical registration through exponentiated lie algebra; FWE, family wise error; GMV, gray matter volume; HC, healthy control; IFG, inferior frontal gyrus; LTDH, Lifetime Drinking History scale; MPRAGE, magnetization-prepared rapid gradient echo; MRI, magnetic resonance imaging; MNI, Montreal Neurological Institute; RT, reaction time; SPM8, Statistical Parametric Mapping 8; SSD, stop-signal delay; SSRT, stop-signal reaction time; TPMs, tissue probability maps

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http://dx.doi.org/10.1016/j.pscychresns.2015.05.006
0925-4927/

especially when increased inhibitory control was required, as compared with controls and patients with lesions in the orbitofrontal cortex (Swick et al., 2008).

Numerous studies have shown reduced GMV in the IFG in AD patients (Pfefferbaum et al., 1997; Fein et al., 2002; Mechtcheriakov et al., 2007; Grodin et al., 2013). This atrophy has often been associated with longer lifetime alcohol use (Fein et al., 2002) and weaker performance on tasks assessing executive functions, such as attentional set shifting (Trick et al., 2014), trail-making (Chanraud et al., 2007) and fear recognition (Trick et al., 2014). However, associations between structural brain measures and stop-signal task performance in AD patients remain largely unexplored. Therefore, the goal of our study was to investigate whether GMV differences in AD patients relative to healthy controls were related to task performance on a stop-signal task.

First, we hypothesized that prefrontal GMV would be reduced in AD patients compared with a matched sample of healthy control (HC) participants. Second, within the AD patient group, we expected that a lower volume of prefrontal areas would be related to poor response inhibition (i.e., high SSRTs) and faster reaction times on go trials. Third, to explore whether GMV differences and response inhibition were related to the toxic effects of alcohol, we performed additional correlation analyses for these measures and the lifetime alcohol intake of each participant in the AD patient group only.

2. Methods

2.1. Participants

Recently detoxified (<6 months), right-handed, male AD in patients ($n=22$, mean age=42.1 years; $SD=6.2$; range=26–51) and HC participants ($n=21$, mean age=42 years; $SD=6.4$, range=29–53), matched for age, sex, education and intelligence, underwent magnetic resonance imaging (MRI) in a 3-Tesla scanner. Exclusion criteria for all participants were female sex, left-handedness, age older than 55 years, axis I psychiatric disorders according to DSM-IV criteria except for alcohol dependence in the AD patient group (screened by the Mini-International Neuropsychiatric Interview, M.I.N.I., plus an International Neuropsychiatric Interview; Sheehan et al., 1998), a history of neurological diseases and psychoactive medication. Additional exclusion criteria for the control group were scores above 8 on the Alcohol Use Disorder Identification Test (AUDIT; Saunders et al., 1993), as screened in a telephone interview before the experiment.

The study took place at the Charité-Universitätsmedizin Berlin and was approved by the local ethics committee. Before entering the study, all participants gave written informed consent in accordance with the 1964 Declaration of Helsinki. Participants received financial compensation.

2.2. Behavioral measures

2.2.1. Questionnaires

To assess lifetime alcohol intake and drug abuse for both groups, we interviewed participants on the Lifetime Drinking History scale (LTDH; Skinner and Sheu, 1982), evaluating lifetime alcohol intake in kilograms. AUDIT scores of the AD patients were obtained on the day of testing. Scores on the Matrix Reasoning subtest of the Wechsler Adult Intelligence Scale (WAIS; Kaufman and Lichtenberger, 2005) were used as a proxy for general intelligence.

2.2.2. Stop-signal task

AD patients performed a stop-signal task, which was based on the paradigm used by Tian et al. (2012) and consisted of two blocks with 80 go and 20 stop trials per block. The stop-signal task was programmed in MATLAB (MathWorks Company, Natick, MA) and the Psychtoolbox (Brainard, 1997). Fig. 1 illustrates the experimental design of the stop-signal task. For go trials, participants were instructed to respond as fast as possible to an arrow on the screen (left or right), using the arrow buttons on the keyboard (left or right). Arrows pointed left and right in a randomized order and were presented for 600 ms, after which a cross was presented for an interval of 1400, 1800 or 2200 ms. On stop trials, an arrow flipped upwards shortly after the onset of the trial. In these cases, participants had to inhibit the previously prepared motor response. The interval between the go and stop signals (stop-signal delay; SSD) depended on the proportion of successfully inhibited responses. To this end, we used an adaptive staircase algorithm. The SSD started with 250 ms and was made more difficult after successful inhibition by adding 50 ms to the SSD of the next trial. In contrast, when participants failed to inhibit their stop response, the SSD was decreased by 50 ms, to a minimum of 50 ms. The staircase procedure converged to a critical SSD representing the time delay required to succeed in withholding a response in 50% of the stop trials. The task can be understood in terms of a horse race model, with a go process and a stop process racing towards a finish (Logan, 1994). The go process prepares and generates the movement, whereas the stop process inhibits the initiation of movements. Participants were instructed to respond as quickly and as accurately as possible.

Participants' reaction times (RTs) on go trials, as well as their accuracy on go trials and stop trials (stop inhibition rate) and the SSD were recorded. The time required to inhibit a movement after seeing the stop signal (stop-signal reaction

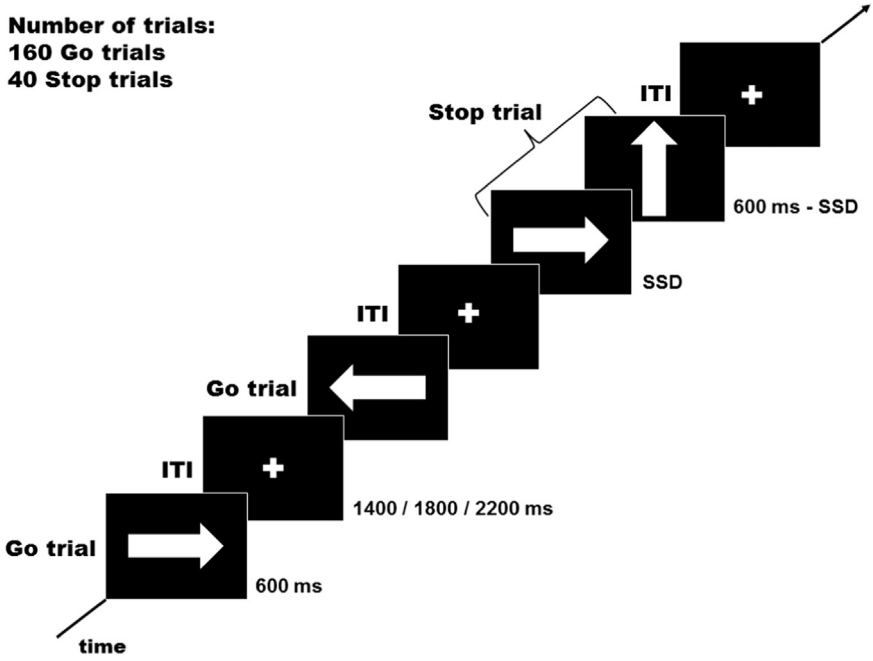

Fig. 1. Schematic display of the stop-signal task, based on Gan et al. (2014) and Tian et al. (2012). The task consisted of 2 blocks, with 80 go and 20 stop trials in each block. In go trials, participants were instructed to respond as fast as possible to an arrow on the screen (left or right), using the arrow buttons on the keyboard (left or right). In stop trials, an arrow flipped upwards shortly after the onset of the trial. In these cases, participants had to inhibit their response. The interval between the stop signal and the go signal, the stop-signal delay (SSD), was changed dynamically to obtain a 50% inhibition rate.